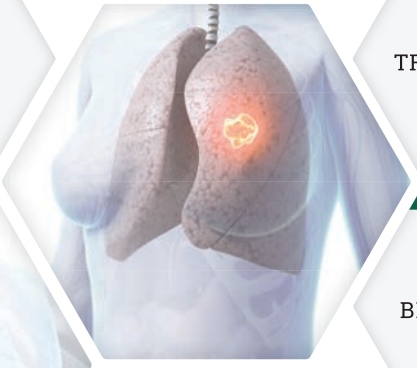
TrackerBook

Selected publications on Therapeutic Drug Monitoring in Peer-reviewed journals

Anti-CD-20

RITUXIMAB



Anti-HER2

TRASTUZUMAB

Anti-VEGF

BEVACIZUMAB

Anti-IL6-R

TOCILIZUMAB

Anti-TNFα

CERTOLIZUMAB

Anti-IL17A

SECUKINUMAB

Anti-TNFα

ETANERCEPT

Anti-IL12/IL23

USTEKINUMAB

Anti-TNFα

INFLIXIMAB

Anti-TNFα

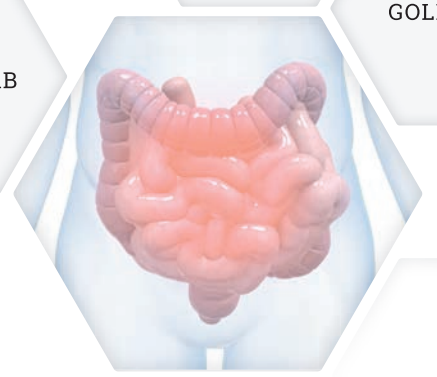
ADALIMUMAB

Anti-TNFα

GOLIMUMAB

Anti-α4-β7

VEDOLIZUMAB



Theradiag

INNOVATION FOR BIOTHERAPIES

SUMMARY

Petitdidier N, Beaugerie L, Carbonnel F , Bourrier A, Treton X, Sylvie Rajca S, Georgia Malamut G, Abitbol V, Allez M, Pelletier AL, Marthey L, Jouet P, Benamouzig R, Amiot X, Bouhnik Y, Amiot A, **Real-world use of therapeutic drug monitoring of CT-P13 in patients with inflammatory bowel disease** Clin Res Hepatol Gastroenterol. 2020 Jan 7.

Paul S, Roblin X. **Letter: immunogenicity of anti-TNF in elderly IBD patients.** Aliment Pharmacol Ther. 2019 Aug;50(3):336.

Fernandes SR, Bernardo S, Simões C, Gonçalves AR, Valente A, Baldaia C, Moura Santos P, Correia LA, Tato Marinho R. **Proactive Infliximab Drug Monitoring Is Superior to Conventional Management in Inflammatory Bowel Disease**. Inflamm Bowel Dis. 2019 Jun 27.

Ungar B, Ben-Shatach Z, Ben-Haim G, Yavzori M, Picard O, Fudim E, Kopylov U, Veyrard P, Del Tedesco É, Paul S, Eliakim R, Ben-Horin S, Roblin X. **Infliximab therapy intensification upon loss of response: Is there an optimal trough level?** Dig Liver Dis. 2019 Mar 5.

Attar A, Duru G, Roblin X, Savarieau B, Brunel P, Lamure M, Peyrin-Biroulet L**. Cost savings using a test-based de-escalation strategy for patients with Crohn's disease in remission on optimized infliximab: A discrete event model study.** Dig Liver Dis. 2019 Jan;51(1):112-119.

Ilias A, Szanto K, Gonczi L, Kurti Z, Golovics PA, Farkas K, Schafer E, Szepes Z, Szalay B, Vincze A, Szamosi T, Molnar T, Lakatos PL. **Outcomes of Patients With Inflammatory Bowel Diseases Switched from Maintenance Therapy with a Biosimilar to Remicade.** Clin Gastroenterol Hepatol. 2019 Jan 7.

Jentzer A, -Emmanuelle Berger A, Labetoulle R, Haccourt A, Roblin X, Paul S. **Short Communication: Evaluation of infliximab and anti-infliximab LISA-TRACKER immunoassays for the therapeutic drug monitoring of SB2 infliximab biosimilar.** Ther Drug Monit. 2018 Sep 21.

Poullenot F, Nivet D, Paul S, Riviere P, Roblin X, Laharie D. **Severe endoscopic lesions are not associated with more infliximab fecal loss in acute severe ulcerative colitis.** Dig Liver Dis. 2018 Jul 10.

Nasser Y, Labetoulle R, Harzallah I, Berger AE, Roblin X, Paul S. **Comparison of Point-of-Care and Classical Immunoassays for the Monitoring Infliximab and Antibodies Against Infliximab in IBD.** Dig Dis Sci. 2018 Jun 9.

Dutzer D, Nasser Y, Berger AE, Roblin X, Paul S. **Letter: new thresholds need to be defined when using point of care assays to monitor infliximab trough levels in IBD patients.** Aliment Pharmacol Ther. 2018 Jun;47(11):1571-1573.

Guidi L, Pugliese D, Panici Tonucci T, Berrino A, Tolusso B, Basile M, Cantoro L, Balestrieri P, Civitelli F, Bertani L, Marzo M, Felice C, Gremese E, Costa F, Viola F, Cicala M, Kohn A, Gasbarrini A, Rapaccini GL, Ruggeri M, Armuzzi A. **Therapeutic drug monitoring is more cost-effective than a clinically-based approach in the management of loss of response to infliximab in inflammatory bowel disease: an observational multi-centre study**. J Crohns Colitis. 2018 May 31.

Avouac J, Moltó A, Abitbol V, Etcheto A, Salcion A, Gutermann L, Klotz C, Elhai M, Cohen P, Soret PA, Morin F, Conort O, Chast F, Goulvestre C, Jeunne CL, Chaussade S, Kahan A, Roux C, Allanore Y, Dougados M. **Systematic switch from innovator infliximab to biosimilar infliximab in inflammatory chronic diseases in daily clinical practice: The experience of Cochin University Hospital, Paris, France.** Semin Arthritis Rheum. 2017 Oct 5.

Roblin X, Boschetti G, Duru G, Williet N, Deltedesco E, Phelip JM, Peyrin-Biroulet L, Nancey S, Flourié B, Paul S. **Distinct Thresholds of Infliximab Trough Level Are Associated with Different Therapeutic Outcomes in Patients with Inflammatory Bowel Disease: A Prospective Observational Study**. Inflamm Bowel Dis. 2017 Sep 22.

Bor R, Farkas K, Fábián A, Bálint A, Milassin Á, Rutka M, Matuz M, Nagy F, Szepes Z, Molnár T. **Clinical role, optimal timing and frequency of serum infliximab and anti-infliximab antibody level measurements in patients with inflammatory bowel disease.** PLoS One. 2017 Mar 31;12(3):e0172916.

Roblin X, Duru G, Williet N, Del Tedesco E, Cuilleron M, Jarlot C, Phelip JM, Boschetti G, Flourié B, Nancey S, Peyrin-Biroulet L, Paul S. **Development and Internal Validation of a Model Using Fecal Calprotectin in Combination with Infliximab Trough Levels to Predict Clinical Relapse in Crohn's Disease**. Inflamm Bowel Dis. 2017 Jan;23(1):126-132.

Gonczi L, Vegh Z, Golovics PA, Rutka M, Gecse KB, Bor R, Farkas K, Szamosi T, Bene L, Gasztonyi B, Kristóf T, Lakatos L, Miheller P, Palatka K, Papp M, Patai Á, Salamon Á, Tóth GT, Vincze Á, Biro E, Lovasz BD, Kurti Z, Szepes Z, Molnár T, Lakatos PL. **Prediction of Short- and Medium-term Efficacy of Biosimilar Infliximab Therapy. Do Trough Levels and Antidrug Antibody Levels or Clinical And Biochemical Markers Play the More Important Role?** J Crohns Colitis. 2016 Nov 12.

Lee MW, Connor S, Ng W, Toong CM. **Comparison of infliximab drug measurement across three commercially available ELISA kits.** Pathology. 2016 Aug 23.

Gecse KB, Lovász BD, Farkas K, Banai J, Bene L, Gasztonyi B, Golovics PA, Kristóf T, Lakatos L, Csontos ÁA, Juhász M, Nagy F, Palatka K, Papp M, Patai Á, Lakner L, Salamon Á, Szamosi T, Szepes Z, Tóth GT, Vincze Á, Szalay B, Molnár T, Lakatos PL. **Efficacy and Safety of the Biosimilar Infliximab CT-P13 Treatment in Inflammatory Bowel Diseases: A Prospective, Multicentre, Nationwide Cohort.** J Crohns Colitis. 2016 Feb;10(2):133-40.

Paul S, Roblin X, Peyrin-Biroulet L. **Letter: infliximab de-escalation based on trough levels in patients with inflammatory bowel disease.** Aliment Pharmacol Ther. 2015 Oct;42(7):939-40.

Rinaudo-Gaujous M, Roblin X, Marotte H, Paul S. **The antibody response against human and chimeric anti-TNF therapeutic antibodies primarily targets the TNF binding region.** Ann Rheum Dis. 2015 Aug;74(8):e40.

Roblin X, Marotte H, Leclerc M, Del Tedesco E, Phelip JM, Peyrin-Biroulet L, Paul S. **Combination of C-reactive protein, infliximab trough levels, and stable but not transient antibodies to infliximab are associated with loss of response to infliximab in inflammatory bowel disease.** J Crohns Colitis. 2015 Jul;9(7):525-31.

Paul S, Del Tedesco E, Marotte H, Rinaudo-Gaujous M, Moreau A, Phelip JM, Genin C, Peyrin-Biroulet L, Roblin X. **Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. Inflamm Bowel Dis.** 2013 Nov;19(12):2568-76.

Roblin X, Williet N, Boschetti G, Phelip JM, Del Tedesco E, Berger AE, Vedrines P, Duru G, Peyrin-Biroulet L, Nancey S, Flourie B, Paul S **Addition of Azathioprine to the Switch of anti-TNF in Patients With IBD in Clinical Relapse With Undetectable anti-TNF Trough Levels and Antidrug Antibodies: A Prospective Randomised Trial** Gut. 2020 Jan 24.

Fay S, Ungar B, Paul S, Levartovsky A, Yavzori M, Fudim E, Picard O, Eliakim R, Ben-Horin S, Roblin X, Kopylov U. **The Association Between Drug Levels and Endoscopic Recurrence in Postoperative Patients with Crohn's Disease Treated with Tumor Necrosis Factor Inhibitors.** Inflamm Bowel Dis. 2017 Aug 22.

Johnston EL, Warner BD, Digby-Bell JL, Unsworth N, Anderson S, Sanderson J D, Arkir Z, Irving PM **Utilisation of anti-TNF levels in a UK tertiary IBD centre.** Frontline Gastroenterol. 2017 Jul;8(3):189-195.

Ward MG, Warner B, Unsworth N, Chuah SW, Brownclarke C, Shieh S, Parkes M, Sanderson JD, Arkir Z, Reynolds J, Gibson PR Irving PM. **Infliximab and adalimumab drug levels in Crohn's disease: contrasting associations with disease activity and influencing factors.** Aliment Pharmacol Ther. 2017 Jul;46(2):150-161.

Roblin X, Attar A, Lamure M, Savarieau B, Brunel P, Duru G, Peyrin-Biroulet L. **Cost savings of anti-TNF therapy using a test-based strategy versus an empirical dose escalation in Crohn's disease patients who lose response to infliximab.** Journal of Market Access & Health Policy, [S.l.], v. 3, oct. 2015.

Ben-Horin S, Chowers Y, Ungar B, Kopylov U, Loebstein R, Weiss B, Eliakim R, Del Tedesco E, Paul S, Roblin X. **Undetectable anti-TNF drug levels in patients with long-term remission predict successful drug withdrawal.** Aliment Pharmacol Ther. 2015 Aug;42(3):356-64.

Martelli L, Olivera P, Roblin X, Attar A Peyrin-Biroulet L. **Cost-effectiveness of drug monitoring of anti-TNF therapy in inflammatory bowel disease and rheumatoid arthritis: a systematic review.** J Gastroenterol. 2017 Jan;52(1):19-25.

Little RD, Chu IE, van der Zanden EP, Flanagan E, Bell SJ, Gibson PR, Sparrow MP, Shelton E, Connor SJ, Roblin X, Ward MG. **Comparison of adalimumab serum drug levels when delivered by pen versus syringe in patients with inflammatory bowel disease. An international, multicentre cohort analysis.** J Crohns Colitis. 2019 May 15.

Labetoulle R, Roblin X, Paul S. **Prolonged Persistence of Adalimumab Transferred From Mother to Infant During Pregnancy.** Ann Intern Med. 2018 Mar 6.

Gonczi L, Kurti Z, Rutka M, Vegh Z, Farkas K, Lovasz BD, Golovics PA, Gecse KB, Szalay B, Molnar T, Lakatos PL. **Drug persistence and need for dose intensification to adalimumab therapy; the importance of therapeutic drug monitoring in inflammatory bowel diseases**. BMC Gastroenterol. 2017 Aug 8;17(1):97.

Ungar B, Kopylov U, Engel T,Yavzori M, Fudim E, Picard O, Lang A, Williet N, Paul S, Chowers Y, Bar-Gil Shitrit A, Eliakim A, Ben-Horin A, Roblin X. **Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab.** Aliment Pharmacol Ther. 2017 Jan;45(2):276-282.

Roblin X, Paul S. **Letter: stool adalimumab detection in ulcerative colitis and Crohn's disease.** Aliment Pharmacol Ther. 2015 Jul;42(2):240.

Roblin X, Rinaudo M, Del Tedesco E, Phelip JM, Genin C, Peyrin-Biroulet L, Paul S. **Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases.** Am J Gastroenterol. 2014 Aug;109(8):1250-6.

Roblin X, Marotte H, Rinaudo M, Del Tedesco E, Moreau A, Phelip JM, Genin C, Peyrin-Biroulet L, Paul S. **Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases.** Clin Gastroenterol Hepatol. 2014 Jan;12(1):80-84.e2.

Grossi V, Infantino M, Manfredi M, Basile U, Gulli F, Marino M, Li Gobbi F, Damiani A, Atzeni F, Benucci M. **Anti-adalimumab and anti-certolizumab antibodies titers after discontinuation of adalimumab: two case reports.** Clin Chem Lab Med. 2019 Oct 30.

Samaan MA, Cunningham G, Tamilarasan AG, Beltran L, Pavlidis P, Ray S, Mawdsley J, Anderson SH, Sanderson JD, Arkir Z, Irving PM **Therapeutic Thresholds for Golimumab Serum Concentrations During Induction And Maintenance Therapy in Ulcerative Colitis: Results from the GO-LEVEL Study** Aliment Pharmacol Ther . 2020 Jul;52(2):292-302.

Berger AE, Duru G, de Vries A, Marini JC, Aoucheta D, Cornillie F, Nancey S, Detrez I, Gils A, Roblin X, Paul S. **Comparison of immunoassays for measuring serum levels of golimumab and antibodies against golimumab in ulcerative colitis: a retrospective observational study**. Ther Drug Monit. 2019 Feb 26.

Painchart C, Brabant S, Duveau N, Nachury M, Desreumaux P, Branche J, Gérard R, Prevost CLD, Wils P, Lambin T, Boualit M, Labalette M, Pariente B. **Ustekinumab Serum Trough Levels May Identify Suboptimal Responders to Ustekinumab in Crohn's Disease.** Dig Dis Sci. 2019 Oct 10.

Soufflet N, Boschetti G, Roblin X, Cuercq C, Williet N, Charlois AL, Duclaux-Loras R, Danion P, Mialon A, Faure M, Paul S, Flourie B, Nancey S. **Concentrations of Ustekinumab During Induction Therapy Associate With Remission in Patients With Crohn's Disease.** Clin Gastroenterol Hepatol. 2019 Mar 6.

Guidi L, Pugliese D, Tonucci TP, Bertani L, Costa F, Privitera G, Tolusso B, Di Mario C, Albano E, Tapete G, Gremese E, Papa A, Gasbarrini A, Rapaccini GL, Armuzzi A. **Early vedolizumab trough levels predict treatment persistence over the first year in inflammatory bowel disease.** United European Gastroenterol J. 2019 Nov;7(9):1189-1197. Epub 2019 Sep 3.

Pouillon L, Rousseau H, Busby-Venner H, De Carvalho Bittencourt M, Choukour M, Gauchotte G, Zallot C, Danese S, Baumann C, Peyrin-Biroulet L. **Vedolizumab Trough Levels and Histological Healing During Maintenance Therapy in Ulcerative Colitis.** J Crohns Colitis. 2019 Jan 29.

Paul S, Williet N, Di Bernado T, Berger AE, Boschetti G, Filippi J, Del Tedesco E, Nancey S, Flourie B, Roblin X. **Soluble Mucosal Addressin Cell Adhesion Molecule 1 and Retinoic Acid are Potential Tools for Therapeutic Drug Monitoring in Patients with Inflammatory Bowel Disease Treated with Vedolizumab: A Proof of Concept Study**. J Crohns Colitis. 2018 May 31.

Ben-Horin S, Ungar B, Kopylov U, Lahat A, Yavzori M, Fudim E, Picard O, Peled Y, Eliakim R, Del Tedesco E, Paul S, Roblin X. **Safety, efficacy and pharmacokinetics of vedolizumab in patients with simultaneous exposure to an anti-tumour necrosis factor**. Aliment Pharmacol Ther. 2018 Apr;47(8):1117-1125.

Yacoub W, Williet N, Pouillon L, Di-Bernado T, De Carvalho Bittencourt M, Nancey S, Lopez A, Paul S, Zallot, Roblin X, Peyrin-Biroulet L. **Early vedolizumab trough levels predict mucosal healing in inflammatory bowel disease: a multicentre prospective observational study.** Aliment Pharmacol Ther. 2018 Jan 31.

Gouynou C, Pouillon L, Rousseau H, Zallot C, Baumann C, Peyrin-Biroulet L. **Early changes in the pharmacokinetic profile of vedolizumab-treated patients with IBD may predict response after dose optimisation.** Gut. 2018 Jan 13.

Williet N, Boschetti G, Fovet M, Di Bernado T, Claudez P, Del Tedesco E, Jarlot C, Rinaldi L, Berger A, Phelip JM, Flourie B, Nancey S, Paul S, Roblin X. **Association Between Low Trough Levels of Vedolizumab During Induction Therapy for Inflammatory Bowel Diseases With Need for Additional Doses Within 6 months**. Clin Gastroenterol Hepatol. 2016 Nov 24.

Lauret A, Moltó A, Abitbol V, Gutermann L, Conort O, Chast F, Goulvestre C, Le Jeunne C, Chaussade S, Roux C, Batteux F, Dougados M, Allanore Y, Avouac J **Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice**. Semin Arthritis Rheum. 2020 Feb 19.

Valido A, Silva-Dinis J, Saavedra M, Iria I, Gonçalves J, Lopes JP, Fonseca JE. **Efficacy, immunogenicity, and cost analysis of a systematic switch from originator infliximab to biosimilar CT-P13 of all patients with inflammatory arthritis from a single center.** Acta Reumatol Port. 2019 Nov 22.

Benucci M, Damiani A, Li Gobbi F, Bandinelli F, Infantino M, Grossi V, Manfredi M, Noguier G, Meacci F. **Correlation between HLA haplotypes and the development of antidrug antibodies in a cohort of patients with rheumatic diseases.** Biologics: Targets and Therapy 2018:12 37–41.

Dénarié D, Rinaudo-Gaujous M, Thomas T, Paul S, Marotte H. **Methotrexate Reduced TNF Bioactivity in Rheumatoid Arthritis Patients Treated with Infliximab.** Mediators Inflamm. 2017 Epub 2017 Mar 2.

Benucci M, Gobbi FL, Bandinelli F, Damiani A, Infantino M, Grossi V, Manfredi M, Parisi S, Fusaro E, Batticciotto A, Sarzi-Puttini P, Atzeni F, Meacci F. **Safety, efficacy and immunogenicity of switching from innovator to biosimilar infliximab in patients with spondyloarthritis: a 6-month real-life observational study.** Immunol Res. 2016 Jul 23.

Zufferey P, Perreau M, So A. **High level of anti-drug antibodies after intra-articular injection of anti-TNF.** Rheumatology (Oxford). 2015 Dec;54(12):2291-2.

Quistrebert J, Hässler S, Bachelet D, Mbogning C, Musters A, Tak PP, Wijbrandts CA, Herenius M, Bergstra SA, Akdemir G, Johannesson M, Combe B, Fautrel B, Chollet-Martin S, Gleizes A, Donnellan N, Deisenhammer F, Davidson J, Hincelin-Mery A, Dönnes P, Fogdell-Hahn A, De Vries N, Huizinga T, Abugessaisa I, Saevarsdottir S, Hacein-Bey-Abina S, Pallardy M, Broët P, Mariette X; ABIRISK Consortium. **Incidence and risk factors for adalimumab and infliximab anti-drug antibodies in rheumatoid arthritis: A European retrospective multicohort analysis. Semin Arthritis Rheum.** 2018 Oct 12. pii: S0049-0172(18)30176-8.

Daïen CI, Daïen V, Parussini E, Dupuy AM, Combe B, Morel J. **Etanercept concentration in patients with rheumatoid arthritis and its potential influence on treatment decisions: a pilot study.** J Rheumatol. 2012 Aug;39(8):1533-8. D

Marotte H, Rinaudo-Gaujous M, Petiet C, Fautrel B, Paul S **Tapering Without Relapse in Rheumatoid Arthritis Patients With High TNF Blocker Concentrations: Data from STRASS Study** Ann Rheum Dis . 2020 Jul;79(7):e81.

Vincent FB, Pavy S, Krzysiek R, Lequerré T, Sellam J, Taoufik Y, Mariette X, Miceli-Richard C. **Effect of serum anti-tumour necrosis factor (TNF) drug trough concentrations and antidrug antibodies (ADAb) to further anti-TNF short-term effectiveness after switching in rheumatoid arthritis and axial spondyloarthritis.** Joint Bone Spine. 2016 Oct;83(5):595-7.

Paul S, Marotte H, Kavanaugh A, Goupille P, Kvien TK, de Longueville M, Mulleman D, Sandborn WJ, Vande Casteele N **Exposure-Response Relationship of Certolizumab Pegol and Achievement of Low Disease Activity and Remission in Patients With Rheumatoid Arthritis** Clin Transl Sci. 2020 Feb 26.

Bastida C, Ruiz-Esquide V, Pascal M, de Vries Schultink AHM, Yagüe J, Sanmartí R, Huitema ADR, Soy D. **Fixed dosing of intravenous tocilizumab in rheumatoid arthritis. Results from a population pharmacokinetic analysis.** Br J Clin Pharmacol. 2018 Jan 4.

Benucci M, Meacci F, Grossi V, Infantino M, Manfredi M, Bellio E, Bellio V, Li Gobbi F, Bazzichi L, Moscato P, Caputo D, Saviola G, Talotta R, Sarzi-Puttini P, Atzeni F. **Correlations between immunogenicity, drug levels, and disease activity in an Italian cohort of rheumatoid arthritis patients treated with tocilizumab.** Biologics. 2016 Mar 11;10:53-8.

Combier A, Nocturne G, Henry J, Belkhir R, Pavy S, Le Tiec C, Descamps E, Seror R, Mariette X. **Immunization to rituximab is more frequent in systemic autoimmune diseases than in rheumatoid arthritis: ofatumumab as alternative therapy.** Rheumatology (Oxford). 2019 Oct 9.

Mota F, Neves E, Oliveira JC, Selores M, Torres T. **Importance of immunogenicity testing for cost-effective management of psoriasis patients treated with adalimumab.** Acta Dermatovenerol Alp Pannonica Adriat. 2017 Jun;26(2):33-35.

Mahil SK, Arkir Z, Richards G, Lewis CM, Barker JN, Smith CH. **Predicting treatment response in psoriasis using serum levels of adalimumab and etanercept: a single-centre, cohort study.** Br J Dermatol. 2013 Aug;169(2):306-13.

Toro-Montecinos M, Ballescá F, Ferrandiz C, Teniente-Serra A, Martinez-Caceres E, Carrascosa JM1. **Usefulness and correlation with clinical response of serum ustekinumab levels measured at 6 weeks versus 12 weeks.** J Dermatolog Treat. 2018 May 10:1-5.

Seitz-Polski B, Dahan K, Debiec H, Rousseau A, Andreani M, Zaghrini C, Ticchioni M, Rosenthal A, Benzaken S, Bernard G, Lambeau G, Ronco P, Esnault VLM. **High-Dose Rituximab and Early Remission in PLA2R1-Related Membranous Nephropathy.** Clin J Am Soc Nephrol. 2019 Aug 7;14(8):1173-1182.

Boyer-Suavet S, Andreani M, Cremoni M, Brglez V, Benzaken S, Bernard G, Nachman P, Esnault V, Seitz-Polski B. **Rituximab bioavailability in primary membranous nephropathy**. Nephrol Dial Transplant. 2019 Mar 30.

Boyer-Suavet S, Andreani M, Lateb M, Savenkoff B, Brglez V, Benzaken S, Bernard G, Nachman PH, Esnault V, Seitz-Polski B**. Neutralizing Anti-Rituximab Antibodies and Relapse in Membranous Nephropathy Treated with Rituximab** Front Immunol. 2019; 10: 3069

Inflammatory Bowel Diseases

Anti-TNFα

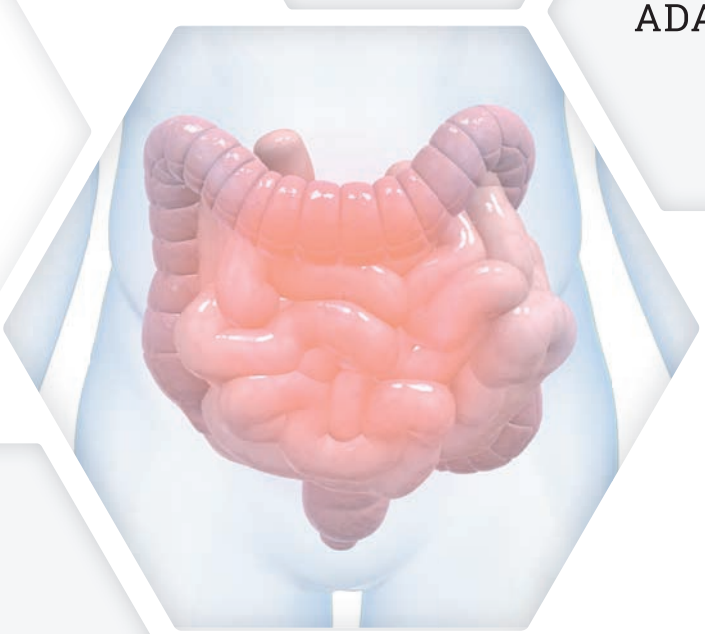
CERTOLIZUMAB

Anti-TNFα

INFLIXIMAB

Anti-TNFα

ADALIMUMAB



Anti-α4-β7

VEDOLIZUMAB

Anti-TNFα

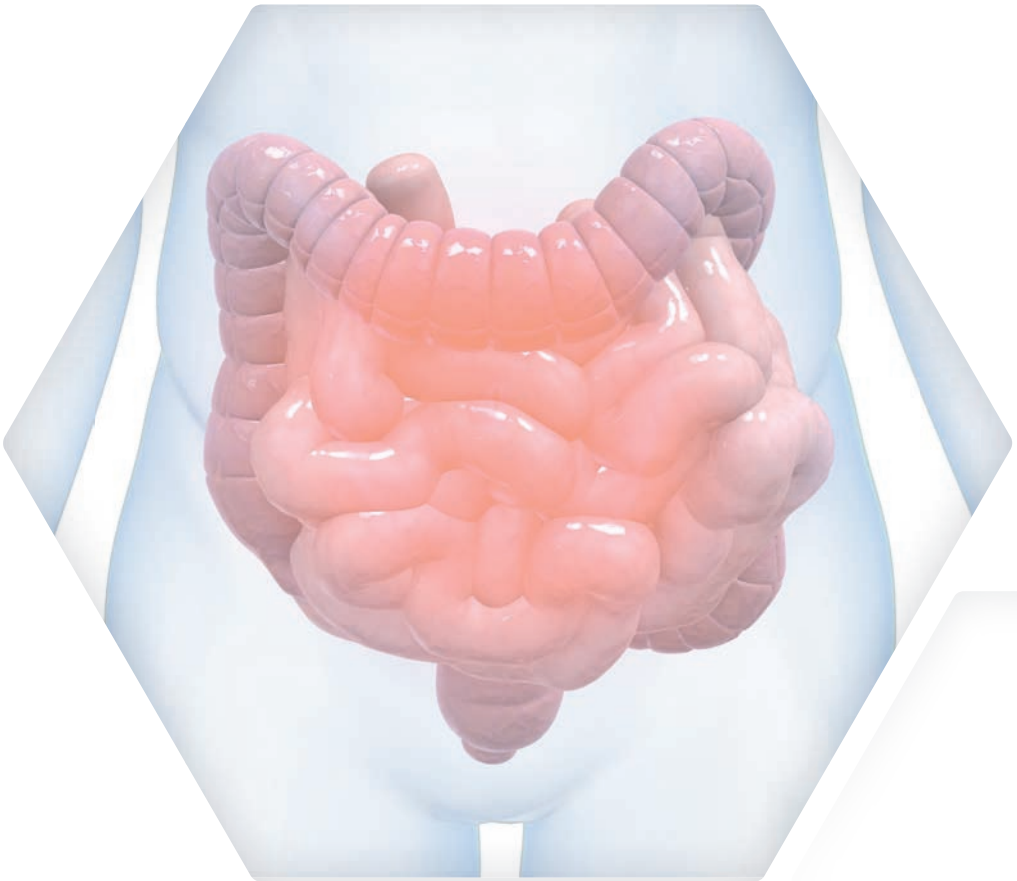
GOLIMUMAB

Anti-IL12/IL23

USTEKINUMAB

Anti-TNFα

INFLIXIMAB



IFX Biosimilars

IBD

2020

REAL-WORLD USE OF THERAPEUTIC DRUG MONITORING OF CT-P13 IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Petitdidier N*, Beaugerie L, Carbonnel F, Bourrier A,Treton X, Rajca S, Malamut G , Abitbol V , Allez M ,Pelletier AL , Marthey L , Jouet P, Benamouzig R , Amiot X , Bouhnik Y , Amiot A

*Department of Gastroenterology, Henri Mondor Hospital, APHP, EC2M3-EA 7375, Paris Est-Créteil (UPEC) Val de Marne University, Creteil, France

ABSTRACT

BACKGROUND: Whether therapeutic drug monitoring (TDM) of infliximab should be implemented in daily practice is an ongoing controversy.

METHODS: Between September 2015 and December 2016, 364 patients with IBD were treated with CT-P13 in 13 gastroenterology departments and were followed up for 54 weeks. Disease activity, CT-P13 trough concentration and anti-CT-P13 antibody (ACA) were recorded

RESULTS: Steroid-free clinical remission rates at week 54 were 67.0% and 56.4% in patients with CD and UC, respectively. CT-P13 trough concentrations were measured in 70.7% of the patients. The mean CT-P13 trough concentration was 4.2±4.3µg/mL. The presence of ACA was observed in 53 (15.9%) patients. CT-P13 trough concentration was collected in a proactive approach in 62.8% of cases and in a reactive approach in 37.2%. Among patients who submitted to TDM, CT-P13 therapy was optimized in 88.7% of the reactive group and in 22.5% of the proactive group (P<0.001).

CONCLUSIONS: In a real-world cohort of patients with IBD treated with CT-P13, more than two-thirds of the patients underwent TDM. CT-P13 optimization was much less common in the proactive approach than in the reactive approach.

KEY POINTS

Table 2 Proportions of patients with various CT-P13 trough concentration cut-offs in 333 patients treated with CT-P13 maintenance therapy measured between week 14 and week 54 according to the type of inflammatory bowel disease.

	Week 14 to 54					
	Crohn's disease	(*n* = 203)		Ulcerative colitis	(*n* = 130)	
Infliximab trough concentration	Steroid-free clinical remission (*n* = 134)	No steroid-free remission (*n* = 69)	*P*	Steroid-free clinical remission (*n* = 75)	No steroid-free remission (*n* = 55)	*P*
> 1 µg/mL	104 (77.6%)	29 (42.0%)	< 0.001	65 (86.7%)	37 (67.3%)	0.01
> 3 µg/mL	70 (52.2%)	21 (30.4%)	0.004	47 (62.7%)	24 (43.6%)	0.03
> 7 µg/mL	23 (17.2%)	11 (15.9%)	0.99	25 (33.3%)	12 (21.8%)	0.17
> 10 µg/mL	13 (9.7%)	7 (10.1%)	0.99	15 (20.0%)	6 (10.9%)	0.23

Variables are presented as *n* (%). *P* values are based on a two-sided chi-square test.

Table 2. Proportions of patients with various CT-P13 trough concentration cut-offs in 333 patients treated with CT-P13 maintenance therapy measured between week 14 and week 54 according to the type of inflammatory disease .

Table 3 The predictors associated with therapeutic infliximab trough concentration (> 3 µg/mL) between week 14 and week 54 in 203 patients with Crohn's disease with CT-P13.

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Presence of anti-infliximab antibody	0.11 (0.04–0.32)	< 0.001	0.11 (0.03–0.39)	0.001
CRP > 10 mg/L	0.25 (0.12–0.50)	< 0.001	0.27 (0.12–0.60)	0.001
Male gender	0.50 (0.28–0.87)	0.02	0.47 (0.25–0.92)	0.03
Steroid-free clinical remission	2.50 (1.35–4.63)	0.004		
Platelets > 280/mm^3	0.51 (0.28–0.92)	0.03		
Uncomplicated phenotype	0.56 (0.32–0.98)	0.05	0.44 (0.23–0.87)	0.02

CRP: C-reactive protein; HR: hazard ratio; CI: confidence interval. HR with 95% confidence interval (CI) was estimated using binary logistic regression.

Table 3. The predictors associated with therapeutic infliximab trough concentration (>3µg/mL) between week 14 and week 54 in 203 patients with Crohn's disease with CT-P13.

- This study demonstrates the benefit of routine, proactive TDM in anticipation of a subsequent loss of response.

- CT-P13 therapy was optimized less frequently in the proactive group than in the reactive group (p<0,001)

- One-quarter of patients monitored in the Proactive approach had CT-P13 optimization

- Optimization of CT-P13 therapy was noted in almost all patients in the reactive group

- At week 14, 67,7% and 51,5% of patients were in the steroid-free clinical remission in the CD and the UC groups respectively.

-At week 54, 67.0% and 57.7% of patients were in steroid-free clinical remission in the CD and the UC groups respectively.

First study assessing real-world use of TDM in patients with active IBD treated with CT-P13

LETTER: IMMUNOGENICITY OF ANTI-TNF IN ELDERLY IBD PATIENTS

IFX

IBD

2019

* Paul S, Roblin X.

*Immunology and Immunomonitoring Laboratory, CHU Saint-Etienne, Saint-Etienne, France

ABSTRACT

BACKGROUND: The efficacy of infliximab appears to be different depending on the patient's age with earlier onset of loss of response in patients aged over 60 years. The mechanism of this loss of response is unknown. Moreover, as for autoimmunity, a more advanced age could be related to decreased immunogenicity and immunosenescence

METHODS: In a prospective study, we aimed to determine if the pharmacokinetics of infliximab in patients over 60 years was equivalent to that of younger patients and to assess if treatment response in IBD patients is age-dependent. We included 110 patients from our IBD cohort (74 with Crohn's disease; 13 patients over 60 years; females: 44.5%), 42 with unfavourable pharmacokinetic (undetectable TLI with high anti-infliximab antibodies (ATI)> 100 ng/mL), 42 with therapeutic levels (>3 µg/mL) and 26 patients with low or undetectable TLI without ATI.

RESULTS: Patients with ATI > 100 ng/ml were found more frequently in the over 60 group: 69.2% vs 34.0% (P = 0.014). Univariable analysis revealed four factors which were associated with the appearance of high levels of ATI without detectable infliximab, age over 60 years (OR: 4.36 95% confidence interval [1.32-17.09], P = 0.02), infliximab monotherapy (OR: 6.77, [1.12-13.25], P = 0.01) CRP > 5 mg/L (OR: 2.82 [1.10-7.53], P = 0.033) and faecal calprotectin >150 µg/g of stool (OR: 4.87 [1.12-24.74], P = 0.021). Using multivariable analysis, two factors were associated with an immunogenic failure (age >60 years (OR: 2.9 [1.09-9.12], P = 0.045) and combination treatment with an immunomodulator (OR: 0.6 [0.32-0.89], P = 0.02).

CONCLUSIONS: Despite immunosenescence, we observed a higher immunogenicity of infliximab in the elderly with a significant higher proportion of patients with ATI. During this period where infliximab monotherapy could be offered for patients over 60 years of age, our results confirmed the issue reported by Singh et al, and we think that we should consider combination therapy with methotrexate or low dose of thiopurine5 to avoid an unfavourable pharmacological profile and diminish the serious side effects reported with thiopurines in this population.

KEY POINTS

- This study shows that the elderly have higher infliximab immunogenicity compared to younger patients

- 69.2% of elderly patients developed antidrug antibodies at a rate > 100 ng/ml

- Age >60 years is associated with an immunogenic failure (OR: 2.9 [1.09-9.12], P = 0.045)

-Combination treatment with an immunomodulator is associated with an immunogenic failure (OR: 0.6 [0.32-0.89], P = 0.02).

First study showing that the efficacy of IFX is different according to patient's age.

IFX

IBD

2020

PROACTIVE INFLIXIMAB DRUG MONITORING IS SUPERIOR TO CONVENTIONAL MANAGEMENT IN INFLAMMATORY BOWEL DISEASE

*Fernandes SR, Bernardo S, Simoes C, Gonçalves AR,Valente A, Baldaia C, Santos PM , Correia LA , Marinho RT

*Department of Gastroenterology and Hepatology Unit, Hospital Santa Maria, Centro Hospitalar Universitário de Lisboa Norte, Lisboa, Portugal.

ABSTRACT

BACKGROUND: Increasing evidence supports the use of reactive therapeutic drug monitoring (TDM) in Crohn's disease (CD) and ulcerative colitis (UC) following secondary loss of response. It is still unknown if proactive TDM can improve clinical outcomes.

METHODS: Consecutive patients completing infliximab (IFX) induction therapy were prospectively allocated into a proactive TDM protocol (pTDM). Before the fourth infusion and every 2 infusions, IFX trough levels and antidrug antibodies were measured using a drug-sensitive assay (Theradiag, Lisa Tracker). Treatment was proactively escalated aiming at an IFX trough level between 3 and 7 ug/mL (CD) and 5 and 10 ug/mL (UC). A retrospective cohort treated with IFX but without TDM served as the reference group. End points included the need for surgery, hospitalization, treatment discontinuation, and mucosal healing at 2 years of follow-up.

RESULTS: Two hundred five patients were included, 56 in the proactive regimen. Treatment escalation was more common in pTDM patients (76.8% vs 25.5%; P < 0.001), who also required less surgery (8.9% vs 20.8%; P = 0.032) and presented higher rates of mucosal healing (73.2% vs 38.9%; P < 0.0001). Proactive TDM significantly decreased the odds of reaching any unfavorable outcome (odds ratio, 0.358; 95% confidence interval, 0.188–0.683; P = 0.002).

CONCLUSIONS: Proactive TDM is associated with fewer surgeries and higher rates of mucosal healing than conventional non-TDM-based management.

KEY POINTS

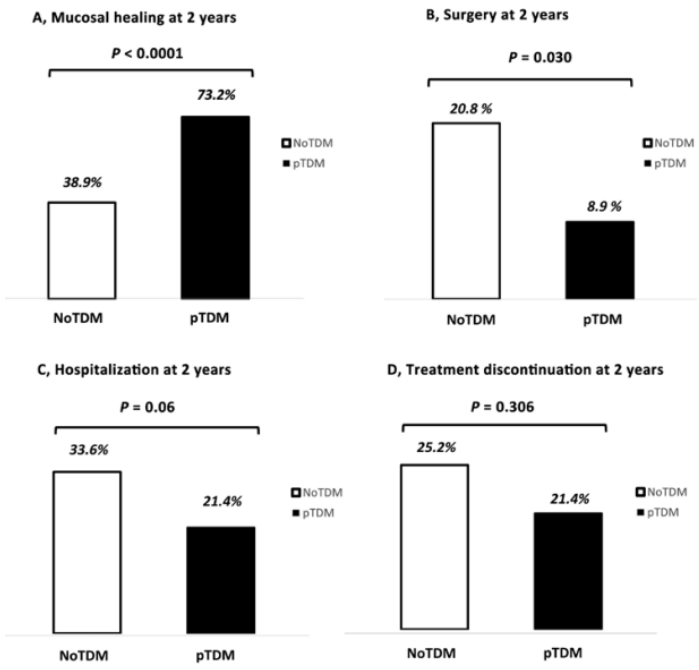


Figure 2. Proportions of patients with mucosal healing (A), surgery(B), hospitalization (C) and treatment discontinuation (D) at 2 years of infliximab treatment

- This study demonstrates the benefit of proactive drug monitoring in patients with CD and UC compared to empirical dosing over a 2 years period

- Cumulative treatment escalation rates were more common in the proactive TDM group than in the no-TDM group: 60.7% vs 16.8% (p<0.001) at 1 year and 76.8% vs 25.5% (p<0.001) at 2 years

- The proportion of patients achieving mucosal healing at 2 years of biologic treatment was highest in the pTDM group (73.2% vs 38.9%; p<0.0001), with significance in both UC(69.6% vs 27.6%; p=0.003) and CD (75.8% vs 41.7% p<0.001)

- By the end of the 2-year follow-up, surgery was required in 8.9% of patients in the pTDM group and 20.8% in the no-TDM group.

- In subgroup analysis the need for hospitalization reached statistical difference in UC (17.4% vs 44.8%; p=0.035) but not in CD (24.2% vs 30.8%; p=0.306)

- In pTDM, immunomodulation had no influence on rates of mucosal healing, treatment discontinuation, hospitalization, surgery or any unfavourable outcome.

Proactive TDM is associated with less surgeries and compound unfavourable outcomes compared to conventional management

IFX

IBD

2019

INFLIXIMAB THERAPY INTENSIFICATION UPON LOSS OF RESPONSE: IS THERE AN OPTIMAL THROUGH LEVEL?

Ungar B*, Ben-Shatach Z, Ben-Haim G, Yavzori M, Picard O, Fudim E, Kopylov U, Veyrard P, Del Tedesco É, Paul S, Eliakim R, Ben-Horin S, Roblin X

*Department of Gastroenterology Sheba Medical Center Tel Hashomer, Sackler School of Medicine , Tel-Aviv University, Israel.

ABSTRACT

BACKGROUND: Loss of response (LOR) to infliximab occurs in ~30% of IBD patients. At time of LOR, lower infliximab-trough-levels (TL), in the absence of anti-drug-antibodies (ATI), have been associated with the need for therapy escalation. Nevertheless, few studies have examined the outcome of infliximab-therapy intensification, based on different TL.The aim of this study is to evaluate the impact of infliximab-TL on efficacy of therapy intensification (dose-elevation/interval-shortening).

METHODS: This was a retrospective observational study performed at two tertiary-centers between 2013-2017. Study population included IBD patients who underwent infliximab therapy escalation (dose elevation/interval shortening) due to clinical LOR. Patients with TL < 3 µg/ml or positive ATI were excluded. TL and clinical scores before intensification and after 6, 12 months were obtained prospectively.

RESULTS: Forty-eight IBD patients were included; 23(49%), and 29(60%) reached clinical remission by 6, 12 months before intensification. TL among patients in clinical remission were significantly lower than among those clinically active, both at 6 (p = 0.001, median TL 4.7,8.7 µg/ml, IQR 3.6-8.1, 5.9-16 µg/ml) and 12 months (p = 0.005, median TL 4.6,8.7 µg/ml, IQR 3.6-8, 5.3-16 µg/ml), respectively.

CONCLUSIONS: In IBD patients experiencing clinical LOR to infliximab in the absence of ATI, success of doubling the dose was inversely associated with baseline TL. Patients with baseline TL above 9 mcg/ml were very unlikely to reach clinical remission.

KEY POINTS

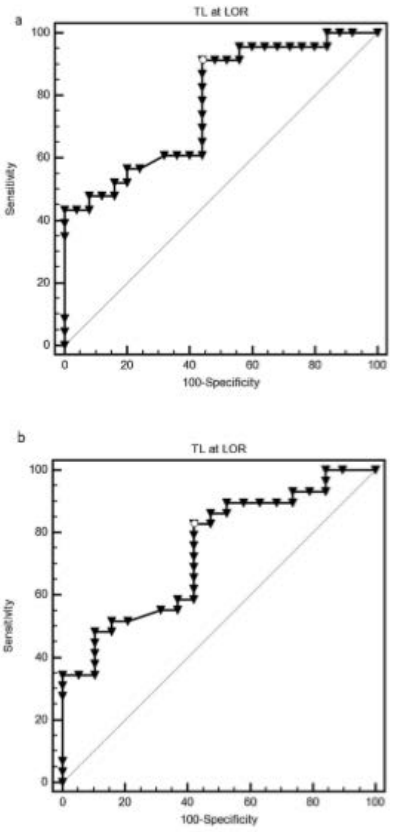


Table 1. (a) Infliximab through level below 4.8µg/ml were optimal for clinical remission at 6 months (AUC=0.77,p=0.0001,91% specificity,66% sensitivity). (b) Infliximab through level below 4.8µ,g/ml were optimal for clinical remission at 12 months (AUC=0.74,p=0.001,83% specificity,58% sensitivity).

- This study focused on IBD patients who developed LOR, with positive TL > 3µg/mL and non-identifiable ATI (i.e. non-immunogenic loss of response)

- This study shows that we should definitely try to intensify when IFX TL is over 3 µg/mL

- Infliximab TL below 4.8 µg/mL are best associated with clinical remission, both 6 months and 12 months after intervention, but intensification can be still effective in most patients when applied in patients with TL < 7 µg/mL

- In the present study, infliximab therapy escalation resulted in clinical remission in 49% of the patients by 6 months and 60% of the patients by 12 months.

- Patients experiencing non-immunogenic loss of response with baseline TL above 9µg/ml were very unlikely to reach clinical remission upon doubling the dose of infliximab

In patients experiencing non-immunogenic loss of response, dose intensification would be more effective in patients with lower infliximab through levels.

IFX

IBD

2018

COST SAVINGS USING A TEST-BASED DE-ESCALATION STRATEGY FOR PATIENTS WITH CROHN'S DISEASE IN REMISSION ON OPTIMIZED INFLIXIMAB: A DISCRETE EVENT MODEL STUDY

Alain Attar*, Gérard Duru, Xavier Roblin, Bernard Savarieau, Pierre Brunel, Michel Lamure, Laurent Peyrin-Biroulet

* Department of Gastroenterology, Nutritional Support, Beaujon Hospital, Clichy, France

ABSTRACT

BACKGROUND: Drug de-escalation is considered in Crohn's disease patients in sustained remission on optimized infliximab treatment.

AIM We built a model to **evaluate the magnitude of cost savings in patients'disease course with or without drug de-escalation guided by infliximab trough levels.**

METHODS: We designed 4 virtual cohorts (P1–P4) of 10,000 patients in clinical remission on optimized infliximab treatment followed for 2 years. P1: no drug de-escalation — 10 mg/kg/8 weeks; P2: drug de-escalation from 10 mg/kg/8 weeks to 5 mg/kg/8 weeks according to trough levels; P3: no drug de-escalation — 10 mg/kg/6 weeks; and P4: drug de-escalation from 10 mg/kg/6 weeks to 10 mg/kg/8 weeks according to trough levels. For P2 and P4 cohorts, drug de-escalation was decided if trough levels were ≥7 µg/mL and no de-escalation if trough levels were <7 µg/mL. Only costs related to drug administration were considered.

RESULTS: The cost differences when comparing P1 versus P2 and P3 versus P4 were 7.6% and 4.6%, respectively, corresponding to costs savings of €30.5 millions and €20.3 million for 10,000 patients.

CONCLUSION: **Over a 2-year period, infliximab de-escalation according to trough levels led to cost saving of about 6%, corresponding to around €25.4 million.**

KEY POINTS

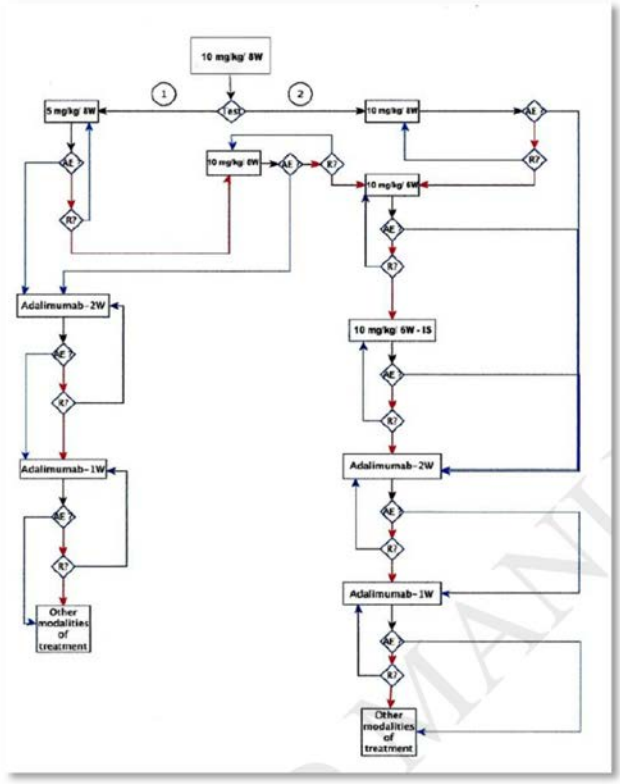


Figure 1. Discrete event simulation of the flow of events used to compute life sequence charts distribution. Figure 1 describe the flow of events for patients in the P2 cohort at 10 mg/kg of infliximab every 8 weeks de-escalated (path 1, sub-cohort P2a) or not (path 2, sub-cohort P2b). 10 or 5 mg/kg/ 8W: IFX 10 or 5 mg/kg every 8 weeks. R: clinical response; AE: Adverse events; Adalimumab-2W: Adalimumab every 2 weeks; Adalimumab-1W: Adalimumab every 1 week; Blue arrow = 'Yes', red arrow = 'No',1 : supra-therapeutic (>7 µg/mL), 2: normal or low range ITL (<7 µg/mL).

- The original mathematic modeling approach developed to simulate the dynamics of discrete events in entire medical paths followed by the patient (including events that occurred in response to treatment, their potential adverse events and treatment changes during the whole simulation period) revealed significant cost savings when applying TDM during a drug de-escalation strategy.

- Note that this study is a reflection of what is being done in France in 2015 and can be difficult to extrapolate to other health care systems.

- Although the cost of treatment has decreased with the increasing use of IFX biosimilars, TDM reduces the amount of infliximab administered.

These findings confirm that de-escalation is cost effective when using TDM and may be considered in selected patients.

IFX Biosimilars

IBD

2019

OUTCOMES OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE SWITCHED FROM MAINTENANCE THERAPY WITH A BIOSIMILAR TO REMICADE

U Ilias A*, Szanto K, Gonczi L, Kurti Z, Golovics PA, Farkas K, Schafer E, Szepes Z, Szalay B, Vincze A, Szamosi T, Molnar T, Lakatos PL

*First Department of Medicine, Semmelweis University, Budapest, Hungary.

ABSTRACT

BACKGROUND: There is evidence that it is safe and effective for patients with inflammatory bowel diseases (IBD) to switch from maintenance therapy with an original infliximab drug to a biosimilar, but little is known about outcomes of reverse switches and/or multiple switches. We aimed to evaluate the effects of a reverse switch (from a biosimilar to Remicade) in a real-life cohort.

METHODS: We performed a prospective observational study of 174 unselected and consecutive patients with IBD (136 with Crohn's disease [CD] and 38 with ulcerative colitis [UC]) who received maintenance therapy with the biosimilar in Hungary. In September 2017, patients were switched from the biosimilar (CT-P13) to Remicade, due to reimbursement policies. In our cohort, 8% (n = 14) patients had been previously exposed to the originator Remicade. We collected clinical and biochemical information from patients at baseline (time of the switch) and 16 and 24 weeks thereafter. Clinical remission was defined as a Crohn's disease activity index <150 points or no fistula drainage, or a partial Mayo score <3 points for patients with UC. Serum drug trough levels and anti-drug antibodies were measured at baseline and week 16.

RESULTS: There was no significant difference in the proportion of patients in clinical remission at week 8 before the switch (82.5% with CD and 82.9% with UC), at baseline (80.6% with CD and 81.6% with UC), at week 16 (77.5% with CD and 83.7% with UC), or at week 24 (CD 76.3% with CD and 84.9% with UC) (P = .60 among groups for patients with CD and P = .98 among groups for patients with UC). For all patients, mean serum trough levels of infliximab were 5.33 ± 4.70 μg/mL at baseline and 5.69 ± 4.94 μg/mL at week 16 (P = .71); we did not find significant differences in prevalence of anti-drug antibody at baseline (16.2%) compared with week 16 (16.9%) (P = .87). Four infusion reactions occurred, until week 24 of follow up. There was no difference in outcomes or trough or antidrug antibody levels between patients with or without previous exposure to Remicade

CONCLUSIONS: We collected data from a real-life cohort of patients with CD or UC who were switched from maintenance therapy with a biosimilar to Remicade or were treated with only Remicade. No significant changes were observed in remission, trough levels, or antidrug antibodies in patients switched from the biosimilar to Remicade. No new safety signals were detected.

KEY POINTS

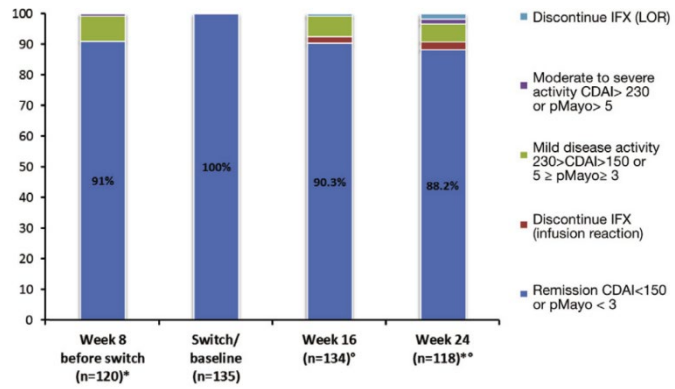


Figure 1. Clinical activity before and after reverse switch in IBD patients in remisson at switch. * Week 8 data before baseline and week 24 data are only available from 3 centers.Two patients were lost to follow-up.LOR, loss of response

	Switch		Week 16	
All IBD patients on maintenance IFX therapy (n = 130)	Single-dose IFX[a] (n = 111)	Increased-dose IFX[b] (n = 19)	Single-dose IFX[a] (n = 111)	Increased-dose IFX[b] (n = 19)
Serum IFX trough level, μg/mL	5.33 ± 4.70		5.69 ± 4.94	
	5.34 ± 4.62	5.26 ± 5.31	5.49 ± 4.62	6.87 ± 6.52
Anti-drug antibody positivity (>10 ng/mL)	16.2		16.9	
High anti-drug antibody positivity (>200 ng/mL)	8.5		8.5	

Values are mean ± SD or %.
IBD, inflammatory bowel disease; IFX, infliximab.
[a]IFX dose: 5 mg/kg of body weight.
[b]IFX dose: 10 mg/kg of body weight.

Table 3. Trough levels and Antidrug Antibodies in IBD patients

- This is the first cohort study evaluating reverse switching from CT-P13 biosimilar to the originator IFX over a 24-weeks follow-up.

- No change was observed in clinical disease activity based on CDAI and pMAYO score during follow-up.

- 90.3% of all patients who were in clinical remission at switch and baseline sustained clinical remission up to week 16 and 88.2% up to week 24

- There was no significant difference between the proportion of patients in clinical remission at week 8 before switch, at switch and baseline and at week 16 and 24.

- No significant difference was observed in mean serum IFX TLs between switch and baseline and week 16 [5.33 +/-4.70μg/ml vs 5.69 +/-4.94μg/ml; p=0.71)

-No significant differences were observed in ADA formation [overall ADA positivity: 16.2 % vs 16.9% at baseline and week 16, p=0.87]

No evidence of change in clinical efficacy, safety and immunogenicity after reverse switching from IFX biosimilar to the originator infliximab is shown

Biosimilar IFX

IBD

2018

SHORT COMMUNICATION: EVALUATION OF INFLIXIMAB AND ANTI-INFLIXIMAB LISA-TRACKER IMMUNOASSAYS FOR THE THERAPEUTIC DRUG MONITORING OF SB2 INFLIXIMAB BIOSIMILAR

Alexandre Jentzer*, Anne-Emmanuelle Berger*, Rémi Labetoulle*, Alice Haccourt*, Xavier Roblin, Stephane Paul*

* Laboratory of Immunology and Immunomonitoring, Clinical Investigation Center Inserm 1408, GIMAP EA3064, hospital of Saint-Etienne, France.

ABSTRACT

BACKGROUND: SB2, an infliximab (IFX) biosimilar to the reference infliximab (R.I.) product (Remicade®), received approval in EU for all IFX indications. Many decision algorithms based on the measurement of IFX trough levels and antibodies to infliximab (ATI) are being increasingly used to optimize IFX treatment. The aim of our study was to evaluate if the biosimilar SB2 could be efficiently monitored using the LISA-TRACKER IFX and anti-IFX assays developed by Theradiag (Croissy Beaubourg, France).

METHODS: Standard curves of R.I. and SB2 were compared and then accuracy of the LISAT-RACKER IFX assay in detecting the spiked concentration of SB2 was measured. Levels of IFX from SB2 spiked samples and R.I. clinical samples were calculated. Intra-run and inter-run imprecision were also measured with SB2 spiked samples. Ability of polyclonal antibodies directed against R.I. to block the detection of SB2 using the LISA-TRACKER IFX assay and the capacity of SB2 to block the detection of anti-R.I. antibodies using the LISA-TRACKER anti-IFX assay were tested.

RESULTS: Twelve patients treated with SB2 including 2 patients with SB2-specific antibodies were measured with the LISA-TRACKER anti-IFX assay. We demonstrated that the LISA-TRACKER assay is suitable for the quantification of SB2 in human serum samples. **The percentage of recovery was between 82% and 113%. High intra-run and inter-run imprecision were obtained with the LISA-TRACKER infliximab assay for the quantification of SB2** (SD ranged from 3.3 to 17.9%). **The SB2-blocking capacity of R.I. polyclonal antibodies in spiked samples was demonstrated with inhibition between 80% and 97%. SB2 trough levels and anti-SB2 antibodies has also been confirmed in SB2-treated patients**.

CONCLUSION: **LISA TRACKER IFX and anti-IFX assays are suitable for the monitoring of patients treated with SB2.**

KEY POINTS

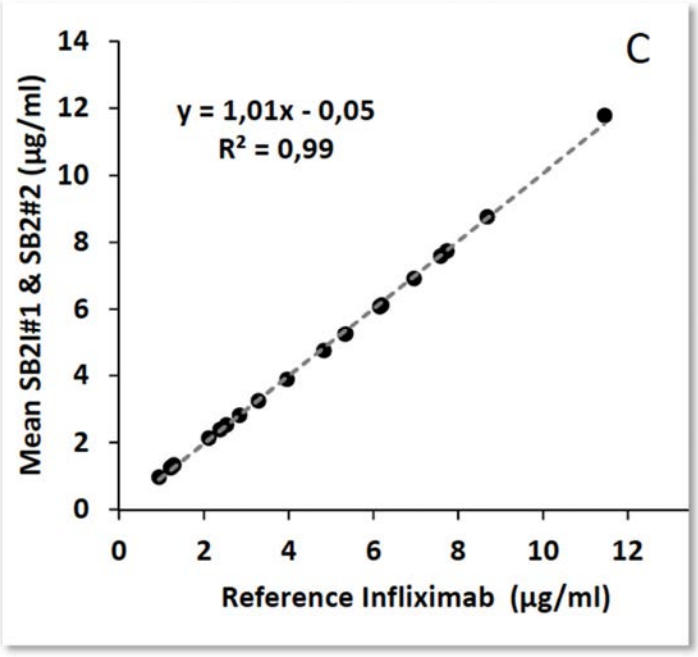


Figure 1. Measurement of levels of infliximab in patient or spiked samples (SB2 and Reference infliximab) according to the Infliximab standard curves. The determination of coefficient of determination (R2) and slopes were determined (n=15) mean SB2 batche#1 & batch#2 vs R.I. (R2 = 0.99; slope: 1). All the quantifications were carried out using the LISA-TRACKER infliximab assay.

- The study demonstrates that the LISA-TRACKER assays (IFX and anti-IFX antibodies assays) are capable of reproducible quantification of SB2 and ATI in human serum samples without any interference.
- The detection of SB2 and anti-SB2 in patients with LISA-TRACKER assays confirmed the suitability of these assays to monitor treated patients.
- The LISA-TRACKER immunoassay may be useful to follow the switch from R.I. to SB2 in clinical practice. Future studies with patients treated with SB2 are needed to monitor the therapeutic consequences of a switch and post-marketing surveillance seems to be necessary in order to appreciate therapeutic follow-up.

With a perfect correlation of dosages between the R.I. and SB2, as well as in detection of ATI, authors have shown the interchangeability of dosages between reference products and biosimilars.

Digestive and Liver Disease, Volume 50 - October 2018 – IFX fecal excretion in patients with acute severe UC.

IFX

UC

2018

SEVERE ENDOSCOPIC LESIONS ARE NOT ASSOCIATED WITH MORE INFLIXIMAB FECAL LOSS IN ACUTE SEVERE ULCERATIVE COLITIS

Florian Poullenot*, Dorothée Nivet*, Stéphane Paul, Pauline Riviere*, Xavier Roblin, David Laharie*.

* CHU de Bordeaux, Hôpital Haut-Lévêque, Service d'Hépato-gastroentérologie, Bordeaux, Pessac, France

ABSTRACT

BACKGROUND: It has been observed that early infliximab (IFX) fecal excretion in patients with acute severe ulcerative colitis (ASUC) was associated with low treatment response.

METHODS: Consecutive patients admitted for a steroid-refractory ASUC requiring IFX and who underwent flexible sigmoidoscopy before starting the drug were included in a case-control, prospective, two-center study. Cases were patients with SEL and controls those without SEL. Plasmatic and fecal IFX concentrations were measured at day 1 and 2.

RESULTS: Among the 15 patients analyzed (10 men; median age: 49 years), 6 were cases harboring SEL at baseline. IFX was detected in the stool in 2/6 (33%)of cases and 4/9 (44%) of controls (p = 1) and no difference was observed between the two groups regarding plasmatic concentrations at day 1 or 2 (p = 1).

CONCLUSION: **In ASUC, SEL were not associated with more loss of IFX in the stool or lower plasmatic levels. Early IFX pharmacokinetics in this setting does not seem related to endoscopic severity**.

KEY POINTS

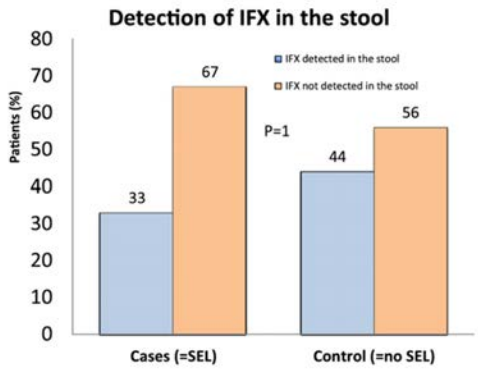


Figure 1. Proportion of patients admitted for acute severe ulcerative colitis with or without severe endoscopic lesions having detectable infliximab in the stools at day 1 or 2. IFX = infliximab; SEL = severe endoscopic lesions.

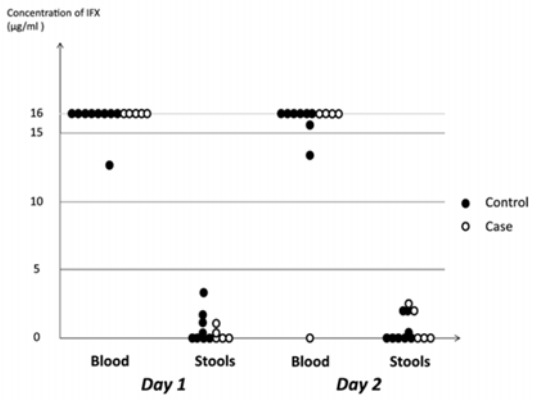


Figure 2. Concentrations of infliximab in blood and stools at day 1 and 2 in acute severe ulcerative colitis patients according to the presence of severe endoscopic lesions at baseline. IFX = infliximab.

- The study analyses IFX blood and stool concentrations in 15 anti-TNF naïve patients with ASUC divided into 2 groups according to the severity of their endoscopic lesions: Cases (=SEL) versus Controls (=no SEL).

- Based on pharmacokinetic measurements at day 1 and 2, authors could not confirm the relation-ship between UC endoscopic severity and fecal IFX excretion. No correlation was found between blood and fecal IFX concentrations. No association was found between serum IFX levels and treatment response. Note that most of serum concentrations of IFX at day 1 and 2 exceeded the upper limit of 16 µg/mL and constituted an important limitation in the study.

- Results do not support the use of increased doses of IFX in ASUC patients with deep ulcerations or mucosal detachment.

Benefits of higher IFX doses in ASUC patients with deep ulcerations are challenged. Preliminary results highlight the complexity of the mechanisms involved in the pharmacokinetics of IFX in ASUC.

Digestive Diseases and Sciences, Volume 63, Number 10, June 2018 – Comparison_ELISAs_RDT_DDS

IFX

IBD

2018

COMPARISON OF POINT-OF-CARE AND CLASSICAL IMMUNOASSAYS FOR THE MONITORING INFLIXIMAB AND ANTIBODIES AGAINST INFLIXIMAB IN IBD

Yara Nasser*, Rémi Labetoulle*, Ines Harzallah*, Anne-Emmanuelle Berger*, Xavier Roblin, Stephane Paul*

* Laboratoire d'Immunologie et d'Immunomonitoring, CIC Inserm 1408, GIMAP EA3064, CHU Saint-Etienne, France

ABSTRACT

OBJECTIVE: The primary objective is to assess whether the POC assays to measure infliximab residual trough level in the serum of IBD patients were non-inferior to the ELISA techniques available on the market, and to determine which of them was the most robust. The second is to compare three different ELISA kits for monitoring anti-infliximab antibodies (ATI).

METHODS: The assays were carried out on patients' sera using four ELISA kits from four different suppliers (three with a monoclonal antibody and one polyclonal) and two rapid techniques provided by BÜHLMANN (Quantum Blue®) and R-Biopharm (Ridaquick) for monitoring infliximab levels. ATI were measured by three ELISA sets (Grifols, Theradiag, and R-Biopharm) which have different positivity limits and different units.

RESULTS: **We measured infliximab residual level and ATI in the serum of 90 IBD patients** (85 treated with infliximab and five with adalimumab). **All of the infliximab assays were very well correlated** when analyzed with Spearman nonparametric correlation ($0.93 \leq r \leq 0.99$), and **the two POC assays were also excellently correlated ($r = 0.98$).** The ATI monitoring kits revealed a correlation ranging from 0.73 to 0.96 when comparing positive and negative patients. When normalizing the quantitative values between the different ELISA tests (expressed arbitrarily by using multiples of the positivity limits defined by each supplier), the Spearman *r* coefficient ranged from 0.81 to 0.93.

CONCLUSION: **The available evidence allows us to conclude that all of the infliximab monitoring assays correlate well and may be used for IFX monitoring**; **albeit variations in measured IFX concentration among different assays remain present, these assays could be interchangeable**. The ATI monitoring techniques are all capable of detecting ATI-positive patients, but because of the difference in the positivity limits and the measurement units, it is better to follow a patient rate with one definite kit.

KEY POINTS

	Suppliers	Antibody	Range	Dilution	Method	Time (min)
IFX trough levels	Lisa-Tracker (Theradiag)	Fc-Specific Monoclonal	0.3–16 (µg/ml)	1/200	ELISA	150
	Ridascreen (R-Biopharm)	Monoclonal	0.5–12	1/100	ELISA	100
	Sanquin	Monoclonal	0.02–20 (µg/ml)	1/100	ELISA	150
	Promonitor (Grifols)	Monoclonal	0.2–14.4 (µg/mL)	1/200	ELISA	150
	Ridaquick (R-Biopharm)	Monoclonal	0.5–10 (µg/mL)	1/500	Marked colloidal gold nanoparticles detection	30
	Quantum Blue®(BÜHLMANN)	Monoclonal	0.4–20 (µg/ml)	1/20	Marked colloidal gold nanoparticles detection	30
Antibodies to infliximab (ATI)	Theradiag		10–200 (ng/ml)	1/2	ELISA	150
	R-Biopharm		20–1000 (ng/ml)	1/200	ELISA	115
	Grifols		5–288 (AU/ml)	1/2	ELISA	150

Table 1. Description of the different assays used for the measure of IFX and ATI trough levels.

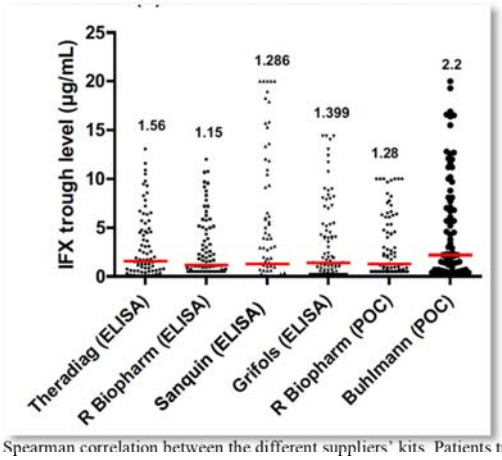


Figure 1. Nonparametric Spearman correlation between the different suppliers' kits. Patients trough level distribution within the different assays, the red line representing the median.

- Authors reported a comparison between 4 available ELISA techniques and 2 POC methods for the measurements of IFX and anti-IFX antibodies in serum samples from IBD patients.
- All techniques showed great correlations up to 3µg/ml of IFX trough level. POCs overestimated the IFX levels superiors to 3 µg/ml compared to ELISA tests. ELISAs yielded CV ranging around 7-8% while POC assays had CV around 15-20%.
- POC may be advantageous for non-responding patients allowing the detection of low IFX levels during the patients visit to hospital. However there are still no POC ATI assays available.
- Lisa-Tracker assay coud be useful in the case of anti-TNF switch between IFX and ADA as it allows measuring the cumulative trough levels between the two drugs.

Considering the variation in detection limits and measurement techniques between the different methods compared, authors strongly recommended not to interchange tests when monitoring a patient. Despite a longer time to result, ELISA tests appear more precise for application of the follow-up of patients.

IFX

IBD

2018

NEW THRESHOLDS NEED TO BE DEFINED WHEN USING POINT OF CARE ASSAYS TO MONITOR INFLIXIMAB TROUGH LEVELS IN IBD PATIENTS

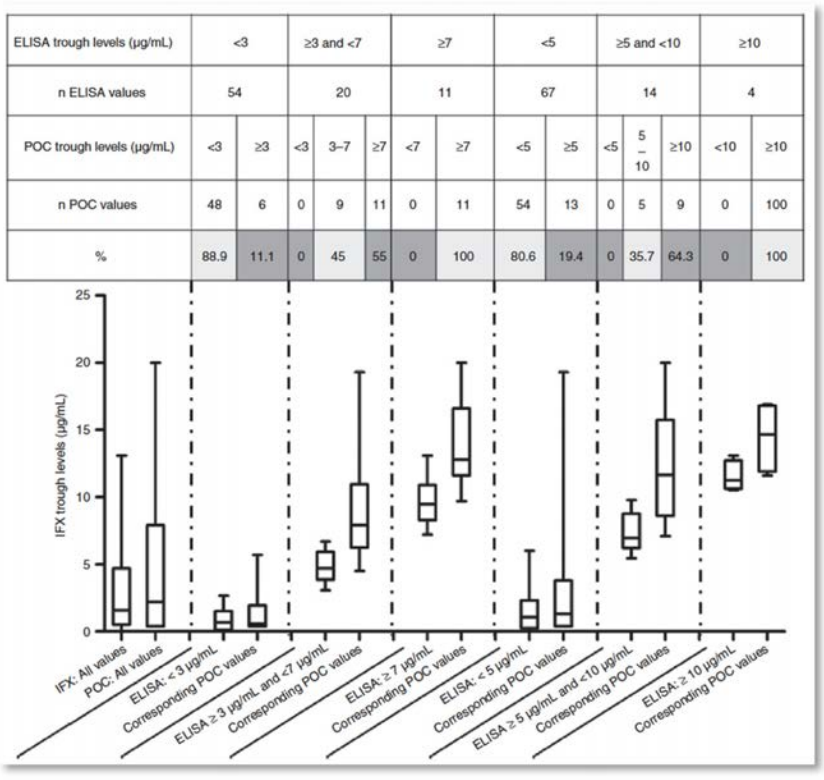
X. Roblin * & S. Paul

* Department of Immunology, University Hospital of Saint-Etienne, France.

ABSTRACT

LETTER

KEY POINTS



ELISA trough levels (µg/mL)	<3		≥3 and <7			≥7		<5		≥5 and <10			≥10	
n ELISA values	54		20			11		67		14			4	
POC trough levels (µg/mL)	<3	≥3	<3	3–7	≥7	<7	≥7	<5	≥5	<5	5 – 10	≥10	<10	≥10
n POC values	48	6	0	9	11	0	11	54	13	0	5	9	0	100
%	88.9	11.1	0	45	55	0	100	80.6	19.4	0	35.7	64.3	0	100

Figure 1. ELISA vs POC comparison according to thresholds and % agreement and differences between the 2 methods. % values agreement: light grey; % values disagreement : dark grey.

- The authors aim to analyse if new specific thresholds need to be defined for POC assays to monitor IFX trough levels in IBD patients. The study was conducted on a cohort of 85 patients and compare the Theradiag Lisa-Tracker ELISA method against the Buhlmann Quantum Blue POC assay.

- The correlation between the ELISA and the POC gave an overall agreement of 89,4%.

- The POC assay gave higher rates of IFX levels leading to an overestimation of the therapeutic IFX trough levels (below the 10µg/mL target) in a significant proportion of patients.

- Authors concluded that the current ELISA 5-10mg/mL target could not be used for the new POC assay.

Considering the shift of the IFX trough levels observed between the ELISA and the new generation POC assays, new thresholds are needed for the cut-off values when using POC.

IFX

IBD

2018

THERAPEUTIC DRUG MONITORING IS MORE COST-EFFECTIVE THAN A CLINICALLY BASED APPROACH IN THE MANAGEMENT OF LOSS OF RESPONSE TO INFLIXIMAB IN INFLAMMATORY BOWEL DISEASE: AN OBSERVATIONAL MULTICENTRE STUDY

Luisa Guidi*, Daniela Pugliese*, Tommaso Panici Tonucci*, Alexandra Berrino, Barbara Tolusso, Michele Basile, Laura Cantoro,Paola Balestrieri, Fortunata Civitelli, Lorenzo Bertani,Manuela Marzo*, Carla Felice*, Elisa Gremese,Francesco Costa, Franca Viola, Michele Cicala, Anna Kohn, Antonio Gasbarrini, Gian Lodovico Rapaccini*, Matteo Ruggeri, Alessandro Armuzzia*

* OU Internal Medicine and Gastroenterology Columbus, Fondazione Policlinico Universitario A. Gemelli IRCCS, Italy

ABSTRACT

BACKGROUND AND AIM: Empirical dose intensification and therapeutic drug monitoring [TDM] of infliximab [IFX] trough levels [ITLs] and antibody to infliximab [ATI] assays are recognized approaches for managing loss of response [LoR] in patients with inflammatory bowel disease [IBD]. The aim of the study was to compare these two interventions in a clinical setting, in terms of effectiveness and cost savings.

METHODS: Consecutive IBD patients experiencing LoR were clinically managed according to a TDM algorithm. A historical group of empirically treated patients, for whom sera for ITLs and ATI assays had been collected, served as the control group. Clinical outcomes 12 weeks after the therapeutic interventions were compared between the two groups. A cost-minimization analysis was performed to compare the economic impact of these two approaches.

RESULTS: **Ninety-six patients were enrolled prospectively and compared with 52 controls**. The two cohorts were similar in characteristics and in the distribution of TDM results. In the prospective cohort, however, **we observed less IFX dose escalations compared with in the controls [45% versus 71%, p = 0.003]. Also, more patients were switched to a different anti-TNFα in the prospective cohort than in the control cohort [25% versus 4%, p = 0.001].** The percentages of patients achieving a clinical response at 12 weeks were 52% and 54% for the prospective and control groups, respectively. **By cost analysis, we estimated a savings of 15% if the TDM algorithm was applied**.

CONCLUSION: In our population, **applying a TDM algorithm for LoR to IFX resulted in less dose escalations, without loss of efficacy, compared with empirical adjustment. In addition, the TDM approach was cost-effective**.

KEY POINTS

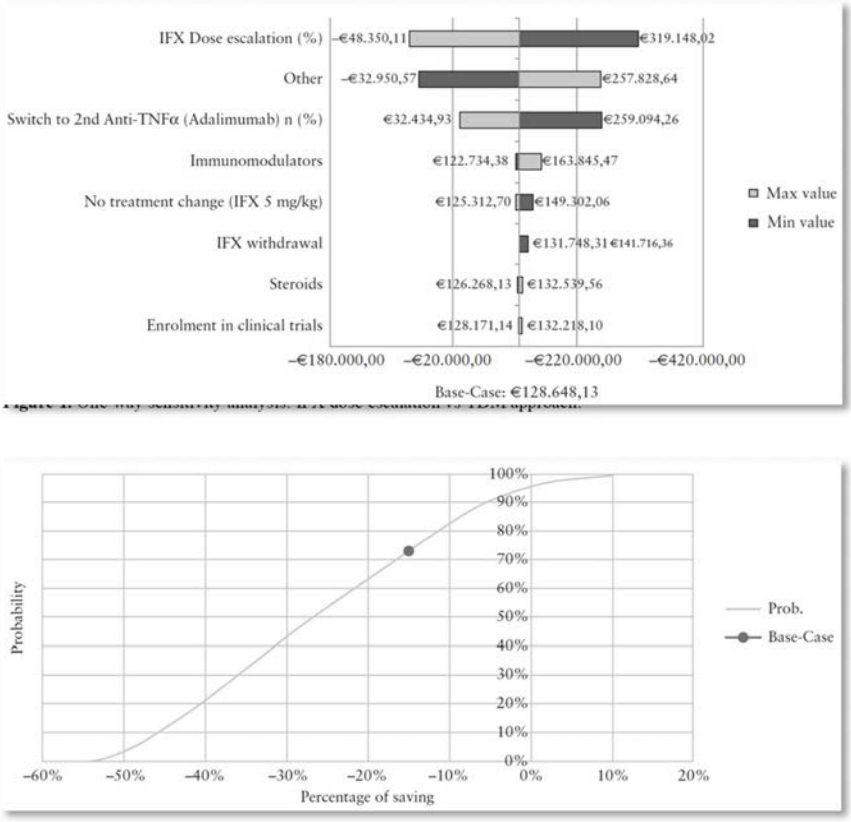


Figure 2. Probabilistic savings curve: IFX dose escalation vs TDM approach.

- This is the first study conducted in a clinical practice setting, with a prospective design and an *a priori* establishment of cut-offs for ITLs (3µ/mL) and ATIs (10ng/mL), that uses therapeutic intervention algorithm and includes a control group.
- Results show that the proposed algorithm in clinical practice generates higher savings than those achieved in the base case (-15%; total cost savings of 128 648.13 euros for 145 patients).
- The analysis also shows that the price of IFX originator, which is 25% higher than the biosimilar version, would need to be reduced by >40% in order to make null the savings the TDM approach would guarantee.
- The study suffers somes limitations among which its non-ransomized nature and the use of an IFX biosimilar that reduces the costs related to therapy.

Physicians and healthcare authorities should promote TDM in clinical practice to best allocate the economic resources in the face of growing use of biologic therapies.

Biosimilar IFX

Chronic Infl. Dis

2018

SYSTEMATIC SWITCH FROM INNOVATOR INFLIXIMAB TO BIOSIMILAR INFLIXIMAB IN INFLAMMATORY CHRONIC DISEASES IN DAILY CLINICAL PRACTICE: THE EXPERIENCE OF COCHIN UNIVERSITY HOSPITAL, PARIS, FRANCE

Avouac J, Moltó A, Abitbol V, Etcheto A, Salcion A, Gutermann L, Klotz C, Elhai M, Cohen P, Soret PA, Morin F, Conort O, Chast F, Goulvestre C, Jeunne CL, Chaussade S, Kahan A, Roux C, Allanore Y, Dougados M

*Department of Rheumatology, Cochin Hospital of APHP, France

ABSTRACT

OBJECTIVE: To investigate effectiveness of systematic switching treatment from innovator infliximab to biosimilar infliximab, and its associated factors.

METHODS: In this prospective observational study, all adult patients receiving maintenance therapy with innovator infliximab in Cochin University Hospital were systematically switched to biosimilar infliximab. Effectiveness was assessed by the retention rate of biosimilar infliximab at the time of the third infusion. Sensitivity analyses for effectiveness included changes of disease activity parameters and infliximab trough levels between baseline and the last visit as well as the occurrence of adverse events leading to drug discontinuation. Factors associated with biosimilar infliximab discontinuation at the last visit were explored.

RESULTS: total of 260 patients fulfilled the inclusion criteria, including 31 rheumatoid arthritis (RA), 131 axial spondyloarthritis (axSpA) and 64 inflammatory bowel diseases. **The retention rate was 85% (221/260 patients) at the time of the third biosimilar infusion**. Between baseline and the last visit (mean follow-up of 34 weeks), 59 patients (23%) discontinued biosimilar infliximab, mainly due to experienced inefficacy (n = 47, 80%). **No clinical or biological factors were associated with biosimilar discontinuation. No serious adverse events occurred. No change in objective disease activity parameters or infliximab trough levels was detected. However, a significant increase of BASDAI (2.94 ± 2.20 vs. 3.18 ± 2.21, P = 0.046, before vs. after switch, respectively) was observed in patients with axSpA. Innovator infliximab was re-established in 47/59 patients (80%).**

CONCLUSION: **No changes in drug trough levels or objective parameters were observed after the systematic switch to biosimilar infliximab in a real clinical practice setting.** Only changes in patient-reported outcomes were observed, suggesting attribution effects rather than pharmacological differences.

KEY POINTS

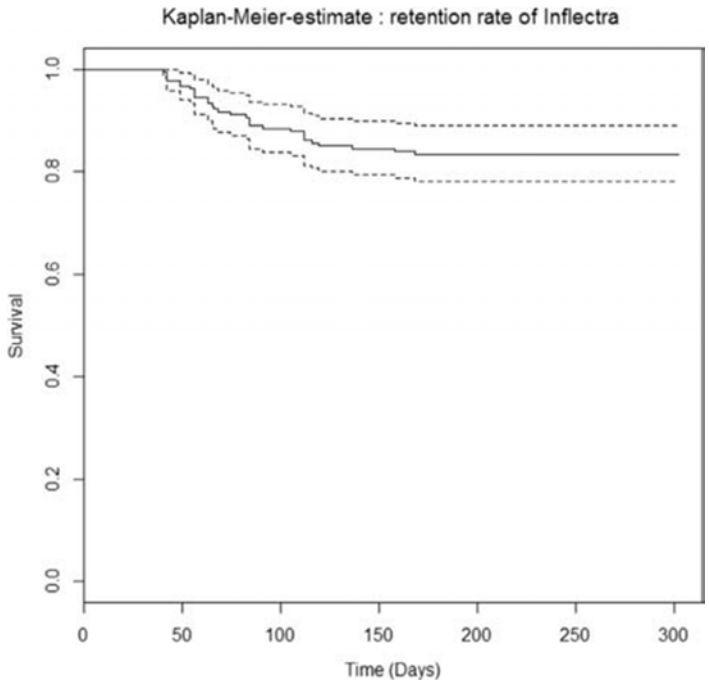


Figure 2. Estimation of the retention rate of biosimilar infliximab by Kaplan-Meier.

- The authors report one of the first studies of a systematic switch from innovator to biosimilar IFX in patients with chronic inflammatory disorders with a follow up of more than 8 months.
- The observational study focuses on sample cohorts from several clinical departments within Cochin Hospital and provides full result assessment by a tertiary center.
- To compare different individual disease activity measures, between baseline and the last visit, a Global Disease Activity Score was generated. Further validation is needed to assess its relevance.
- Patients experiencing biosimilar CT-P13 discontinuation had a higher number of biologics before IFX treatment and mainly concerned patients with axSpA.

Based on various inflammatory conditions and long-term innovator infliximab treated patients, the study supports the adoption of switching from reference infliximab to its biosimilar CT-P13 (traded names Inflectra® or Remsima®)

IFX

IBD

2017

DISTINCT THRESHOLDS OF INFLIXIMAB TROUGH LEVEL ARE ASSOCIATED WITH DIFFERENT THERAPEUTIC OUTCOMES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A PROSPECTIVE OBSERVATIONAL STUDY

Xavier Roblin, MD, PhD,* Gilles Boschetti, MD, PhD, Gérard Duru, PhD, Nicolas Williet, MD,* Emilie Deltedesco, MD,*Jean M. Phelip, MD, PhD,* Laurent Peyrin-Biroulet, MD, PhD, Stéphane Nancey, BD, PhD, Bernard Flourié, MD, PhD, and Stéphane Paul, PhD

*Department of Gastroenterology, University Hospital of Saint Etienne, France

ABSTRACT

BACKGROUND: Several studies have reported a strong correlation between infliximab (IFX) trough levels (trough levels of infliximab [TLI]) and clinical remission (CR). **We aimed to determine threshold values of TLI associated with the occurrence of CR, with or without normal inflammatory biomarkers, including serum C-reactive protein (CRP) and fecal calprotectin (fCal).**

METHODS: We included prospectively all consecutive patients with inflammatory bowel disease under IFX therapy (5 mg/kg every 8 wk) for at least 6 months. Disease activity (using the Crohn's Disease Activity Index or Mayo score) was recorded, and TLI, CRP, and fCal were measured before IFX infusion.

RESULTS: Two hundred thirteen patients (131 Crohn's disease) were included. The median TLIs were higher in patients who achieved CR compared with those in patients who did not (2.6 versus 1.2 mg/mL, P < 0.01). The median TLI were higher in patients achieving CR with CRP normalization or CR with fCal, 250 mg/g in comparison with patients with persistent elevated CRP or fCal (3.5 versus 1.6 mg/mL, P < 0.01 and 4.9 versus 1.8 mg/mL, P < 0.001, respectively). Finally, the median TLIs were higher in patients achieving CR with normal CRP and fCal,50 mg/g in comparison with patients without strictly normal biomarkers (5.9 versus 2.1 mg/mL, P < 0.001). **The more the expected level of response to IFX was stringent, the more the median TLI and optimal thresholds were high.**

CONCLUSIONS: Threshold values of TLI differ according to therapeutic outcomes expected in patients with inflammatory bowel disease under maintenance therapy with IFX.

KEY POINTS

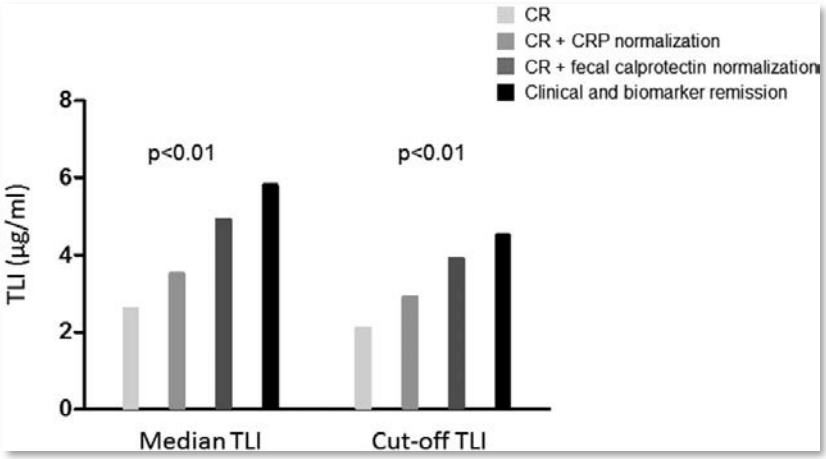


Figure 2. Variation of trough levels of IFX (TLI) according to therapeutic outcomes. Median TLI and threshold values varied significantly according to the clinical and biological outcomes. The highest TLI and cutoff values were associated with clinical and biological remission.

Therapeutic outcomes	Optimal cutoff for TLI
Absence of remission	TLI < 2,1 ug/mL
Absence of remission with CRP normalization	TLI < 2,9 ug/mL
Absence of remission with fcal <250ug/g	TLI < 3,9 ug/mL
Absence of clinical and biomarker remission	TLI < 4,9 ug/mL

- The study defines therapeutic outcomes, in patients with IBD under IFX therapy, according to clinical remission (CR) and the normalization of inflammatory markers such as CRP and fCal

- The authors describe 4 different therapeutic outcome situations where the median TLI varies significantly

- The study determines optimal threshold levels of TLI to discriminate between patients with or without CR and biomarker remission

- No difference was found between CD and UC patients under IFX therapy, indicating that the phenotype has no impact on drug bioavailability

The higher level of TLI in relationship with normalization of clinical biomarkers such as CRP and fecal Caprotectin, the more likely the patient with IBD show favorable response to IFX

IFX

IBD

2017

CLINICAL ROLE, OPTIMAL TIMING AND FREQUENCY OF SERUM INFLIXIMAB AND ANTI-INFLIXIMAB ANTIBODY LEVEL MEASUREMENTS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Renàta Bor*, Klaudia Farkas*, Anna Fàbiàn*, Anita Bàlint*, Agnes Milassin*, Mariann Rutka*, Mària Matuz, Ferenc Nagy*, Zoltàn Szepes*, Tamàs Molnàr*

*Department of Medecine, University of Szeged, Hungary

ABSTRACT

BACKGROUND : Serum infliximab (IFX) and antibody-to-infliximab (ATI) levels are objective parameters, that may have a great role in the therapeutic decisions during maintenance biological therapy.

RESEARCH DESIGN AND METHODS : 48 inflammatory bowel disease patients receiving maintenance IFX therapy were prospectively enrolled and divided into adequate (complete remission N = 20) and inadequate responder (partial response, loss of response, dose escalation; N = 28) groups. Blood samples were collected just before (trough level, TL) and two (W2aTL) and six weeks (W6aTL) after the administration of IFX.

RESULTS : Single measurement of ATI titer was insufficient for predicting therapeutic response due to transient expression of ATI, however, using the three points' measurements, significant difference has been detected between the adequate and inadequate responder group (5.0% vs 35.7%; p = 0.016). The mean value of TL was significantly higher in the adequate responder group (3.11±1.64 vs.1.19±1.11; p<0.001) without further difference on the second and sixth week. **Sensitivity and specificity for predicting the therapeutic response were 85.0% and 71.4% based on the cut-off value of TL 2.0 μg/ml.**

CONCLUSION : **Simultaneous measurement of serum IFX level prior to administration of regular IFX infusion and ATI titers significantly increase the diagnostic accuracy for the therapeutic decision in patients uncertainly responding to the therapy**. The measurement of W2aTL and W6aTL levels did not result in further improvement in the prediction of therapeutic response.

KEY POINTS

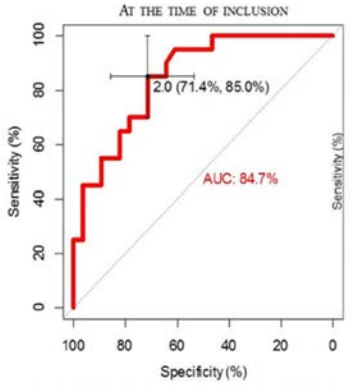


Figure 2. ROC analysis of IFX trough levels (TL) associated with current and long-term response.

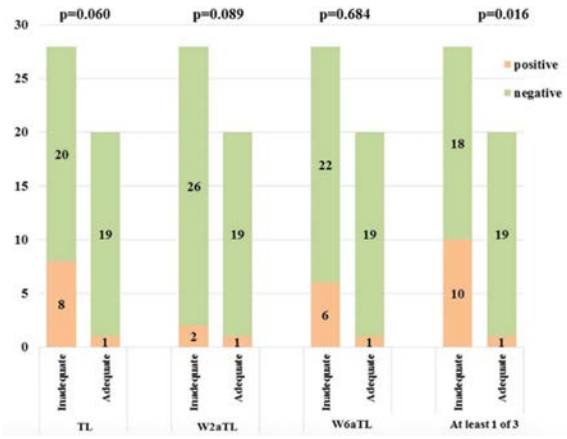


Figure 4. Proportion of ATI positivity in the adequate and inadequate responder groups.

- This study shows that prediction of therapeutic outcomes appears relevant only at the time of inclusion: cut-off value of trough level is observed at 2 μg/ml; AUC 84.7%.

- ATI detection is observed in patients with low /undetectable IFX level suggesting transient expression and accelerated drug elimination.

- In case of dose escalation (10mg/kg), therapeutic prediction of IFX level could not be confirmed.

- Note that original IFX and biosimilar IFX compounds were considered equal in the study.

Despite the small set of patient samples and some analysis limitations, simultaneous measurement of single sampling of serum IFX and ATI levels appear effective in the prediction of therapeutic outcomes prior the administration of regular infusion

IFX

IBD

2017

DEVELOPMENT AND INTERNAL VALIDATION OF A MODEL USING FAECAL CALPROTECTIN IN COMBINATION WITH INFLIXIMAB TROUGH LEVELS TO PREDICT CLINICAL RELAPSE IN CROHN'S DISEASE

Xavier Roblin, PhD,* Gerard Duru, PhD, Nicolas Williet, MD, Emilie Del Tedesco, MD, Murielle Cuilleron, MD, Camille Jarlot, MD, Jean Marc Phelip, PhD, Gilles Boschetti, MD, Bernard Flourié, PhD, Stephane Nancey, PhD, Laurent Peyrin-Biroulet, PhD, and Stephane Paul, MD

*Department of Gastroenterology, University Hospital of Saint Etienne, France

ABSTRACT

BACKGROUND: The best non-invasive method predicting clinical relapse remains undetermined in infliximab (IFX)-treated patients with Crohn's disease.

METHODS: All patients with CD on IFX maintenance treatment and in clinical remission for at least 16 weeks, between 2011 and 2014, were enrolled in **a prospective single-center study**. The Crohn's Disease Activity Index (CDAI), fecal calprotectin, C-reactive protein levels, antibodies (ATI), and trough level (TLI) of IFX were measured at every IFX infusion. **The best thresholds of TLI (2 versus 3 mg/mL) and calprotectin (50 versus 250 mg/g stools) were identified across four logistic regression models.**

RESULTS: One hundred nineteen patients (mean age: 34 6 12 years, mean disease duration: 7.8 years) were included. Mean follow-up was 20.4 months, and 17% of the patients were on IFX and azathioprine at inclusion. During follow-up, 37 patients (31.1%) relapsed, 78% within the first 6 months. The clinical characteristics of the relapsed and non-relapsed patients were similar. After logistic regression, faecal calprotectin. 250 mg/g stools (OR: 4.09; 95% CI, 1.01–16.21; P=0.049) and TLI <2 mg/mL (OR: 14.85; 95% CI, 3.67–60; P < 0.0001) were associated with loss of response. A training cohort of 55 patients was isolated randomly to implement prediction rules for loss of response. The best predictive rules were the combination of a TLI <2 mg/mL and a faecal calprotectin level .250 mg/g stools (78.3%). These rules were validated on a test cohort of 64 patients with an accuracy of 87%, (sensitivity= 0.94, specificity =0.84, positive predictive value =0.73, and negative predictive value = 0.97).

CONCLUSIONS: In IFX-treated patients with CD in clinical remission, a combination of TLI (<2 mg/mL) and fecal calprotectin (>250 mg/g of stools) is a good model for predicting loss of response. In contrast with previous data, low TLIs ranging from 2 to 3 mg/mL should neither systematically lead to the optimization of IFX use nor a switch in the treatment.

KEY POINTS

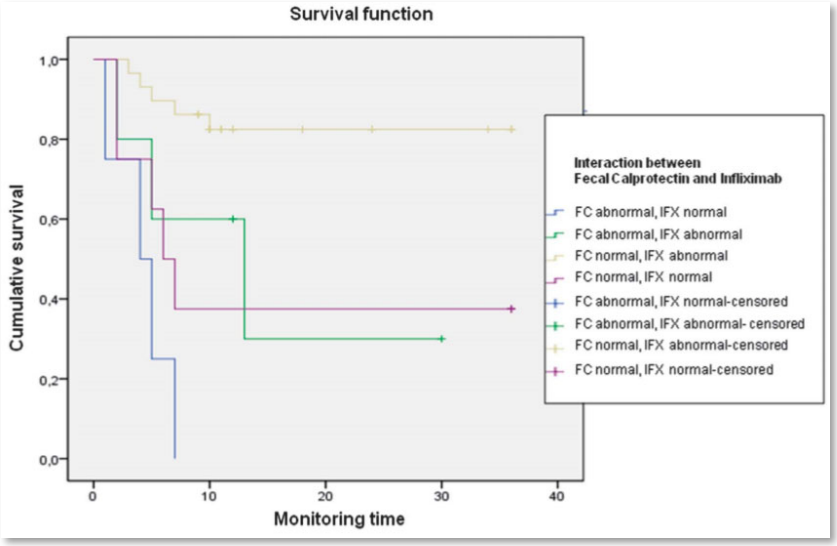


Figure 3. LOR during follow-up according to TLI (< or > 2 mg/mL) and fecal calprotectin levels (< or > 250 mg/mL) at inclusion (Kaplan–Meier regression). Log-rank test (Mantel Cox) ¼ 20.59; P < 0.001.

TABLE 5. Comparison of Different Predictive Rules of LOR According to CRP in the Training Cohort

Model	TLI <2 µg/mL and Calprotectin >250 µg/g Stools	CRP >5 mg/L and Calprotectin >250 µg/g Stools	TLI <2 µg/mL and CRP >5 mg/L	TLI <2 µg/mL and Calprotectin >250 µg/g Stools and CRP >5 mg/L
Sensitivity	0.94	0.36	0.52	0.94
Specificity	0.84	0.92	0.90	0.84
PPV	0.73	0.70	0.73	0.73
NPV	0.97	0.73	0.77	0.96
Accuracy, %	87	74	77	87

- The study shows that calprotectin seems to be a biomarker of inflammation in the tissue and low TLI as the explanation of why patients relapse

- The results highlight the clinical utility of IFX trough levels to predict LOR

- The study suggests that the best threshold of TLI for the prediction of LOR is 2 mg/mL

- The following score: (TLI <2 mg/mL and fecal calprotectin [>250 mg/g of stools]) best predicts a short-term clinical relapse with a high accuracy of 87% in patients in clinical remission under IFX.

The new model using faecal calprotectin in combination with Infliximab trough levels can be used to identify a subgroup of patients requiring therapeutic optimization

Biosimilar IFX

IBD

2017

PREDICTION OF SHORT- AND MEDIUM-TERM EFFICACY OF BIOSIMILAR INFLIXIMAB THERAPY. DO TROUGH LEVELS AND ANTIDRUG ANTIBODY LEVELS OR CLINICAL AND BIOCHEMICAL MARKERS PLAY THE MORE IMPORTANT ROLE?

Lorant Gonczi*, Zsuzsanna Vegh*, Petra Anna Golovics*, Mariann Rutka, Krisztina Barbara Gecse*, Renata Bor,Klaudia Farkas, Tamás Szamosi, László Bene, Beáta Gasztonyi, Tünde Kristóf, László Lakatos, Pál Miheller, Károly Palatka, Mária Papp, Árpád Patai, Ágnes Salamon, Gábor Tamás Tóth, Áron Vincze, Edina Biro, Barbara Dorottya Lovasz*, Zsuzsanna Kurti*, Zoltan Szepes, Tamás Molnár, Peter L. Lakatos*

*First Department of Internal Medicine, Semmelweis University, Budapest, Hungary

ABSTRACT

BACKGROUND AND AIMS: Biosimilar infliximab CT-P13 received European Medicines Agency [EMA] approval in June 2013 for all indications of the originator product. In the present study, we aimed to evaluate the predictors of short- and medium-term clinical outcome in patients treated with the biosimilar infliximab at the participating inflammatory bowel disease [IBD] centres in Hungary.

METHODS: Demographic data were collected and a harmonised monitoring strategy was applied. Clinical and biochemical activities were evaluated at Weeks 14, 30, and 54. Trough level [TL] and anti-drug antibody [ADA] concentrations were measured by enzyme-linked immunosorbent assay [ELISA] [LT-005, Theradiag, France] at baseline at 14, 30 and 54 weeks and in two centres at Weeks 2 and 6.

RESULTS: **A total of 291 consecutive IBD patients** (184 Crohn's disease [CD] and 107 ulcerative colitis [UC]) were included. **In UC, TLs at Week 2 predicted both clinical response and remission at Weeks 14 and 30** (clinical response/remission at Week 14: area under the curve [AUC] = 0.81, p < 0.001, cut-off: 11.5 µg/ml/AUC = 0.79, p < 0.001, cut-off: 15.3µg/ml; clinical response/remission at Week 30: AUC = 0.79, p = 0.002, cut-off: 11.5 µg/ml/AUC = 0.74, p = 0.006, cut-off: 14.5 µg/ml), whereas **ADA positivity at Week 14 was inversely associated with clinical response at Week 30** [58.3% vs 84.8% ,p = 0.04]. **Previous anti-tumour necrosis factor [TNF] exposure was inversely associated with short-term clinical remission** [Week 2: 18.8% vs 47.8%, p = 0.03, at Week 6: 38.9% vs 69.7%, p = 0.013, at Week 14: 37.5% vs 2.5%, p = 0.06]. In CD, **TLs at Week 2 predicted short-term** [Week 14 response/remission, AUCTLweek2 = 0.715–0.721, p = 0.05/0.005] **but not medium-term clinical efficacy**. In addition, early ADA status by Week 14 [p = 0.04–0.05 for Weeks 14 and 30], early clinical response [p < 0.001 for Weeks 30/54] and normal C-reactive protein [CRP] at Week 14 [p = 0.005–0.0001] and previous anti-TNF exposure [p = 0.03 -0.0001 for Weeks 14, 30, and 54] were associated with short and medium-term clinical response and remission.

CONCLUSIONS: **In UC, early TLs were predictive for short- and medium-term clinical efficacy, whereas in CD, Week 2 TLs were associated only with short-term clinical outcomes.**

KEY POINTS

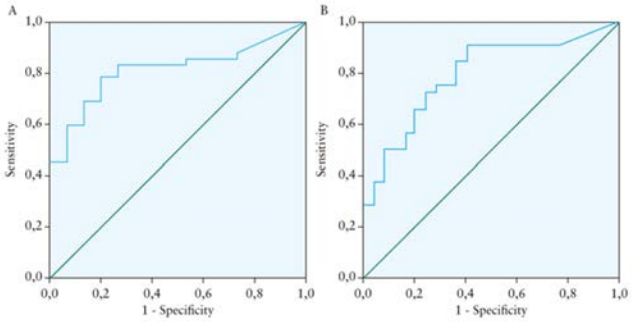


Figure 1. A. Predictive power of infliximab trough levels [TL] measured at Week 2 for identifying **clinical response at Week 14 in patients with ulcerative colitis** [AUCTLWeek2 = 0.81, p < 0.001, cut-off: 11.5 µg/ml]. B. Predictive power of infliximab trough levels measured at Week 2 for identifying **clinical remission at Week 14 in patients with ulcerative colitis** [AUCTLWeek2 = 0.79, p < 0.001, cut-off: 15.3 µg/ml]. AUC, area under the curve.

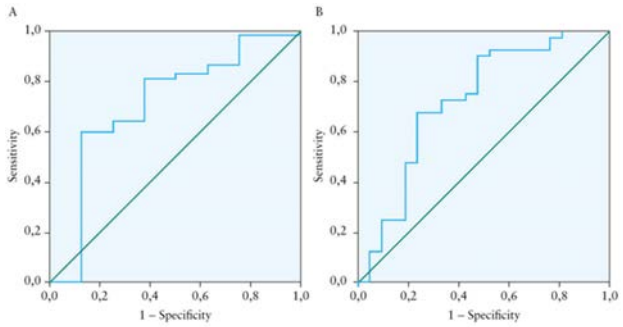


Figure 3. A. Predictive power of infliximab trough levels [TL] measured at Week 2 for identifying **clinical response at Week 14 in patients with Crohn's disease** [AUCTLWeek2 = 0.72, p = 0.05, 95% CI: 0.496–0.933, cut-off: 16.9 µg/ml]. B. Predictive power of infliximab trough levels measured at Week 2 for identifying **clinical remission at Week 14 in patients with Crohn's disease** [AUCTLWeek2 = 0.72, p = 0.005, 95% CI: 0.575–0.868, cut-off: 20.4µg/ml].

- The study shows that trough levels of CT-P13 measured at Week 2 in CD patients are associated both with clinical response and remission at Week 14.

- Authors found that previous anti-TNF exposure is negatively correlated with clinical remission from week 14 until the end of the study in CD patients treated with biosimilar IFX.

- However, in UC patients, the correlation between previous anti-TNF exposure and clinical outcomes was only predictive when through levels were measured at week 2.

- The study reveals a potential predictive role of Therapeutic Drug Monitoring in IBD patients under biosimilar CT-P13.

Despite some limitations in the study design, previous exposure to originator IFX appears as a relevant factor associated with long term clinical outcome in CD patients and only short-term clinical efficacy in UC.

IFX

IBD

2016

COMPARISON OF INFLIXIMAB DRUG MEASUREMENT ACROSS THREE COMMERCIALLY AVAILABLE ELISA KITS

Lee MW*, Connor S, Ng W, Toong CM.

* Department of Immunology, Liverpool Hospital, Sydney, Australia

ABSTRACT

BACKGROUND: The monitoring of infliximab drug levels aids in the management of several autoimmune diseases, notably inflammatory bowel disease. Several commercial kits are now available and approved by the Therapeutic Goods Administration (TGA) for the measurement of infliximab levels, but there have been limited verification or comparison studies to date. Finding an assay that most accurately measures infliximabis essential for optimal drug titration and patient management. We performed this study to **compare the performance of the Grifols Promonitor, Theradiag Lisatracker and R-Biopharm Ridascreen enzyme linked immunosorbent assay (ELISA) kits.**

METHODS: Preparations of serum containing known concentrations of infliximab were assayed using each kit, including in the presence of interference from anti-infliximab antibodies, autoantibodies and other biological agents.

RESULTS: The Lisatracker kit provided the most accurate determination of infliximab drug levels, however it yielded false positive results at low concentrations of infliximab. The average coefficients of variation (CVs) for the kits were 8% for Lisatracker, 5% for Ridascreen and 11% for Grifols. Infliximab measurements across all kits were affected by interference from antibodies to infliximab (ATI).

CONCLUSIONS: This study identified the Lisatracker kit as the most accurate in quantifying infliximab levels, although it was limited by false positive results at low concentrations of infliximab as well as interference from ATI. This has important implications for the monitoring and management of patients receiving infliximab therapy.

KEY POINTS

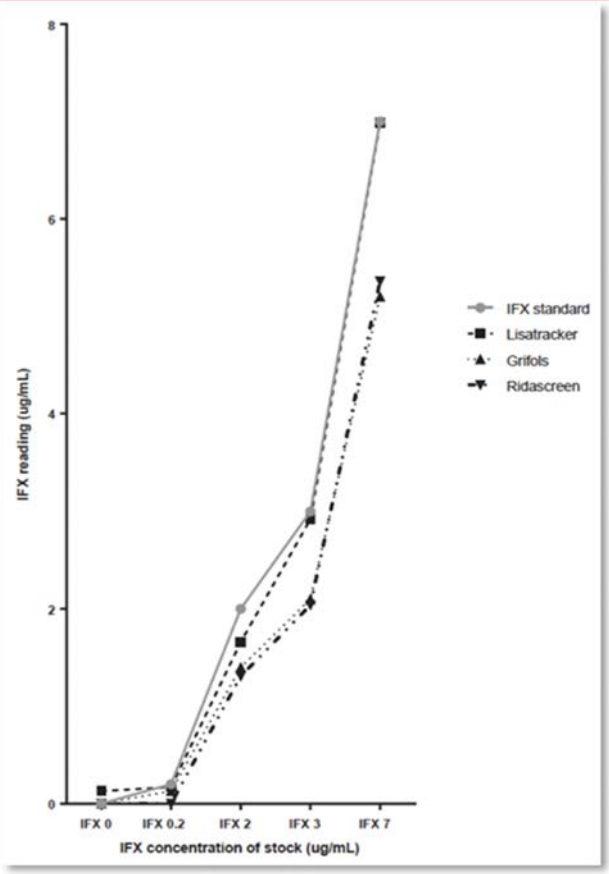


Figure 2. Comparison of infliximab results between kits. The curve with circles plots the infliximab concentrations of the prepared standard samples, at 0 µg/mL, 0.2 µg/mL, 2 µg/mL, 3 µg/mL and 7 µg/mL. Please refer to the key forresults from each kit.

- Due to the lack of gold standard assay to provide the true value of IFX in patient samples, standard serum samples from healthy controls were spiked with known concentrations of IFX. A high affinity monoclonal ATI was added to each IFX concentration to achieve ATI levels in the detectable range of 0.01µg/mL to 10µg/mL.

- Sample were all run on an automated ELISA processor under the supervision of each company application specialists and blindly tested in 3 external laboratories.

- For all kits, rheumatoid factor nor paraprotein did produce any significant interference.

- Discrepancies in CVs obtained, compared to those stated in the product insert reflect the true performance of the assays in laboratory practice.

The Lisatracker kit produced the closest results to the true concentration of IFX. All kit results were adversely affected by the presence of high-affinity neutralising ATI and other interfering biological agents.

Biosimilar IFX

IBD

2016

EFFICACY AND SAFETY OF THE BIOSIMILAR INFLIXIMAB CT-P13 TREATMENT IN INFLAMMATORY BOWEL DISEASES: A PROSPECTIVE, MULTICENTRE, NATIONWIDE COHORT

Krisztina B. Gecse*, Barbara D. Lovász*, Klaudia Farkas, János Banai, László Bene,d Beáta Gasztonyi, Petra Anna Golovics*, Tünde Kristóf, László Lakatos, Ágnes Anna Csontos, Márk Juhász, Ferenc Nagy, Károly Palatka, Mária Papp, Árpád Patai, Lilla Lakner, Ágnes Salamon, Tamás Szamosi, Zoltán Szepes, Gábor T. Tóth, Áron Vincze, Balázs Szalay, Tamás Molnár, Péter L. Lakatos*

*First Department of Internal Medicine, Semmelweis University, Budapest, Hungary

ABSTRACT

BACKGROUND AND AIMS: Biosimilar infliximab CT-P13 is approved for all indications of the originator product in Europe. Prospective data on its efficacy, safety, and immunogenicity in inflammatory bowel diseases are lacking.

METHODS: A prospective, nationwide, multicentre, observational cohort was designed to examine the efficacy, safety, and immunogenicity of CT-P13 infliximab biosimilar in the induction treatment of Crohn's disease [CD] and ulcerative colitis [UC]. Demographic data were collected and a harmonised monitoring strategy was applied. Early clinical remission, response, and early biochemical response were evaluated at Week 14, steroid-free clinical remission was evaluated at Week 30. Therapeutic drug level was monitored using a conventional enzyme-linked immunosorbent assay.

RESULTS: In all, 210 consecutive inflammatory bowel disease [126 CD and 84 UC] patients were included in the present cohort. At Week 14, 81.4% of CD and 77.6% of UC patients showed clinical response and 53.6% of CD and 58.6% of UC patients were in clinical remission. **Clinical remission rates at Week 14 were significantly higher in CD and UC patients who were infliximab naïve**, compared with those with previous exposure to the originator compound [$p < 0.05$]. **Until Week 30, adverse events were experienced in 17.1% of all patients**. Infusion reactions and infectious adverse events occurred in 6.6% and 5.7% of all patients, respectively.

CONCLUSIONS: This prospective multicentre cohort shows that **CT-P13 is safe and effective in the induction of clinical remission and response in both CD and UC. Patients with previous infliximab exposure exhibited decreased response rates and were more likely to develop allergic reactions.**

KEY POINTS

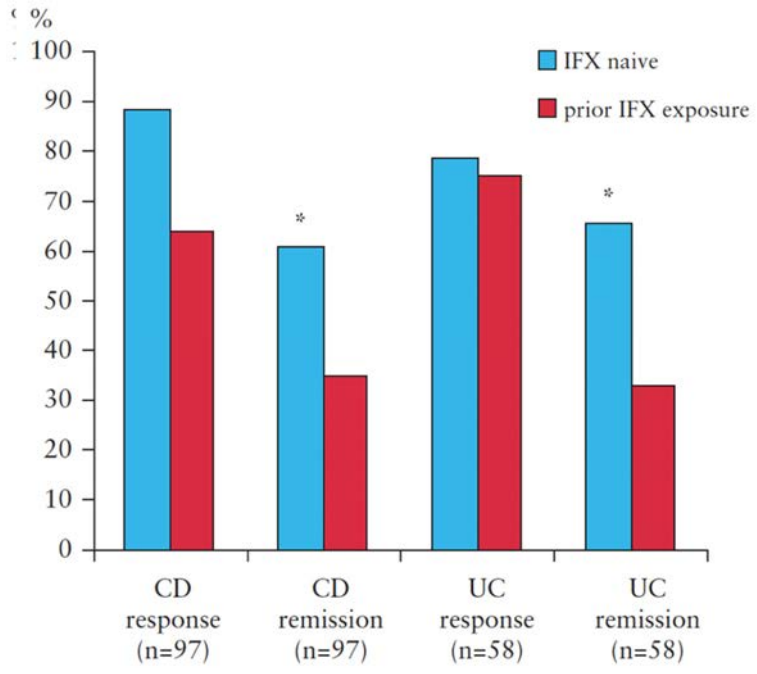


Figure 2. Clinical remission and response at **Week 14** in IFX-naïve and exposed patients. *$p < 0.05$, both in CD and in UC, as compared with previous exposure. CD, Crohn's disease; UC, ulcerative colitis; IFX, infliximab.

- This study reports new pharmacokinetic data of CT-P13 performance in CD and UC patients naïve or not previously exposed to the originator IFX drug for 1 year.
- The authors report that 26% of patients had received previous anti-TNF treatment, 22,3% with the originator IFX and 3,9% with Adalimumab.
- IFX originator exposure was associated with significant higher baseline of anti-drug antibody positivity in IBD patients as well as higher occurrence of infusion reactions.
- Authors recommend a risk-benefit assessment before initiating any long drug holiday in patients in remission.
- In all IBD patients, clinical improvement during induction was associated with decreased biochemical activity (mean CRP and mean platelet count) compared with baseline.

First real-life study to evaluate clinical and biochemical endpoints of IFX biosimilar CT-P13 treated IBD patients in a new anti-TNF alpha induction and maintenance phase and to demonstrate biosimilarity with the originator compound

IFX

IBD

2015

LETTER: INFLIXIMAB DE-ESCALATION BASED ON TROUGH LEVELS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

S. Paul*, X. Roblin & L. Peyrin-Biroulet

* Laboratoire d'Immunologie et d'Immunomonitoring, CHU de Saint-Etienne, France.

ABSTRACT

LETTER

KEY POINTS

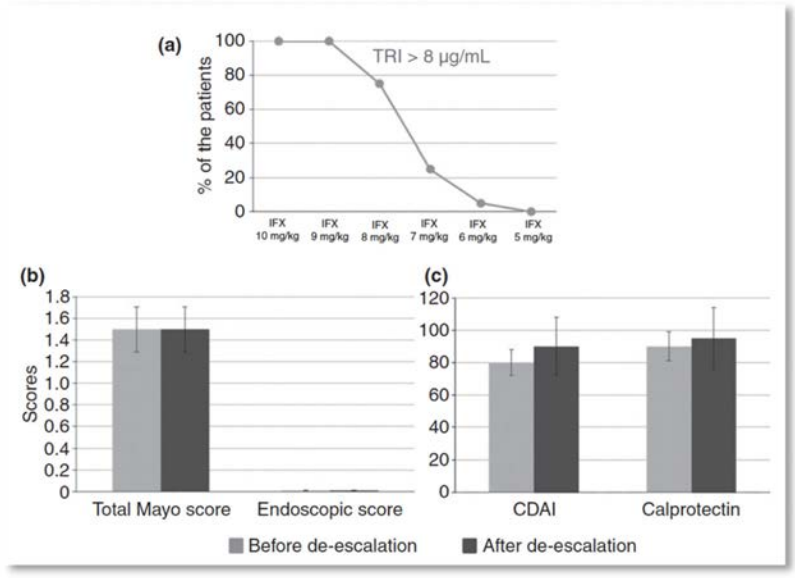


Figure 1. Outcomes of Infliximab de-escalation effects on IBD patients. (a) De-escalation effect on the percentage of patients with infliximab trough levels >8 µg/mL before and after de-escalation; (b) Impact of IFX de-escalation on clinical Mayo or endoscopic scores in ulcerative colitis patients before and after de-escalation; (c) Impact of IFX de-escalation on clinical CDAI (Crohn's disease activity index) score and faecal calprotectin in Crohn's disease patients before and after de-escalation.

- Authors report a long-term outcome in a prospective study of 20 IBD patients under IFX treatment (10 mg/kg every 8 weeks for secondary loss of response).

- All patients were in deep remission and underwent IFX dose de-escalation by 1 mg/kg decrease at each infusion to a dose of 5mg/kg or to get a trough level in the therapeutic range (between 3 to 7 µg/mL).

- Persistence of deep remission was achieved in 18 patients. Most patients achieved the targeted trough levels at 7mg/kg IFX dose.

- Only two patients experienced a clinical relapse following de-escalation at an IFX dose of 8mg/kg despite having a trough level within the normal range (TRI: 5.5 and 4.9 µg/mL respectively).

Progressive dose de-escalation, reducing IFX dose of 1mg/kg every two months appears effective with maintenance of deep remission in the long term in 90% of IBD treated patients. Such strategy may be associated with major cost savings.

IFX

IBD

2015

THE ANTIBODY RESPONSE AGAINST HUMAN AND CHIMERIC ANTI-TNF THERAPEUTIC ANTIBODIES PRIMARILY TARGETS THE TNF BINDING REGION

Fabien Bernard Vincent*, Stephan Pavy*, Roman Krzysiek, Thierry Lequerrée, Jérémie Sellam, Yassine Taoufik, Xavier Mariette*, Corinne Miceli-Richard *

*Department of rheumatology, Hôpital Bicêtre, France

ABSTRACT

RESPONSE TO THE CONCISE REPORT OF

K A van Schie , M H Hart, E R de Groot, S Kruithof, L A Aarden, G J Wolbink & T Rispens
Sanquin Research, Department of Immunopathology, Amsterdam, The Netherlands

KEY POINTS

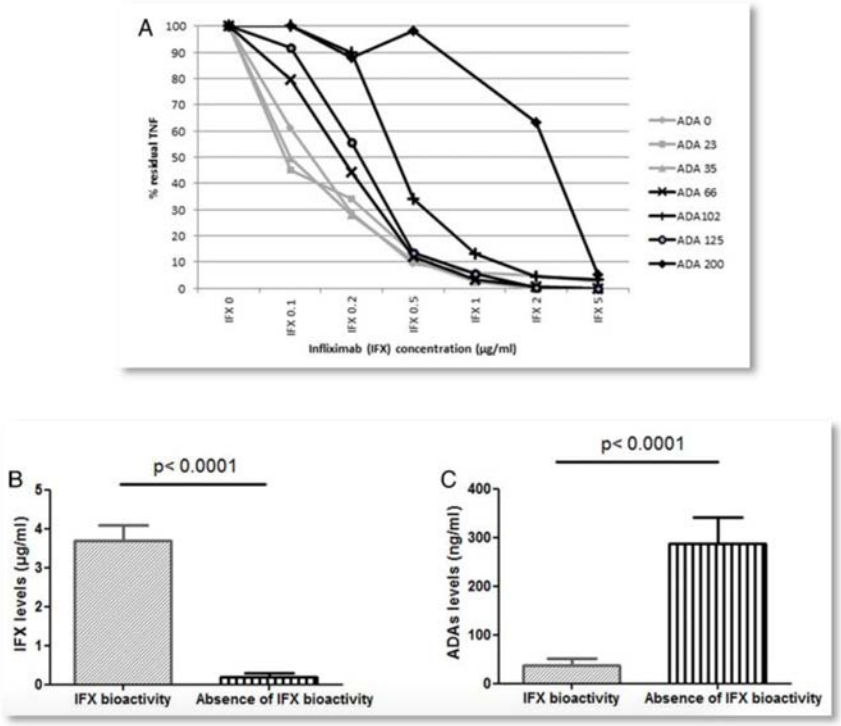


Figure 1. Evaluation of ADAs and IFX bioactivity in patients with IBD treated with IFX using a functional test.
(A) Neutralising capacity of ADAs in patients with IBD (ADAs concentration expressed in µg/mL). Residual TNF represents the quantity of recombinant TNF added not blocked by IFX.
(B) Relation between IFX levels in ELISA and its bioactivity (C) Correlation between ADAs level and IFX bioactivity.
ADAs, antidrug antibodies; IBD, inflammatory bowel disease; IFX, infliximab).

- In this report, authors assess ADAs' biological activity by a functional assay using a reporter HEK-Dual TNF cell line developed for TNF detection (InvivoGen). ADA levels were also measured by ELISA assay (Theradiag). A good correlation was noticed between the two tests showing the capacity of ADAs to block IFX bioactivity.

- Detectable IFX in ELISA was a good surrogate marker of its bioactivity in patients with IBD. In Presence of ADAs in ELISA, no biological IFX was detected with the functional assay too.

- Results are in line with already published data reporting that presence of ADAs is associated with significantly higher risk of loss of clinical response to IFX underlying the importance of ADAs neutralising effect.

Considering the ADAs neutralising capacity, their monitoring during TNF blocker treatment appears to be highly relevant.

IFX

IBD

2015

COMBINATION OF C-REACTIVE PROTEIN, INFLIXIMAB TROUGH LEVELS, AND STABLE BUT NOT TRANSIENT ANTIBODIES TO INFLIXIMAB ARE ASSOCIATED WITH LOSS OF RESPONSE TO INFLIXIMAB IN INFLAMMATORY BOWEL DISEASE

Roblin X*, Marotte H, Leclerc M, Del Tedesco E, Phelip JM, Peyrin-Biroulet L, Paul S.

*Department of Gastroenterology, CHU Saint Etienne, France

ABSTRACT

BACKGROUND: Antibodies to infliximab (ATI) and trough levels to infliximab (TRI) are associated with loss of response in inflammatory bowel diseases (IBD). The best way to predict loss of response (LOR) to infliximab (IFX) is unknown.

METHODS: We conducted a prospective observational cohort study enrolling all IBD patients who were in clinical remission at week 14 after IFX treatment initiation. TRI, ATI and C-reactive protein (CRP) level were measured at week 22 (T1) and thereafter at every other IFX infusion. Loss of clinical response was defined by a flare requiring therapeutic change (IFX dose intensification, initiation of another drug class and/or surgery).

RESULTS: 93 patients (59 Crohn's disease, mean duration of follow up 17.2 months) were included. 32 patients (34.4%) lost clinical response during follow-up. Cumulative probability of LOR was 50% at 20 months. Mean TRI at T1 was significantly lower in IBD patients with stable ATI as compared to those with transient ATI or without ATI (0.052, 3.34 and 4.29 µg/mL, respectively; p=0.001 between no ATI vs. stable ATI, and p=0.005 between stable and transient ATI) (p=0.0001). Three independent factors were predictive of LOR after Cox proportional hazards modelling: TRI > 5.5 µg/mL (HR: 0.21; 95% CI: 0.05-0.89: p=0.034) at T1, CRP > 5mg/L (HR: 2.5; 95% CI: 1.16-5.26; p=0.019) at T1, and stable ATI defined by two consecutive ATI > 20ng/ml (HR: 3.77; 95% CI: 1.45-10.0: p= 0.007). **Transient ATI did not influence LOR**.

CONCLUSIONS: LOR can be predicted based on a combination of CRP, TRI and stable ATI with a high degree of accuracy.

KEY POINTS

Variables	Log-rank test
Stable vs no or transient ATI	0.01
Transient vs no ATI	0.09
ATI > 20ng/ml vs < 20ng/ml	0.01
TRI < 5.5µ/ml vs > 5.5 µg/ml	<0.01
CRP> 5mg/l vs <5mg/ml	<0.01
IS vs ni IS associated	0.2

Table 2. Univariate analysis of factors associated with LOR during the follow-up at T1. ATI: Antibodies to Infliximab, CRP: C-reactive protein, IFX: infliximab, IS, Immunosuppressive drugs.

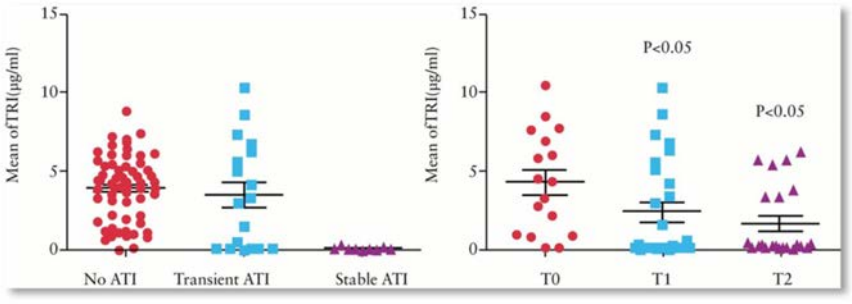


Figure 2. [A] TRI according to ATI status; and [B] kinetics of TRI over time.

- This study confirms that stable ATI defined by at least two consecutive positive ATI levels were strongly and independently associated with LOR, whereas transient ATI had no impact on LOR rates.

- Authors report an inverse correlation between TRI and ATI at the time of the first sample and on all samples. TRI are significantly lower in patients with stable ATI. The decrease in IFX trough level precedes the development of ATI.

- Cut-off of TRI> 5.5 µg/mL was the best threshold value to predict LOR.

- Authors suggest that only primary responders to anti-TNF therapy should be analysed when evaluating the impact of ATI on LOR.

A new algorithm, based on a combination of serum markers and pharmacokinetics, is proposed to be used in clinical practice to guide decision making.

IFX

IBD

2013

THERAPEUTIC DRUG MONITORING OF INFLIXIMAB AND MUCOSAL HEALING IN INFLAMMATORY BOWEL DISEASE: A PROSPECTIVE STUDY

Stephane Paul*, Emilie Del Tedesco, Hubert Marotte, Melanie Rinaudo-Gaujous*, Amelie Moreau*, Jean-Marc Phelip, Christian Genin*, Laurent Peyrin-Biroulet and Xavier Roblin.

*Laboratoire d'immunologie et d'immunomonitoring, University Hospital of Saint Etienne, France

ABSTRACT

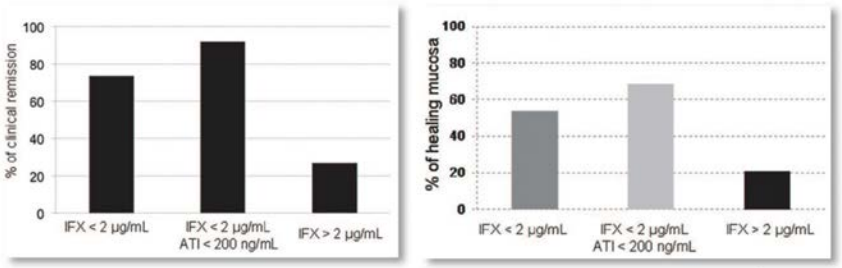
BACKGROUND: Data on the value of therapeutic drug monitoring of infliximab (IFX) to predict mucosal healing (MH) in inflammatory bowel diseases (IBD) are scarce.

METHODS: All consecutive patients with IBD receiving ongoing IFX (5 mg/kg) treatment and developing secondary failure to IFX were enrolled in a prospective study between June 2010 and May 2011. IFX trough levels, antibodies to IFX concentrations, C-reactive protein levels, and fecal calprotectin were measured before IFX optimization and at week 8. A proctosigmoidoscopy was performed on the day of first IFX optimization and at week 8 in all patients with ulcerative colitis (UC). MH was defined by fecal calprotectin, 250 mg/g stools in Crohn's disease (CD) and by an endoscopic Mayo score of 0 or 1 in UC.

RESULTS: This study included 52 patients with IBD: 34 patients with CD (mean Crohn's Disease Activity Index, 300; mean C-reactive protein, 28 ± 10 mg/L; mean fecal calprotectin, 705 ± 300 mg/g) and 18 patients with UC (mean Simple Clinical Colitis Activity Index, 7; mean Mayo endoscopic score, 3). **After IFX dose intensification, half of CD and UC patients achieved MH**. Increase in IFX trough levels (called "delta IFX" in micrograms per milliliter) was associated with MH in both CD and UC (P = 0.001). **A delta IFX >0.5 mg/mL was associated with MH (sensitivity [se], 0.88; specificity [sp], 0.77; P = 0.0001, area under the receiver operating characteristic curve, 0.89)**. On multivariate analysis, the only **factor associated with MH after IFX optimization was a delta IFX >0.5 mg/mL** (likelihood ratio = 2.02; 95% confidence interval, 1.01–4.08; P = 0.048) in patients with IBD.

CONCLUSION: Therapeutic drug monitoring of IFX strongly predicts the likelihood of achieving MH following IFX dose intensification in both CD and UC.

KEY POINTS



(Left) Figure 1. A, Histogram representing the percentage of clinical remission in patients with IFX<2µg/mL, IFX<2 µg/mL + ATI <200 ng/mL or IFX >2 µg/mL before optimization. **(Right) Figure 2. B,** Histogram representing the percentage of MH in patients with IFX <2 µg/mL, IFX <2 µg/mL + ATI <200 ng/mL or IFX >2 µg/mL before optimization.

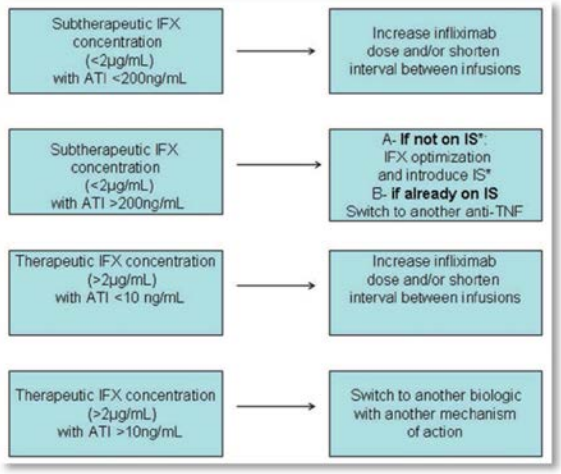


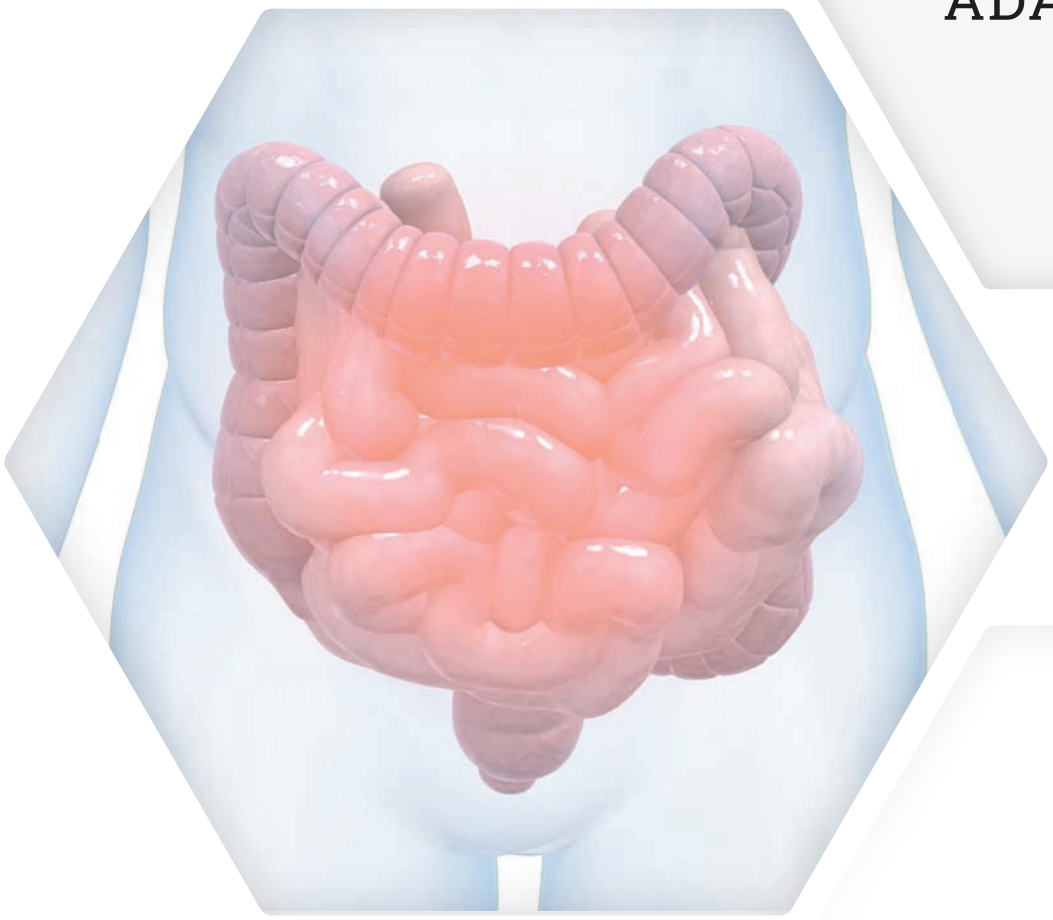
Figure 4. C, Proposed treatment algorithm based on the results of therapeutic drug monitoring of IFX. Asterisk indicates immunosuppressive therapy (IS).

- The study reports results from 2 different studies:
1) a cross-sectional/observational study (103 patients) showing that a cut-off of 200ng/mL for ATI could discriminate responders to IFX from nonresponders (AUROC= 0.61). Moreover, a threshold of less that 2µg/mL for IFX trough level was strongly associated with the absence of clinical remission (CR) in both CD and UC patients.
2) the first prospective and interventional study (52 patients) investigating the clinical utility of isolated cut-offs in prediction of CR and MH rates following dose intensification in both CD and UC patients.
All patients with ATI levels >200ng/mL did not respond to IFX optimization, whereas all patients with IFX trough levels <2µg/mL and ATI levels <200ng/mL responded to IFX dose intensification. Results need to be confirmed on larger scaled cohorts.

ATI and IFX trough level quantifications appear to be helpful to predict CR and MH in IBD patients. Authors propose a new treatment algorithm to help decision making in clinical practice.

Anti-TNFα

INFLIXIMAB



Anti-TNFα

ADALIMUMAB

IFX/ADA

IBD

2020

ADDITION OF AZATHIOPRINE TO THE SWITCH OF ANTI-TNF IN PATIENTS WITH IBD IN CLINICAL RELAPSE WITH UNDETECTABLE ANTI-TNF TROUGH LEVELS AND ANTIDRUG ANTIBODIES: A PROSPECTIVE RANDOMISED TRIAL

Roblin X , Williet N , Boschetti G , Phelip JM , Del Tedesco E , Berger AE , Vedrines P , Duru G , Peyrin-Biroulet L, Nancey S , Flourie B , Paul S

*Department of Gastroenterology, CHU Saint Etienne, France

ABSTRACT

BACKGROUND: In patients with IBD experiencing an immune-mediated loss of response (LOR) to antitumour necrosis factor (anti-TNF), algorithms recommend a switch of anti-TNF without immunosuppressive drug. The aim of our study was to compare in these patients two strategies: either switch to a second anti-TNF alone or with addition of azathioprine (AZA). After randomisation outcomes (time to clinical and pharmacokinetic failure) were compared between the two groups during a 2-year follow-up period.

METHODS: Consecutive IBD patients in immune-mediated LOR to a first optimised anti-TNF given in monotherapy were randomised to receive either AZA or nothing with induction by a second anti-TNF in both arms. Clinical failure was defined for Crohn's disease (CD) as a Harvey-Bradshaw index ≥5 associated with a faecal calprotectin level >250 µg/g stool and for UC as a Mayo score >5 with endoscopic subscore >1 or as the occurrence of adverse events requiring to stop treatment. Unfavourable pharmacokinetics of the second anti-TNF were defined by the appearance of undetectable trough levels of anti-TNF with high antibodies (drug-sensitive assay) or by that of antibodies (drug-tolerant assay).

RESULTS: Ninety patients (48 CDs) were included, and 45 of them received AZA after randomisation. The second anti-TNF was adalimumab or infliximab in 40 and 50 patients, respectively. Rates of clinical failure and occurrence of unfavourable pharmacokinetics were higher in monotherapy compared with combination therapy (p<0.001; median time of clinical failure since randomisation 18 vs >24 months). At 24 months, survival rates without clinical failure and without appearance of unfavourable pharmacokinetics were respectively 22 versus 77% and 22% versus 78% (p<0.001 for both) in monotherapy versus combination therapy. Only the use of combination therapy was associated with favourable outcomes after anti-TNF switch.

CONCLUSIONS: In case of immune-mediated LOR to a first anti-TNF, AZA should be associated with the second anti-TNF.

KEY POINTS

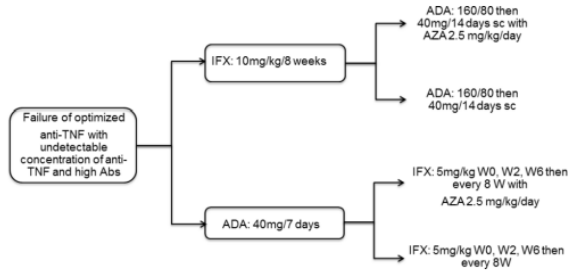


Figure 1. Design of the randomised prospective study. Abs, antibodies; ADA, Adalimumab, ; AZA, azathioprine; IFX, Infliximab;TNF, tumour necrosis factor; W, week. .

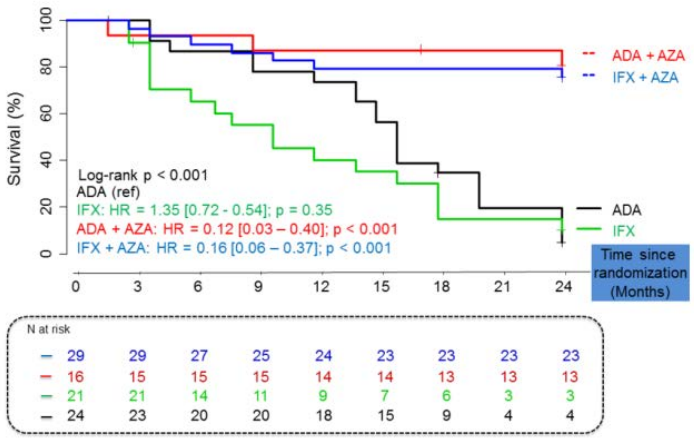


Figure 6. Evolution without unfavourable pharmacokinetics using a drug-sensitive assay according to treatment; ADA, adalimumab; AZA, azathioprine; IFX, infliximab

- This study pointed out the value of a combination therapy of Azathioprine with a second anti-TNF after loss of response to a first anti-TNF

- Clinical and pharmacokinetic evolution is significantly more favourable after a switch to a second anti-TNF with azathioprine compared to a switch without azathioprine

- At 6 months, the percentages of patients without pharmacokinetic failure were 90% and 75% under combination of treatment and monotherapy respectively (p=0.7)

- At 24 months 87% of patients who were in clinical failure had developed unfavourable pharmacokinetics of the second anti-TNF

- At 24 months, survival rates without clinical failure and without appearance of unfavourable pharmacokinetics were respectively 22 versus 77% and 22% versus 78% (p<0.001 for both) in monotherapy versus combination therapy.

- Using a Cox regression model, only the factor combination of treatment was significantly associated with an evolution without pharmacokinetic failure (p<0.001)

After loss of response to a first anti-TNF, the use of combination therapy is significantly associated with favourable outcomes after anti-TNF switch

IFX & ADA

IBD

2017

THE ASSOCIATION BETWEEN DRUG LEVELS AND ENDOSCOPIC RECURRENCE IN POSTOPERATIVE PATIENTS WITH CROHN'S DISEASE TREATED WITH TUMOR NECROSIS FACTOR INHIBITORS

Shmuel Fay, MD,* Bella Ungar, MD,* Stephane Paul, MD, Asaf Levartovsky, MD,* Miri Yavzori, PhD,* Ella Fudim, PhD,* Orit Picard, PhD,* Rami Eliakim, MD,*Shomron Ben-Horin, MD,* Xavier Roblin, MD, and Uri Kopylov, MD*

*Department of Gastroenterology, Sheba Medical Center, Ramat Gan, Israel

ABSTRACT

BACKGROUND: Endoscopic recurrence is associated with a risk of clinical recurrence in patients with Crohn's disease after ileocecal or small bowel resection. **Drug levels and presence of antidrug antibodies are associated with important clinical and endoscopic outcomes in patients with Crohn's disease treated with tumor necrosis factor inhibitors**, such association was not evaluated for endoscopic postsurgical recurrence.

METHODS: Consecutive patients with Crohn's disease treated with anti–tumor necrosis factors after surgery were identified in the databases of the participating centers. Anti–tumor necrosis factor levels and antidrug antibodies were correlated with Rutgeerts score on colonoscopy performed ≥ 6 months postoperatively. **Significant endoscopic recurrence (SER) was defined as Rutgeerts score > 2**.

RESULTS: Seventy-three consecutive patients (32-infliximab, 41-adalimumab) were included in the study. The colonoscopies were performed after a median of 15 (7–43) months after surgery and 8 (6–15) months from treatment onset. SER was demonstrated in 26/73 (35.6%) of the patients. The need for dose optimization, as well as trough infliximab levels (2.4 μg/mL [0.45–4.1] versus 1.1 (0–0.6), P = 0.008) and presence of antidrug antibodies (1/18 [5.6%] versus 10/14 [71.4%], P = 0.0001) were significantly associated with a risk of SER. **The optimal cutoff infliximab level for prediction of SER was 1.8 μg/mL**. **No association between adalimumab levels and antiadalimumab antibodies was demonstrated**.

KEY POINTS

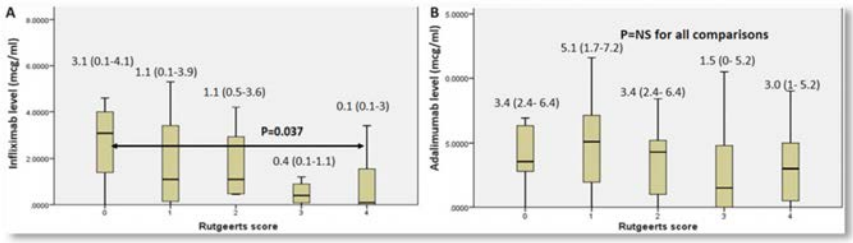


Figure 1. IFX (A) and ADA (B) levels stratified by Rutgeerts score (RS). Data labels apply to median levels and interquartile ranges. P values were calculated using the Kruskal–Wallis test.

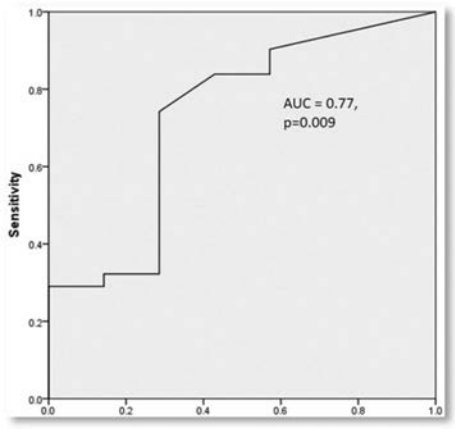


Figure 2. Receiver operator curve analysis for prediction of significant endoscopic relapse by trough IFX levels. AUC, area under the curve.

- In this study, trough anti-TNF levels and antidrug antibodies quantification evaluated by two different immunoassays provided similar clinical information

- Lower trough IFX levels (cut-off < 1,8 μg/mL) are associated with higher risk of endoscopic recurrence (Rutgeerts score >1 or >2) as shown by the predictive SER value (AUC = 0.77). Such result is also observed in anti-TNF-naïve patients (N=20)

- In this study, dose optimisation for IFX appears as the only clinical parameter associated with the risk of endoscopic recurrence

- Confirmation of the results in a large prospective setting is needed

This small retrospective study supports the hypothesis that low IFX trough levels as well as presence of anti-IFX antibodies are correlated with endoscopic recurrence regardless of the RS cut-off value

IFX & ADA

IBD

2016

UTILISATION OF ANTI-TNF LEVELS IN A UK TERTIARY IBD CENTRE

L Johnston*,B D Warner*, J L Digby-Bell*, N Unsworth, S Anderson*,J D Sanderson*, Z Arkir, P M Irving*

*Department of Gastroenterology, Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK

ABSTRACT

OBJECTIVE: To ascertain how anti-tumour necrosis factor (TNF) drug and anti-drug antibody levels testing is used in a 'real-world' setting to optimise inflammatory bowel disease (IBD) treatment.

METHODS:
Design Retrospective cohort study of prospectively collected patient data.
Setting Tertiary IBD centre in London, UK.
Patients All patients at Guy's and St Thomas' Hospitals on anti-TNF who had levels measured between the start of testing in 2012 and October 2014.
Interventions Anti-TNF drug and anti-drug antibody levels as part of routine monitoring.
Main outcome measures Indication for measuring levels and changes in management made as a result of the levels.

RESULTS: 330 infliximab levels were carried out in 199 patients and 143 adalimumab levels were carried out in 103 patients. Levels were primarily done in those with evidence of loss of response; 37% of infliximab levels and 52% of adalimumab levels. **Levels resulted in a change in management in 26% of patients in infliximab group and 25% of patients in adalimumab group; however, this was greater in those with loss of response, 62% and 61% respectively.** Anti-drug antibodies were detected in 7% of patients.

CONCLUSIONS: Our early experience has demonstrated that **measuring anti-TNF drug and anti-drug antibody levels can be useful in the optimisation of IBD management**. In an increasing number of patients, particularly those with evidence of loss of response, it allows early decisions to be made regarding changing therapy. It also offers the potential for significant cost-saving by preventing pointless dose escalation in the context of therapeutic levels or when high-level anti-drug antibodies are present.

KEY POINTS

Indication for performing DLs	No. of IFX DLs performed (total=330)	No. of IFX DLs that contributed to a change in management (total=87)	No. of ADA DLs performed (total=143)	No. of ADA DLs that contributed to a change in management (total=36)
Loss of response	122 (37%)	54 (62%)	74 (52%)	22 (61%)
After standard induction therapy (weeks 12–14)	32 (10%)	4 (5%)	5 (3%)	1 (3%)
Annual reassessment	97 (29%)	8 (9%)	38 (27%)	2 (6%)
After a change in dose of anti-TNF	57 (17%)	12 (14%)	5 (3%)	1 (3%)
Consideration of withdrawal of anti-TNF	10 (3%)	4 (5%)	3 (2%)	1 (3%)
Consideration of dose reduction of anti-TNF	10 (3%)	5 (6%)	17 (12%)	9 (25%)
Consideration of withdrawal of concomitant immunosuppression	2 (<1%)	0	1 (<1%)	0

ADA, adalimumab; DL, drug level; IFX, infliximab; TNF, tumour necrosis factor.

Table 1. Indications for measuring DLs and the percentage of each indication that contributed to a change in management for both IFX and ADA

- The study presents the benefits of Therapeutic Drug Monitoring (TDM) in a UK real-world experience based on a single centre.

- Although, the lack of standardization between assays for Drug levels (DLs) and Anti-TNF antibodies detection, authors report the positive impact of such monitoring on clinical practice in IBD patients under IFX or ADA treatments.

- Measuring levels facilitates early decisions to be made regarding escalation, optimisation of concomitant immunomodulator or drug switch for up to 3/4 of the cases. It is even more helpful in patients with evidence of loss of response.

- The study reveals significant cost savings by implementing TDM in routine (6038 € versus 9178 € in an IFX cohort p<0.001).

Therapeutic Drug Monitoring	Drug level cut-offs in the study
IFX measured at trough level	>2 µg/mL
ADA at any time point in the treatment cycle	>5 µg/mL

This retrospective study highlights that TDM has the potential to become a standard of care in routine testing and algorithm-driven management for IBD patients.

IFX & ADA

IBD

2017

INFLIXIMAB AND ADALIMUMAB DRUG LEVELS IN CROHN'S DISEASE: CONTRASTING ASSOCIATIONS WITH DISEASE ACTIVITY AND INFLUENCING FACTORS

M. G. Ward*, B. Warner, N. Unsworth, S.-W. Chuah, C. Brownclark, S. Shieh, J. D. Sanderson*, Z. Arkir, J. Reynol, P. R. Gibson, M. Parkes P. M. Irving*

* Department of Gastroenterology, Guy's and St. Thomas' NHS Foundation Trust, London, UK

ABSTRACT

BACKGROUND: Discriminative drug level thresholds for disease activity endpoints in patients with Crohn's disease have been consistently demonstrated with infliximab, but not adalimumab.

AIMS: To identify threshold concentrations for infliximab and adalimumab in Crohn's disease according to different disease endpoints, and factors that influence drug levels.

METHODS: We performed a cross-sectional service evaluation of patients receiving maintenance infliximab or adalimumab for Crohn's disease. Serum drug levels were at trough for infliximab and at any time point for adalimumab. Endpoints included Harvey-Bradshaw index, C-reactive protein and faecal calprotectin. 6-tioguanine nucleotide (TGN) concentrations were measured in patients treated with thiopurines.

RESULTS: A total of 191 patients (96 infliximab, 95 adalimumab) were included. Differences in infliximab levels were observed for clinical (P=.081) and biochemical remission (P=.003) and faecal calprotectin normalisation (P<.0001) with corresponding thresholds identified on ROC analysis of 1.5, 3.4 and 5.7 μg/mL. Adalimumab levels were similar between active disease and remission regardless of the endpoint assessed. Modelling identified that higher infliximab dose, body mass index and colonic disease independently accounted for 31% of the variation in infliximab levels, and weekly dosing, albumin and weight accounted for 23% of variation in adalimumab levels. TGN levels did not correlate with drug levels.

CONCLUSIONS: **Infliximab drug levels are associated with the depth of response/remission in patients with Crohn's disease, but no such relationship was observed for adalimumab.** More data are needed to explain the variation in drug levels.

KEY POINTS

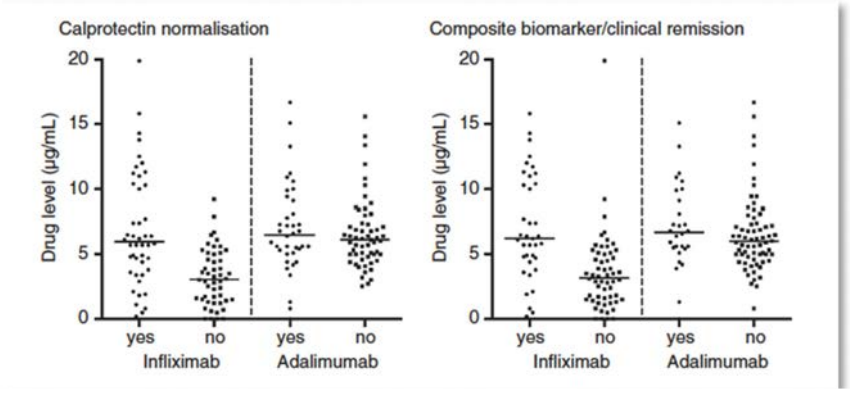


Figure 1 Scatterplots of relationship between infliximab (n=96) and adalimumab (n=95) drug levels and disease indices. Significant differences in infliximab levels were observed for biochemical remission (4.9 vs 2.1 μg/mL, P=.003), calprotectin normalisation (6.0 vs 3.1 μg/mL, P<.0001) and composite remission (6.2 vs 3.2 μg/mL P<.0001). No difference in adalimumab drug levels was observed for any endpoint (P>.15), (Mann-Whitney test). Horizontal bars represent median drug levels.

Drug	Remission type	AUC[95% CI]	*P*-value	Cut-off
Infliximab				
	Clinical	0.67 [0.48, 0.86]	.081	>1.5
	Biochemical	0.71 [0.58, 0.84]	.003	>3.4
	Calprotectin normalisation	0.77 [0.68, 0.87]	<.0001	>5.7
Adalimumab				
	Clinical	0.61 [0.44, 0.77]	.157	>5.1
	Biochemical	0.49 [0.32, 0.67]	.971	>8.5
	Calprotectin normalisation	0.54 [0.42, 0.66]	.436	>7.2

Table 2. Result from ROC curve analysis of Infliximab and adalimumab drug levels associated with remission according to endpoint. Cut-off thresholds reported in mg/mL and calculated using Youden Index.

- The study addresses complex pharmacokinetic dynamics differences between IFX and ADA monoclonal antibodies operating in biological systems. From this retrospective study, the authors explore drug levels that may influence such paradigm
- The analysis is based on the drug exposure (optimal threshold) and expected response in relation to the single or composite therapeutic endpoints: clinical remission, biochemical remission and calprotectin normalisation
- Results show that significant IFX drug levels/thresholds is observed according to different indices of disease activity and remission. This relationship between high cut-offs needed to achieve disease control is not observed for ADA

IFX and ADA drug/trough levels show contrasting pharmacokinetic dynamics in CD during maintenance therapy, suggesting different approaches in making therapeutic decisions and patient monitoring according to the monoclonal antibody used

IFX & ADA

IBD

2015

COST SAVINGS OF ANTI-TNF THERAPY USING A TEST-BASED STRATEGY VERSUS AN EMPIRICAL DOSE ESCALATION IN CROHN'S DISEASE PATIENTS WHO LOSE RESPONSE TO INFLIXIMAB

Xavier Roblin, MD*, Alain Attar, MD, PhD, Michel Lamure, PhD, Bernard Savarieau, MD, Pierre Brunel, PharmaD, Gérard Duru, PhD and Laurent Peyrin-Biroulet, MD, PhD

*Department of Gastroenterology, University Hospital of Saint Etienne, Saint-Etienne, France

ABSTRACT

BACKGROUND: The use of pharmacokinetics is associated with cost savings in anti-tumor necrosis factor (anti-TNF) therapy, but the long-term cost savings in a large cohort of Crohn's disease (CD) patients are unknown.

AIM: The goal of this study was to compare the cost of anti-TNF therapy in two cohorts of CD patients losing response to infliximab, one using a test-based strategy and one an empirical dose escalation.

METHODS: We used a selected mathematical model to describe the trajectories of CD patients based on a discrete event system. This design allowed us to track over a given period a double cohort of patients who moved randomly and asynchronously from one state to another, while keeping all the information on their entire trajectory. **Both cohorts were modeled using state diagram parameters where transition probabilities from one state to another are derived from literature data. Costs were estimated based on the French health care system**.

RESULTS: **Cost savings among the 10,000 CD patients using a test-based strategy were €131,300,293 at 5 years. At 5 years the mean cost saving was €13,130 per patient. The direct cost of the test had no impact on the results until the cost per test reached €2,000**.

CONCLUSIONS: **A test-based strategy leads to major cost savings related to anti-TNF therapy in CD**.

KEY POINTS

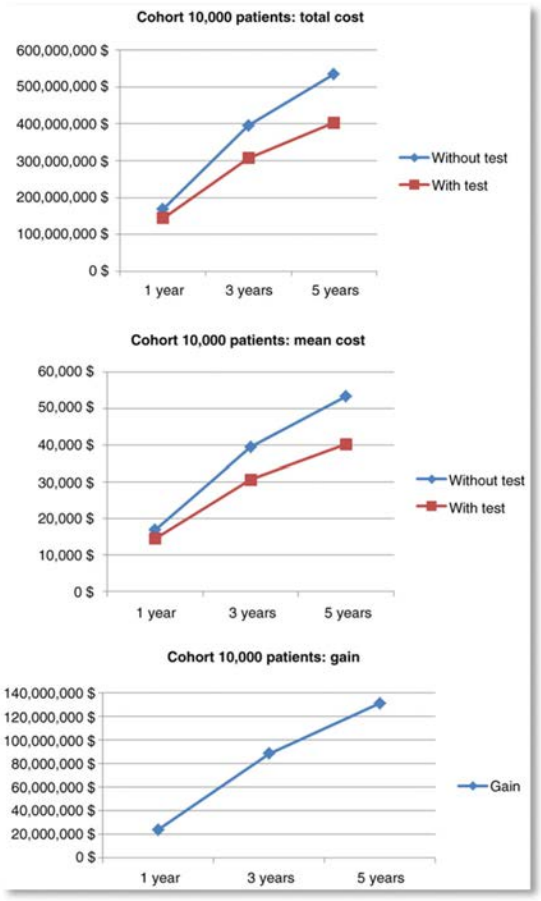


Figure 4. Comparative costs of anti-TNF drugs for the two strategies in 10,000 CD patients.

- This is the first study to report a cost savings analysis of anti-TNF treated IBD patients on a 5-year period, by using a test-based strategy against the clinical empirical scenario.
- To simulate the adaptative and complex system describing the multiple events observed for one patient during the course of its treatment, the authors have used a computational model based on discrete events. Three hypotheses were set up according to the clinical outcomes: IFX > 3mg/mL, no anti-TNF drug antibody (ADAb); IFX <3mg/mL, positive ADAb and IFX<3mg/mL, negative ADAb.
- Direct costs savings of anti-TNF therapy amount to 14,1%, 22,4% and 24,5% of total costs at 1, 3 and 5 years respectively.
- Data extrapolation to other healthcare systems has yet to be determined.

As anti-TNF agents are increasingly used worldwide for the treatment of immune mediated inflammatory diseases, significant health care costs reduction could be made on the long term by applying Therapeutic Drug Monitoring.

Aliment Pharmacol Ther, Volume 42, Number 3, Aug 2015 – anti-TNF drug discontinuation in IBD patients

IFX & ADA

IBD

2015

UNDETECTABLE ANTI-TNF DRUG LEVELS IN PATIENTS WITH LONG-TERM REMISSION PREDICT SUCCESSFUL DRUG WITHDRAWAL

S. Ben-Horin*, Y. Chowers, B. Ungar*, U. Kopylov*, R. Loebstein, B. Weiss, R. Eliakim*, E. Del Tedesco, S. Paul & X. Roblin.

*Department of Gastroenterology, Sheba Medical Center, Tel Hashomer, Israel.

ABSTRACT

BACKGROUND: Low drug levels are associated with emerging loss of response to anti-TNF. However, this may not be the case in patients with long-term remission.

AIM: To investigate the outcome of anti-TNF discontinuation in patients with long-term remission and incidental undetectable drug levels.

METHODS: A retrospective cohort study examining the duration of relapse-free survival in IBD patients in remission who discontinued infliximab or adalimumab having undetectable drug levels.

RESULTS: Forty eight patients who discontinued anti-TNF while in remission and had available drug levels were identified in two centres in France and Israel (infliximab-treated 35, adalimumab-13, Crohn' s disease 30, ulcerative colitis 18, mean treatment duration of 22.7 ± 12.4 months). Endoscopy/MRE before stopping showed absence of active inflammation in 40/42 (95%) of evaluated patients, while inflammatory biomarkers (CRP and/or Calprotectin) were completely normal in only 31/48 (65%) of patients. During 12 months median follow-up, **relapse occurred in 16/20 (80%) of patients who stopped anti-TNF while having measurable drug levels compared with 9/28 (32%) of patients who had undetectable drug levels (OR: 8.4, 95% CI: 2.2- 32, P = 0.002). Relapse-free survival after anti-TNF cessation was significantly longer in patients with absent drug compared to those with detectable drug (P < 0.001, log rank test).** On multivariate analysis, a patient' s decision to stop therapy was weakly associated and abnormal inflammatory biomarkers and detectable drug levels were both strongly and independently associated with a higher risk of relapse after drug discontinuation.

CONCLUSION: **Incidental finding of undetectable anti-TNF drug levels in patients with stable long-term deep remission may identify a subset of patients whose clinical remission is no longer dependent on anti-TNF treatment**.

KEY POINTS

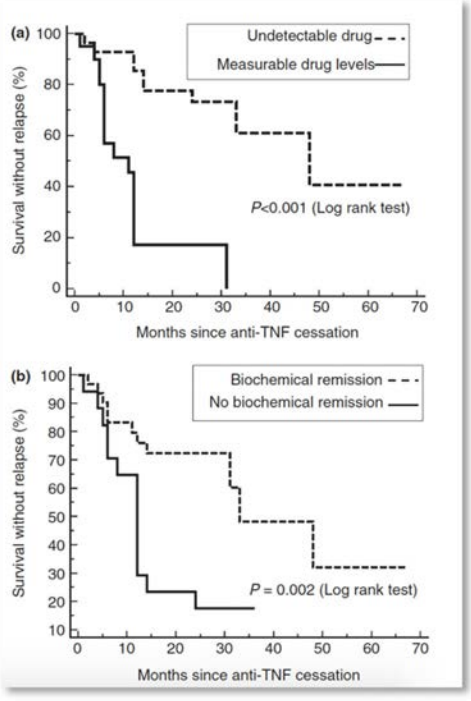


Figure 2. (a) Survival free of clinical relapse after anti-TNF discontinuation in patients with or without measurable anti-TNF drug levels before stopping. (b) Survival free of clinical relapse after anti-TNF disconti--nuation in patients with or without elevated biomarker indices of inflammation before stopping.

- There is unmet clinical need to identify patients in remission in whom anti-TNF discontinuation may be considered, from those at risk of relapse for whom a proactive approach is pertinent.

- The study explores the impact of TDM, biomarkers assessment as well as endoscopic or imaging evaluation before anti-TNF cessation on decision making and clinical outcomes in IBD patient in remission.

- Patient outcomes are depicted and show that the duration of relapse-free survival after drug discontinuation was significantly longer among patients who stopped the drug with undetectable drug level along with normal CRP and/or calprotectin levels compared to those with detectable drug and elevated inflammatory biomarkers.

The study emphasizes the need to evaluate the risk-benefit of discontinuing biotherapy with IBD patients in remission by monitoring the drug levels and inflammatory biomarkers prior drug cessation.

IFX & ADA

IBD & RA

2017

COST-EFFECTIVENESS OF DRUG MONITORING OF ANTI-TNF THERAPY IN INFLAMMATORY BOWEL DISEASE AND RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW

Laura Martelli, Pablo Olivera, Xavier Roblin, Alain Attar, Laurent Peyrin-Biroulet*

*Department of Hepato-Gastroenterology, University Hospital of Nancy-Brabois, Vandoeuvre-lès-Nancy,France

ABSTRACT

BACKGROUND: Therapeutic drug monitoring (TDM) of anti-TNF is increasingly used to manage inflammatory bowel diseases (IBD) and rheumatoid arthritis (RA). The cost-effectiveness of this strategy is debated.

METHODS: All studies comparing the cost-effectiveness of a TDM-based strategy and an empirical dose management of anti-TNF in IBD or RA were screened. Studies were identified through the MEDLINE electronic database (up to July 2016), and annual international meeting abstracts were also manually reviewed.

RESULTS: Seven studies were included: two randomized controlled trials (RCTs) enrolling 332 patients [247 Crohn's disease (CD) and 85 ulcerative colitis (UC)] and five modeling approaches. Four studies included only CD patients, one included both CD and UC patients, and two included only RA patients. Three studies compared the cost-effectiveness of the two strategies in patients with secondary infliximab (IFX) failure (dose-escalation strategy), one in patients in remission on optimized IFX (de-escalation strategy), one in patients starting adalimumab, and two in patients with clinical response to maintenance anti-TNF therapy. The two RCTs demonstrated that **a TDM strategy led to major cost savings, ranging from 28 to 34 %. The three modeling approaches with regard to CD patients demonstrated cost savings ranging from $5396 over a 1-year period to €13,130 per patient at 5 years of follow-up**. **A TDM strategy also led to major cost savings in the two modeling approaches in RA patients.**

CONCLUSIONS: **Available evidence indicates that a TDM strategy leads to major cost savings related to anti-TNF therapy in both IBD and RA patients, with no negative impact on efficacy.**

KEY POINTS

Study	Study design	Disease	Anti-TNF evaluated	Study duration (weeks)	Cost-effectiveness
Steenholdt et al. [18]	Randomized controlled trial	CD	Infliximab	12	Costs for intention-to-treat patients substantially lower (34 %) for patients treated with a TDM strategy than with an empirical dose escalation (€6038 vs. €9178, respectively) ($p < 0.001$)
Vande Casteele et al. [14]	Randomized controlled trial	IBD	Infliximab	52	Dose reduction of IFX in patients with a TC > the target resulted in a 28 % reduction in drug costs ($p < 0.001$). For the maintenance phase, TDM strategy was more cost-effective than clinically based strategy (€20,723 vs. €21,023, respectively, per patient, per year)
Velayos et al. [19]	Modeling approach (Markov model)	CD	Infliximab	52	TDM strategy yielded similar QALYs compared with the empirical dose escalation (0.801 vs. 0.800) but was more cost-effective ($31,870 vs. $37,266, respectively)
Roblin et al. [20]	Modeling approach (discrete event model)	CD	Infliximab	260	At 5 years, cost savings among the 10,000 CD patients using a test-based strategy were €131,300,293, and the mean cost saving per patient was €13,130
Krieckaert et al. [16]	Modeling approach (Markov model)	RA	Adalimumab	156	In 72 % of simulations, TDM strategy saved costs and resulted in more QALYs; in 28 %, it was cost-saving with lower QALYs
Laine et al. [17]	Modeling approach (Markov model)	RA	Infliximab and adalimumab	26	The combined measure of TC and ADAs was cost-saving compared to the non-testing scenario when the monitoring results affected the treatment decision in at least 2–5 of 100 patients
Attar et al. [22]	Modeling approach (discrete event model)	CD	Optimized infliximab	104	The test-based strategy of de-escalation led to cost savings of around 20 % per patient at 2-year follow-up

IBD inflammatory bowel diseases, *CD* Crohn's disease, *RA* rheumatoid arthritis, *TDM* therapeutic drug monitoring, *QALYs* quality-adjusted life-years, *TC* trough concentrations, *IFX* infliximab, *ADAs* anti-drug antibodies

Extract from Table 1. Characteristics of the studies included in the systematic review

- First review about cost effectiveness of a test-based strategy against empirical management of anti-TNF treatment in patients with IBD or RA.

- Computerized search based on specific key words along with a manual selection of studies showing common inclusion criteria and data allowed the authors to identify 7 studies to compare in this meta-analysis.

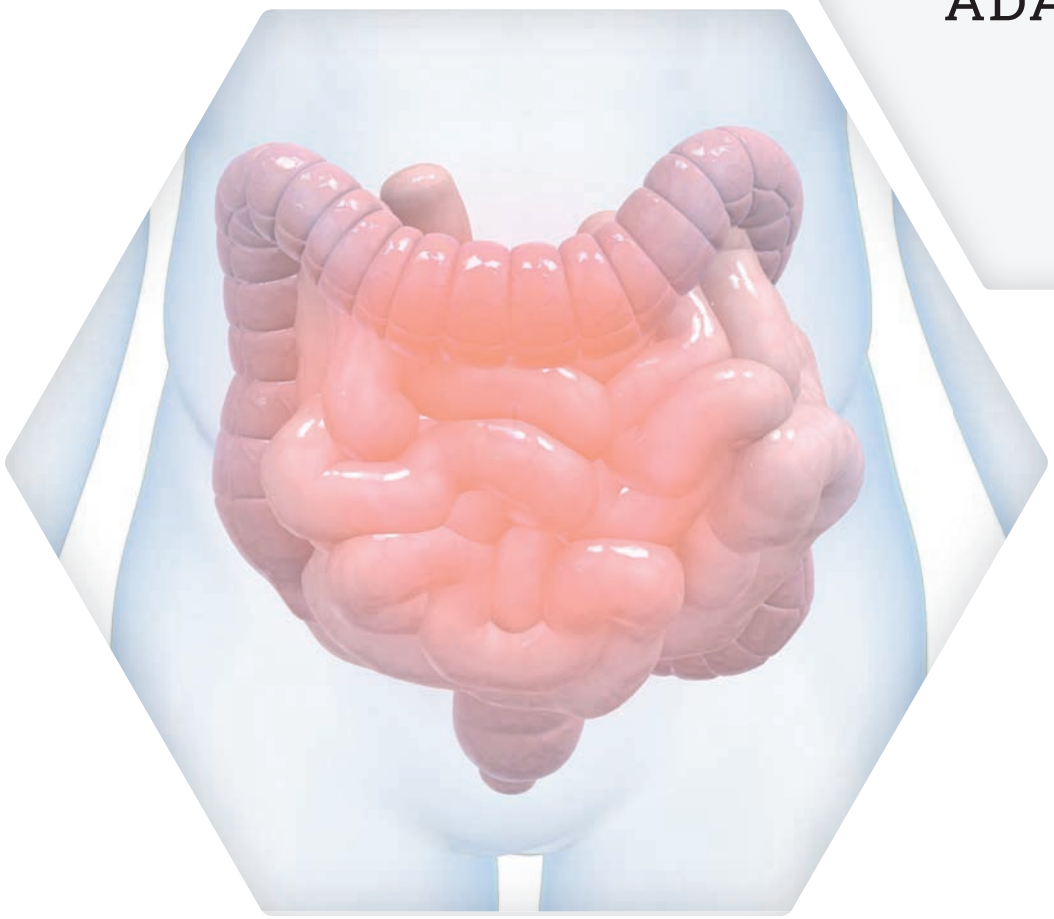
- The review reports the following criteria: study design, disease, targeted drug, study duration, methods used for the analysis, modeling approaches, clinical efficacy of anti-TNF therapy and cost-effectiveness data.

- The authors discuss the pros and cons of the different methodological approaches tested.

In the era of increasing use of biotherapies, the authors have highlighted the cost savings impact of a test-based strategy with Therapeutic Drug Monitoring of anti-TNF in both IBD and RA patients.

Anti-TNFα

ADALIMUMAB



ADA

IBD

2019

COMPARISON OF ADALIMUMAB WHEN DELIVERED BY PEN VERSUS SYRINGUE IN PATIENTS WITH INFLAMMATORY DISEASE. AN OBSERVATIONAL MULTICENTRE COHORT ANALYSIS

Little RD*, Chu IE, van der Zanden EP, Flanagan E, Bell SJ, Gibson PR, Sparrow MP, Shelton E, Connor SJ, Roblin X, Ward MG.

*Department of Gastroenterology, Alfred Health and Monash University, Melbourne, VIC, Australia

ABSTRACT

BACKGROUND: Adalimumab is administered via a pre-filled syringe or spring-loaded pen. In a previous study in Crohn's disease, higher drug levels were observed in syringe users. The aim of this study was to evaluate the impact of delivery device on adalimumab drug levels in patients with Crohn's disease.
METHODS: Consecutive Crohn's disease patients treated with maintenance adalimumab [40 mg fortnightly] were recruited from five centers. The first recorded drug level with matched clinical and biochemical markers of disease activity was compared between pen and syringe users.
RESULTS: Of 218 patients, 64% used pen, with a median faecal calprotectin 110 µg/g and serum C-reactive protein 4 mg/L. In comparison to pen, syringe users had higher albumin [39 vs 42 g/L; p = 0.016], lower Harvey-Bradshaw Index [2 vs 1; p = 0.017], and higher rates of concomitant immunomodulation [54% vs 71%; p = 0.014]. Drug levels were equivalent between pen and syringe users [median 5.3 vs 5.2 µg/ml; p = 0.584], even after controlling for disease activity and immunomodulation. Syringe users at Alfred Health had higher drug levels than pen [6.1 vs 4.5 µg/ml; p = 0.039]; a greater proportion achieved therapeutic levels [75% vs 44%; p = 0.045]. A higher proportion of pen users from Saint-Étienne had therapeutic levels [79% vs 42%; p = 0.027], yet no significant difference in drug levels [7.9 vs 4.5 µg/ml; p = 0.119]
CONCLUSIONS: Delivery device does not appear to significantly affect adalimumab drug levels. Given differences between study sites, studies evaluating administration education and technique are warranted.

KEY POINTS

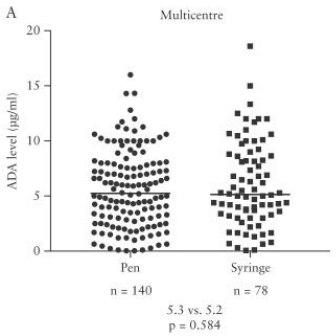


Figure 1. Multicentre adalimumab [ADA] drug levels according to delivery device. Values and horizontal bars reflect medians. Group comparisons via Mann-Whitney test.

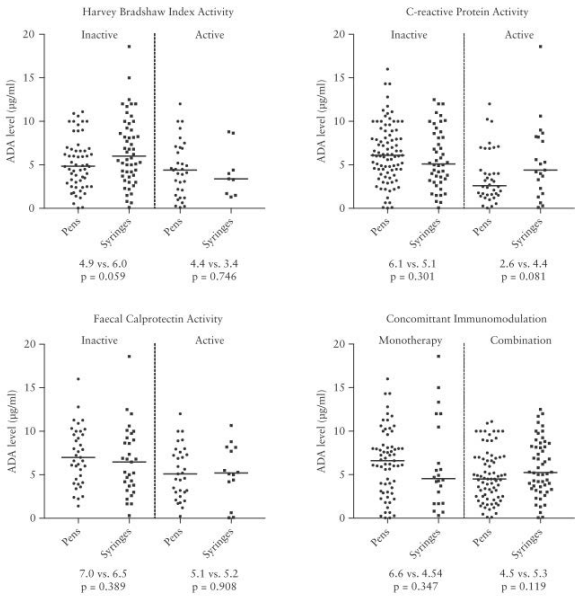


Figure 3. Adalimumab [ADA] levels according to delivery device dichotomised into disease activity or concomitant immunomodulation. Values and horizontal bars reflect medians. Group comparisons via Mann-Whitney test. Threshold for activity as follows: Harvey-Bradshaw Index >4; C-reactive protein >5mg/L; faecal calprotectin >150µg/g

- This study demonstrated no temporal difference in the effect of delivery device on disease outcomes after dose intensification over a 12-months follow-up

- No significant differences were found in drug levels between pen and syringue users overall. Serum concentrations of Adalimumab were equal between pen and syringue users [median 5.3 vs 5.2µg/ml; p=0,584]

- Drug levels did not differ between devices after controlling for clinical and biochemical markers of disease activity, the use of concomitant immunomodulators, and previous anti-TNF exposure

- There was no difference between delivery devices in the frequency of drug failure over a 12-months follow-up of in a small cohort of patients who were intensified to weekly adalimumab, on the basis of secondary loss of response and sub-therapeutic adalimumab drug levels

No delivery devices differences between pen and syringe among CD patients treated with adalimumab

ADA

IBD

2018

PROLONGED PERSISTENCE OF ADALIMUMAB TRANSFERRED FROM MOTHER TO INFANT DURING PREGNANCY

Remi Labetoulle*, Xavier Roblin, Stéphane Paul.

* University Hospital of Saint Etienne, Saint Priest en Jarez, France.

ABSTRACT

CASE REPORT

KEY POINTS

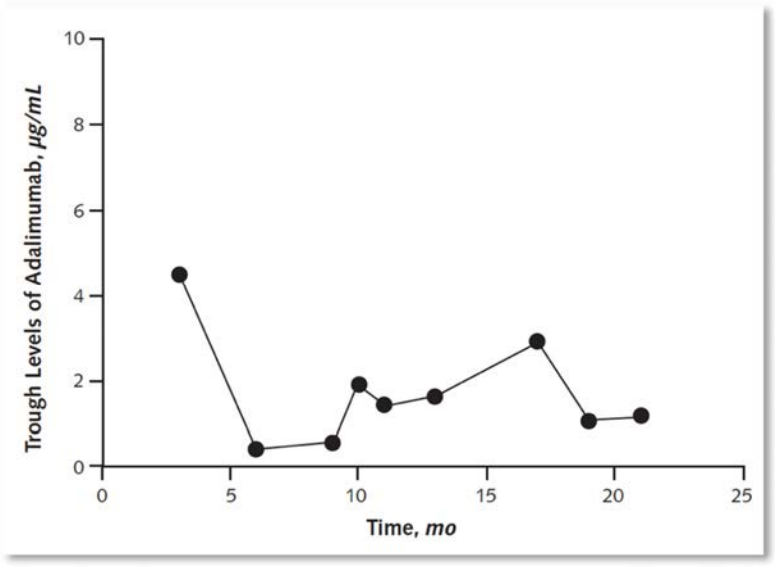


Figure. Trough levels of adalimumab in the infant.

- The objective of the report is to alert clinicians to the possibility of prolonged persistence of ADA in some patients.

This is the case for a 34-year-old woman in the first trimester of pregnancy who presented a clinical relapse of Crohn disease.

Patient information:

- ADA trough level: 3.5 µg/mL
- CDAI score: 240
- Faecal calprotectin level: 950 µg/g of stool
- Clinical decision: increase ADA dosage (40mg per week) until clinical remission and continued for the rest of the pregnancy;

- The infant ADA levels since birth are shown (see figure). Such persistence remains unclear.

- Authors recommend to monitor anti-TNF levels before administering live vaccines.

Delayed clearance of antibodies by immature endoplasmic reticulum may favor the persistence of anti-TNF treatments.

BMC Gastroenterology, Volume 17, Number 97, August 2017 – TDM in IBD

ADA

IBD

2017

DRUG PERSISTENCE AND NEED FOR DOSE INTENSIFICATION TO ADALIMUMAB THERAPY; THE IMPORTANCE OF THERAPEUTIC DRUG MONITORING IN INFLAMMATORY BOWEL DISEASES

Lorant Gonczi*, Zsuzsanna Kurti*, Mariann Rutka, Zsuzsanna Vegh*, Klaudia Farkas, Barbara D. Lovasz Petra A. Golovics*, Krisztina B. Gecse*, Balazs Szalay, Tamas Molnar and Peter L. Lakatos*

* First Department of Medicine, Semmelweis University, Koranyi S 2A, Budapest H-1083, Hungary

ABSTRACT

BACKGROUND: Therapeutic drug monitoring (TDM) aid therapeutic decision making in patients with inflammatory bowel disease (IBD) who lose response to anti-TNF therapy. Our aim was to evaluate the frequency and predictive factors of loss of response (LOR) to adalimumab using TDM in IBD patients.

METHODS: One hundred twelve IBD patients (with 214 TDM measurements, CD/UC 84/28, male/female 50/62, mean age CD/UC: 36/35 years) were enrolled in this consecutive cohort from two referral centres in Hungary. Demographic data were comprehensively collected and harmonized monitoring strategy was applied. Previous and current therapy, laboratory data and clinical activity were recorded at the time of TDM. Patients were evaluated either at the time of suspected LOR or during follow-up. TDM measurements were determined by commercial ELISA (LISA TRACKER, Theradiag, France).

RESULTS: Among 112 IBD patients, LOR/drug persistence was 25.9%/74.1%. The cumulative ADA positivity (>10 ng/mL) and low TL (<5.0 μg/mL) was 12.1% and 17.8% after 1 year and 17.3% and 29.5% after 2 years of adalimumab therapy. Dose intensification was needed in 29.5% of the patients. Female gender and ADA positivity were associated with LOR (female gender: $p < 0.001$, OR:7.8 CI 95%: 2.5–24.3, ADA positivity: $p = 0.007$ OR:3.6 CI 95%: 1.4–9.5).

CONCLUSION: **ADA development, low TL and need for dose intensification were frequent during adalimumab therapy and support the selective use of TDM in IBD patients treated with adalimumab. ADA positivity and gender were predictors of LOR.**

KEY POINTS

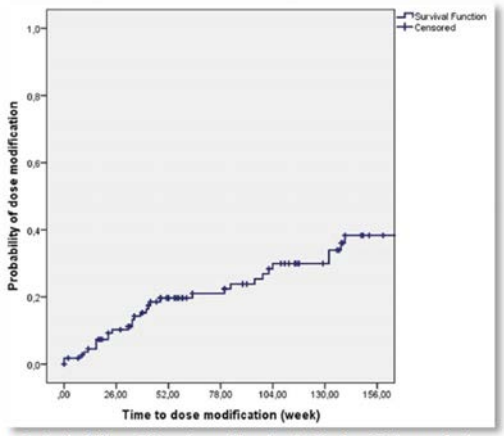


Figure 1. Probability of dose intensification in Kaplan-Meier analysis

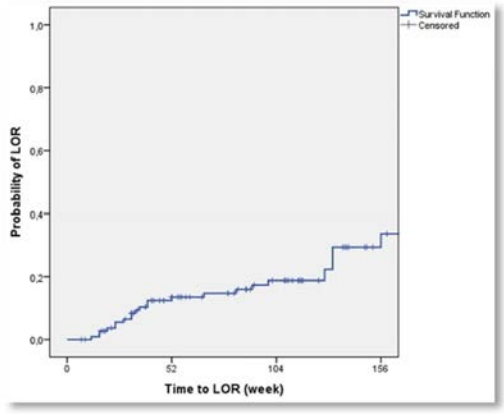


Figure 2. Probability of LOR in Kaplan-Meier an)alysis (LOR: loss of response)

- This prospective study reports that probability of dose intensification and LOR was 19,7% and 17,5% in the 1st year and 30% and 18,8% in the 2nd year of adalimumab therapy as show in figures 1 and 2.
- Results show a significant correlation between ADA positivity and LOR whereas no association between adalimumab trough levels (TL) and LOR was observed.
- LOR appears more frequent in patients with low TL (<5μg/mL) and high ADA levels during long-term therapy. However, no predictors for short term clinical response could be found.
- Dose intensification was associated with the need of steroid therapy in patient with CD (40.7% versus 19.6%, p=0.04).
- As very few studies have investigated the use of routine TDM in adalimumab therapy, further research may help define its usability and benefits.

This paper demonstrates the relevance of DTM assessment during adalimumab therapy in a small cohort of IBD patients. Drug trough levels and ADA positivity appear as major predictive factors in the management of disease activity.

ADA

IBD

2017

ADDITION OF AN IMMUNOMODULATOR CAN REVERSE ANTIBODY FORMATION AND LOSS OF RESPONSE IN PATIENTS TREATED WITH ADALIMUMAB

B. Ungar*, U. Kopylov*, T. Engel*, M. Yavzori*, E. Fudim*, O. Picard*, A. Lang*, N. Williet, S. Paul, Y. Chowers, A. Bar-Gil Shitrit, R. Eliakim*, S. Ben-Horin* & X. Roblin.

*Department of Gastroenterology, Sheba Medical Center Tel Hashomer, Tel-Aviv University, Israel.

ABSTRACT

BACKGROUND: Anti-adalimumab antibodies (AAA) are associated with loss of clinical response (LOR). Addition of an immunomodulator has been shown to reverse immunogenicity and regain response with infliximab monotherapy. Similar data on adalimumab are lacking.

AIM: To study the impact of immunomodulator addition on the emergence of AAA and LOR among adalimumab therapy patients.

METHODS: The databases of three tertiary medical centres were reviewed to identify patients who developed AAA during adalimumab monotherapy with resultant LOR, and received an immunomodulator as a salvage combination therapy. All sera were prospectively analysed using previously described ELISA assays. Clinical response was determined using appropriate clinical scores. Elimination of AAA, designated as ' sero-reversal', elevation of drug levels and regained clinical response were the sought outcomes.

RESULTS: **Twenty-three patients (21 Crohn' s disease, and 2 ulcerative colitis) developed AAA with subsequent LOR** and were thereafter prescribed an immunomodulator as salvage therapy (thiopurine n = 14, methotrexate n = 9). **Eleven patients (48%) underwent sero-reversal with gradual elimination of AAA**, increase in drug trough levels and restoration of clinical response (median time to sero-reversal 5 months). **In 12 patients (52%), immunogenicity and loss of response could not be reversed**. **There was no difference between responders and nonresponders in the type of immunomodulators used or baseline clinical characteristics.**

CONCLUSIONS: In almost half of inflammatory bowel disease patients developing anti-adalimumab antibodies and loss of response, established immunogenicity of adalimumab can be gradually reversed by the addition of immunomodulator therapy with restoration of a clinico-biological response. However, these observations need to be confirmed with larger studies.

KEY POINTS

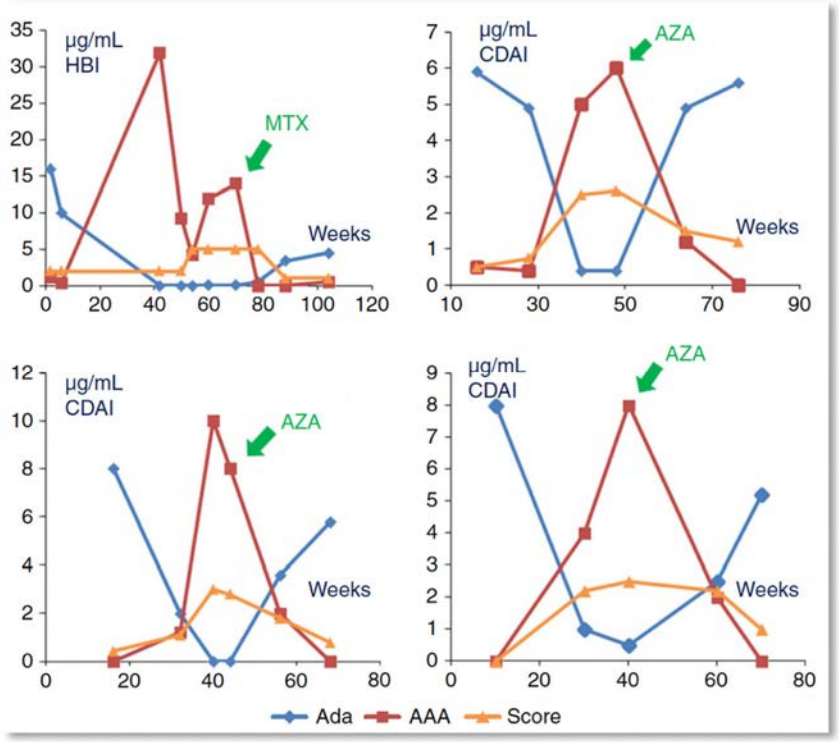


Figure 2. Clinical scores, serum adalimumab & AAA levels in relation to immunomodulator addition in four representative adalimumab therapy patients who have responded to the intervention. Ada, adalimumab; AAA, anti-adalimumab antibody; HBI, Harvey–Bradshaw index; CDAI, Crohn's disease activity index; MTX, methotrexate; AZA, azathioprine. *CDAI values were divided by 100 for graphical presentation.

- This small retrospective study reports the positive impacts of the addition of an immunomodulator in IBD patients with loss of response to adalimumab monotherapy.

- Clinical and immunological response occurred at a median of 5 months, implying that such strategy may not be suitable for very symptomatic patients.

- The Authors reports that no clinical or demographic factors could predict response to the immunomodulator addition.

- Larger scale studies are needed to identify predictive factors and establish optimal immunomodulator dosage.

Co-administration of an immunomodulator to adalimumab therapy appears as a worthwhile therapeutic strategy in case of immunogenic-mediated loss of response in selected moderated to severe IBD patients for whom the arsenal of therapeutic options is limited.

IFX & ADA

IBD

2015

STOOL ADALIMUMAB DETECTION IN ULCERATIVE COLITIS AND CROHN'S DISEASE

X. Roblin * & S. Paul

* Department of Immunology, University Hospital of Saint-Etienne, France.

ABSTRACT

LETTER

KEY POINTS

- Authors present a retrospective study of 36 IBD patients showing faecal calprotectin levels above 1800 µg/g stools. Faecal anti-TNF assays were conducted on all patients. Trough levels of anti-TNF drugs and antibodies were performed and analysed.

- Authors reported anti-TNF trough levels in stool of ulcerative colitis (UC: 22,7%) and Crohn's disease patients (CD: 10%).

- In all cases showing faecal anti-TNF, an endoscopy detected ulcers in the colonic mucosa.

- These data may explain the low serum ADA concentrations observed after induction treatment with an anti-TNF in patients with acute severe IBD.

Faecal anti-ADA can be detected in patients with CD as well as UC, irrespective of the anti-TNF used. The presence of colonic ulcers appears to be a pre-condition of intestinal leak.

ADA

IBD

2014

DEVELOPMENT OF AN ALGORITHM INCORPORATING PHARMACOKINETICS OF ADALIMUMAB IN INFLAMMATORY BOWEL DISEASES

Xavier Roblin* MD, PhD, M Rinaudo MD, E Del Tedesco MD, J M Phelip MD, PhD, C Genin MD, PhD, L Peyrin-Biroulet MD, PhD & S Paul PhD

*Service de Gastrologie-Entérologie-Hépatologie, CHU de Saint-Etienne, Saint-Etienne, France

ABSTRACT

OBJECTIVES: Several decision algorithms based on the measurement of infl iximab (IFX) trough levels and antibodies to IFX have been proposed. Whether such algorithms can be extrapolated to the pharmacokinetics of adalimumab (ADA) has yet to be determined.

METHODS: A prospective study included all consecutive patients with inflammatory bowel disease (IBD) having a disease fl are while being on ADA 40 mg every 2 weeks were included. All patients were primary responders to ADA therapy and were anti-tumor necrosis factor (TNF) naive. ADA trough levels and antibodies against ADA (AAA) were measured blinded to clinical data (Elisa LISA-Tracker, Theradiag). All patients were optimized with ADA 40 mg weekly. Four months later, in the absence of clinical remission (CR; Crohn's disease activity index < 150 for Crohn's disease (CD), and Mayo score < 2 for ulcerative colitis), patients were treated with IFX therapy. Patients were divided into three groups based on ADA trough levels and based on previous studies: group A, ADA > 4.9 µ g/ml; group B, ADA < 4.9 µg/ml and undetectable levels of AAA (< 10 ng/ml); and group C, ADA < 4.9 µg/ml and AAA > 10 ng /ml.

RESULTS: A total of 82 patients were included (55 % CD; mean age = 43 years, disease duration = 7.4 years, duration of ADA therapy = 17 months). After optimization of ADA treatment, 29.2 % of patients achieved CR in group A (N = 41), 67 % in group B (N = 24), and 12 % in group C (N = 17; P < 0.01 between groups A / B and B / C). C-reactive protein level at the time of relapse, disease duration, duration of ADA therapy, and IBD type was not predictive of CR after ADA optimization by univariate analysis. The response to ADA optimization was significantly more durable in group B (15 months) than in groups A and C (4 and 5 months, respectively). Fifty-two patients who failed following ADA optimization (63 %) were treated with IFX, and 30.6 % of them achieved CR. CR rates following IFX initiation were 6.9 %, 25 %, and 80 % in groups A, B, and C, respectively (P < 0.01 between groups C / A and between groups C / B). Duration of response to IFX was significantly higher in group C than in groups A and B (14 vs. 3 and 5 months, respectively, P < 0.01).

CONCLUSIONS: **The presence of low ADA trough levels without AAA is strongly predictive of clinical response in 67 % of cases after ADA optimization. Conversely, low ADA levels with detectable AAA are associated with ADA failure, and switching to IFX should be considered. ADA trough levels > 4.9 µ g / ml are associated with failure of two anti-TNF agents (ADA and IFX) in 90 % of cases, and switching to another drug class should be considered.**

KEY POINTS

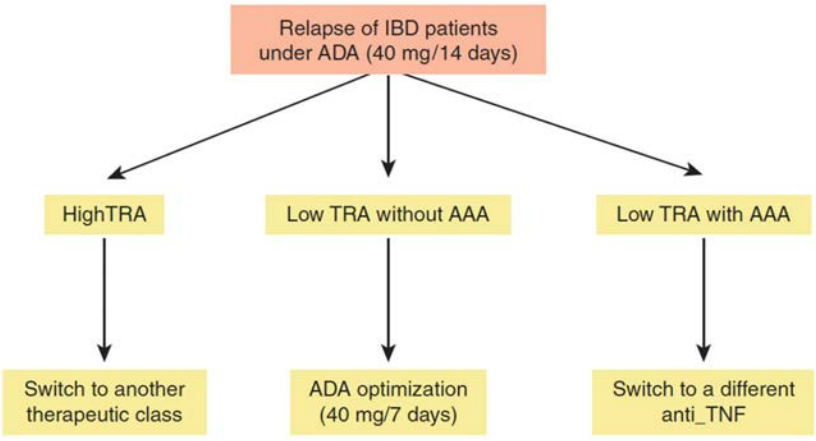


Figure 3. Therapeutic algorithm in function of TRA and antibodies against adalimumab (AAA) in patients with clinical relapse under adalimumab (ADA). IBD, inflammatory bowel disease; TNF, tumor necrosis factor; TRA, trough levels of adalimumab.

- The observational study was conducted in a blind manner between clinicians and immunologists as results of ADA and AAA levels were only available at the end of the study. CD and UC patient data were pooled and no influence of IBD type could be observed.

- The study shows that trough levels of ADA and anti-ADA antibody (AAA) levels influence the response to the switch to IFX therapy.

- The authors could demonstrate that non-responders under ADA therapy, showing high TRA, with no clinical improvement after dose escalation or switch to IFX, should be switched to a non-TNF inhibitor.

Managing loss of response to ADA treatment remains a challenge in clinical practice. The use of a new therapeutic algorithm associated with TRA and AAA levels may help decision making in IBD patients.

ADA

IBD

2014

ASSOCIATION BETWEEN PHARMACOKINETICS OF ADALIMUMAB AND MUCOSAL HEALING IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES

Xavier Roblin*, Hubert Marotte, Melanie Rinaudo, Emilie Del Tedesco*, Amelie Moreau*,Jean Marc Phelip*, Christian Genin, Laurent Peyrin-Biroulet and Stephane Paul

*Department of Gastroenterology, University Hospital of Saint Etienne, France

ABSTRACT

BACKGROUND & AIMS: Little is known about the association between pharmacokinetic features of adalimumab and mucosal healing in patients with inflammatory bowel disease (IBD).

METHODS: We conducted a **cross-sectional study of 40 patients with Crohn's disease (CD) or ulcerative colitis (UC)** who received adalimumab maintenance therapy and underwent endoscopic evaluation of disease activity and pharmacokinetic analysis (measurements of trough levels and antibodies against adalimumab). Patients in clinical remission were identified based on CD activity index scores less than 150 or Mayo scores less than 3 (for those with UC). Patients with mucosal healing were identified based on Mayo endoscopic scores less than 2 (for UC) or the disappearance of all ulcerations (for CD).

RESULTS: The median trough level of adalimumab was higher in patients in clinical remission (6.02 μg/mL) than in patients with active disease (3.2 μg/mL; P [.012). **Trough levels of adalimumab were also higher in patients with mucosal healing (6.5 μg/mL) than in patients without (4.2 μg/mL; P < .005). These results did not vary with type of IBD.** On multivariate analysis, trough levels of adalimumab (relative risk, 0.62; 95% confidence interval, 0.40–0.94; P [.026) and duration of adalimumab treatment (relative risk, 0.82; 95% confidence interval, 0.68–0.97; P[.026) were associated independently with healing mucosa. An absence of mucosal healing was associated with trough levels of adalimumab less than 4.9 μg/mL (likelihood ratio, 4.3; sensitivity, 66%; specificity, 85%).

CONCLUSIONS: Trough levels of adalimumab are significantly higher in IBD patients who are in clinical remission and in those with mucosal healing. Detection of antibodies against adalimumab predicts a lack of mucosal healing.

KEY POINTS

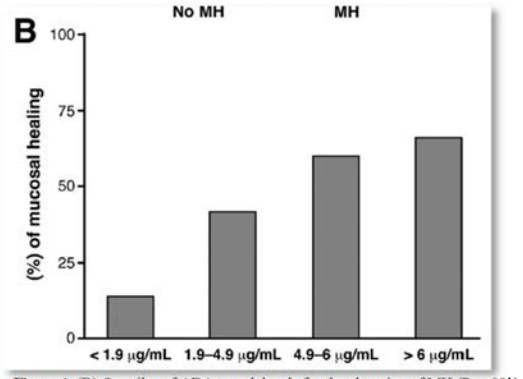


Figure 1. (B) Quartiles of ADA trough levels for the obtention of MH ($P = .001$).

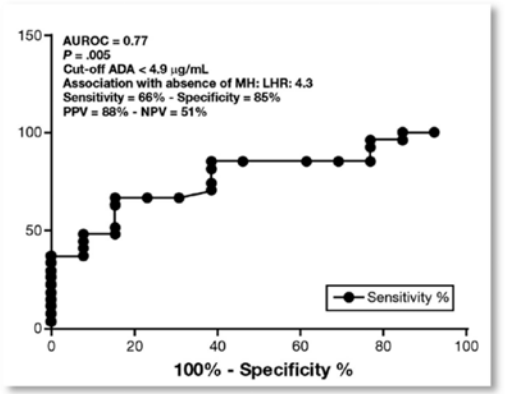


Figure 3. ROC curves for trough levels of ADA in IBD patients (MH vs no MH). NPV, negative predictive value; PPV, positive predictive value.

- This small study investigates the impact of therapeutic drug monitoring of ADA on clinical remission and mucosal healing rates in CD and UC patients.

- The analysis of quartiles shows a strong correlation between ADA trough levels and mucosal healing/clinical remission.

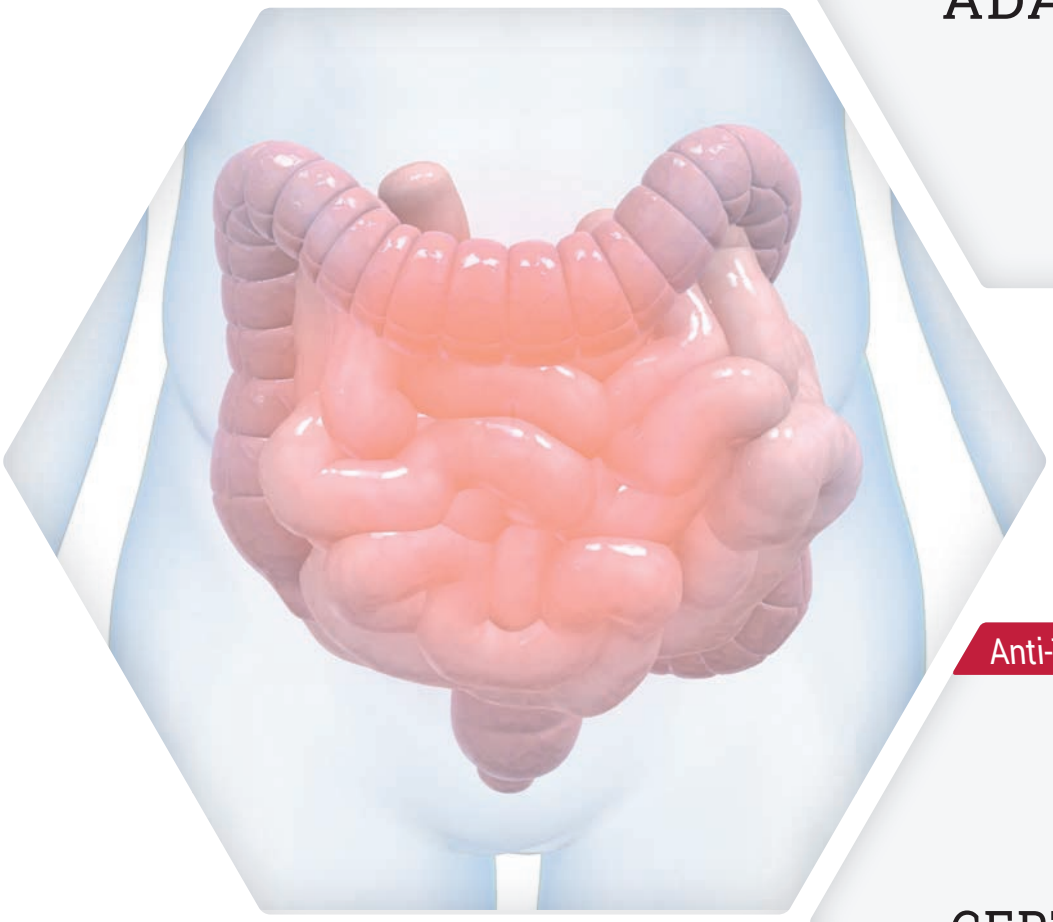
- Authors could identify the optimal cut-off values for ADA trough levels from 4.85 to 4.9 μg/mL for predicting disease outcome.

- 9 out of 40 patients had antibodies against ADA grater than 10ng/mL and only one was in clinical remission.

Therapeutic Drug Monitoring of ADA is associated with Clinical remission in IBD patients. Immunogenicity negatively influences the outcome of ADA treatement in patients.

Anti-TNFα

ADALIMUMAB



Anti-TNFα

CERTOLIZUMAB

ADA/CTZ

IBD

2019

ANTI-ADALIMUMAB AND ANTI-CERTOLIZUMAB ANTIBODIES TITERS AFTER DISCONTINUATION OF ADALIMUMAB: TWO CASES REPORTS

*Grossi V, Infantino M, Manfredi M, Basile U, Gulli F, Marino M, Li Gobbi F, Damiani A, Atzeni F, Benucci M

*Immunology and Allergology Laboratory Unit, San Giovanni di Dio Hospital, Via Torregalli 3, 50143 Florence, Italy

ABSTRACT

No abstracts available

.

KEY POINTS

Patient	Adalimumab (12 months after the last infusion), mg/mL	Anti-adalimumab abs (12 months after the last infusion), ng/mL	Certolizumab (6 months after the last infusion), mg/mL	Anti-certolizumab abs (6 months after the last infusion), ng/mL
#1	<0.3	>160	<0.4	158
#2	0.8	>160	<0.4	>160
	Adalimumab (36 months after the last infusion), mg/mL	Anti-adalimumab abs (36 months after the last infusion), ng/mL	Certolizumab (12 months after the last infusion), mg/mL	Anti-certolizumab abs (12 months after the last infusion), ng/mL
#1	<0.3	>160	0.5	>160
#2	<0.3	>160	0.4	>160

Table 1. Drug and ADAs assessments .

Patients	Adalimumab, µg/mL	Anti-adalimumab, AU/mL	Certolizumab, µg/mL	Anti-certolizumab, AU/mL
#1	0.3	>160	<0.4	<5
#2	0.4	>160	<0.4	<5
#3	>8	<10	<0.4	<5
#4	4.5	<10	<0.4	<5
#5	0.5	137	<0.4	<5
#6	0.3	>160	<0.4	<5
#7	5	<10	<0.4	<5
#8	0.5	137	<0.4	<5
#9	7	<10	<0.4	<5
#10	0.3	>160	<0.4	<5
#11	<0.1	<10	0.4	>160
#12	<0.1	<10	0.6	>160
#13	<0.1	<10	0.4	148
#14	<0.1	<10	0.4	>160
#15	<0.1	<10	0.6	>160
#16	<0.1	<10	0.4	120
#17	<0.1	<10	0.5	138
#18	<0.1	<10	0.4	>160
#19	<0.1	<10	0.4	155
#20	<0.1	<10	0.6	>160

Table 2. Cross-reactivity experiments

- The prevalence of anti-TNF drug antibodies varies considerably among patients.

-In these 2 patients we observed that circulating antibody levels did not decrease below detection levels still after 12 months from the last infusion

-Interestingly, 36 months after the switch to certolizumab, high titers of anti-adalimumab abs seemed to persist and co-exist with high titers of anti-certolizumab abs.

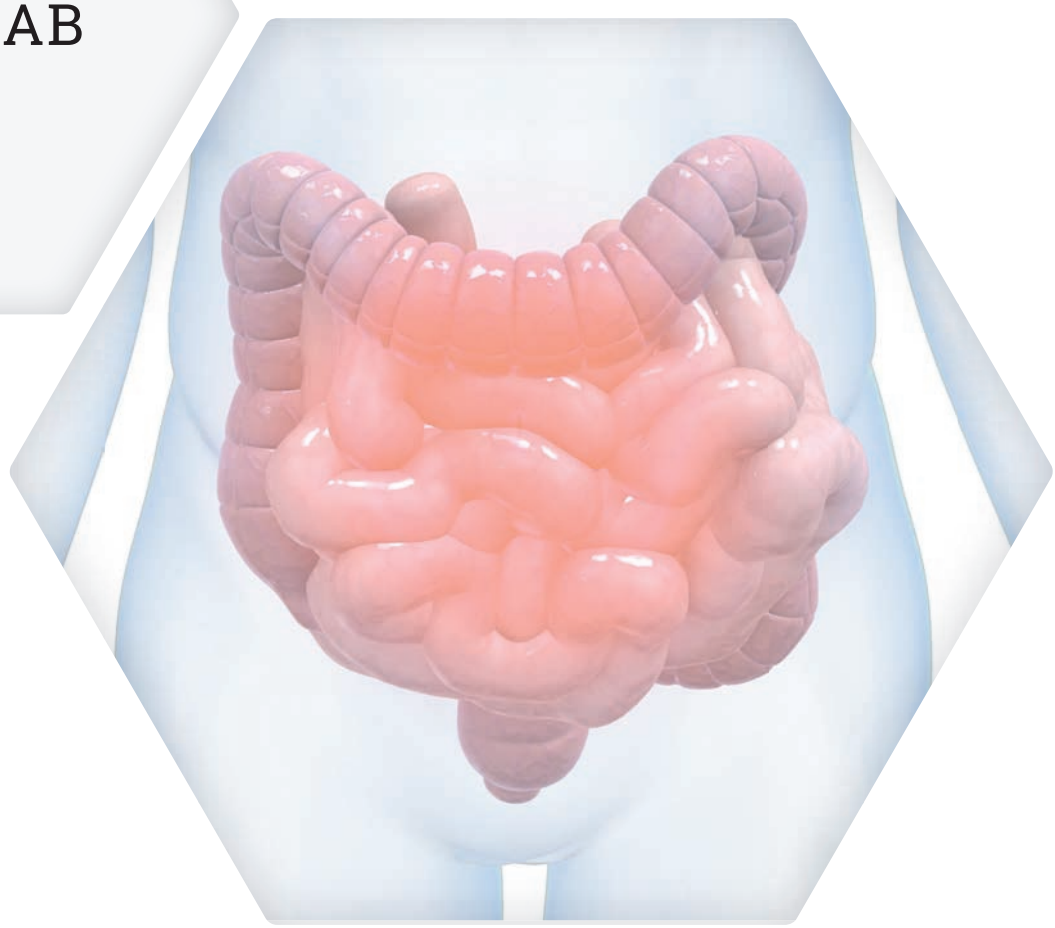
- The detection of circulating anti-adalimumab antibodies that persisted and co-existed with high titers of anti-certolizumab antibodies suggests that the clinical response to a second anti -TNF drug may be conditioned by the development of ADAs against the starting one

- Further studies are needed to elucidate which factors can trigger an immunogenic response in some patients but not in others (genetic differences, HLA allelic variants, disease status, pre-existing reactive T cells and natural antibodies)

Drug persistence in the circulation is still observed after 12 months treatment discontinuation

Anti-TNFα

GOLIMUMAB



GLM

UC

2020

THERAPEUTIC THRESHOLDS FOR GOLIMUMAB SERUM CONCENTRATIONS DURING INDUCTION AND MAINTENANCE THERAPY IN ULCERATIVE COLITIS: RESULTS FROM THE GO-LEVEL STUDY

*Saaman MA, Cunningham G, Tamilarasan AG, Beltran L, Pavlidis P, Ray S, Mawdsley J, Anderson SH, Sanderson JD, Arkir Z, Irving PM

*Gasteroenterology, Guy's and St Thomas' Hospital, London, UK

ABSTRACT

BACKGROUND: Significant associations between serum golimumab concentrations and favourable outcomes have been observed during both induction and maintenance therapy in ulcerative colitis (UC). However, data regarding optimal therapeutic serum golimumab concentration thresholds are limited

METHODS: We aim to identify optimal serum golimumab concentration thresholds during induction and maintenance treatment with golimumab.GO-LEVEL was an open label, phase IV study that included a prospective cohort of UC patients commencing golimumab, as well as a cross-sectional cohort receiving maintenance treatment. Patients commencing induction for active UC (defined as a simple clinical colitis activity index [SCCAI] >5 in addition to a raised faecal calprotectin [FC] >59µg/g or, raised C-reactive protein [CRP] [>5mg/L] or, Mayo endoscopic disease activity 2 or 3) were evaluated at weeks 6, 10 and 14. Patients receiving maintenance therapy were recruited either at the point of flare or during remission. Combined clinical-biochemical remission was defined as SCCAI ≤2 and FC <250µg/g. Serum golimumab concentrations were measured using a commercially available ELISA (LISATRACKER, Theradiag).

RESULTS: Thirty-nine patients were included in the induction cohort, of whom 15 (38%) achieved combined clinical-biochemical remission at week 6. The median serum golimumab concentration of those in combined clinical-biochemical remission was significantly higher than those who were not (5.0 vs 3.1 µg/mL, respectively, P = 0.03). Receiver operating characteristic (ROC) curve analysis demonstrated 3.8 µg/mL as the optimal threshold (sensitivity 0.71, specificity 0.65, area under curve [AUC] 0.72, positive predictive value [PPV] 0.59 and negative predictive value [NPV] 0.79). Sixty-three patients were included in the maintenance cohort; 31 (49%) were in combined remission, 32 (51%) were not. The median serum golimumab concentration of those in combined remission was significantly higher (2.9 vs 2.1 µg/mL, respectively, P = 0.01). ROC curve analysis demonstrated 2.4 µg/mL as the optimal threshold (sensitivity 0.68, specificity 0.66, AUC 0.68, PPV 0.65 and NPV 0.66).

CONCLUSIONS: GO-LEVEL (NCT03124121) offers further evidence regarding golimumab's exposure-response relationship. Clinicians may consider using therapeutic drug monitoring to optimise golimumab dosing aiming to achieve our suggested therapeutic thresholds of 3.8 µg/mL at week 6 and 2.4 µg/mL during maintenance.

KEY POINTS

	Median serum golimumab concentration, µg/mL		
	Week 6	Week 10	Week 14
Clinical response			
Achieved	4.7	2.8	2.1
Not achieved	3.0	2.6	1.9
P value	0.09	0.38	0.27
Clinical remission			
Achieved	4.8	2.5	2.2
Not achieved	3.0	2.7	1.8
P value	0.02	0.77	0.13
Combined clinical-biochemical remission			
Achieved	5.0	2.5	2.4
Not achieved	3.0	3.4	1.8
P value	0.02	0.42	0.08

Table 3. Median serum golimumab concentrations amongst patients who achieved a clinical response, clinical remission and combined clinical-biochemical remission compared to those who did not at weeks 6,10 and 14

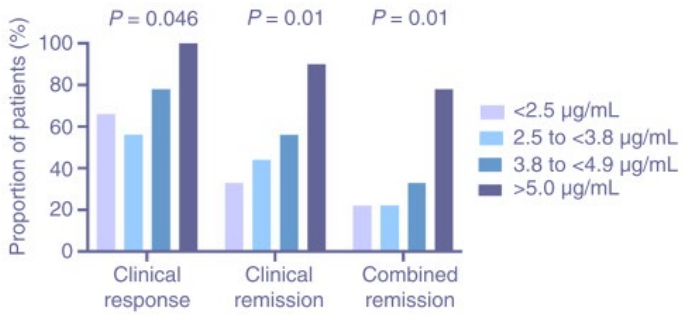


Figure 1: . Proportion of patients in clinical response, clinical remission and combined clinical biochemical remission according to serum golimumab concentration quartile at week 6.

- This study suggests the value of golimumab-monitoring in adapting the therapeutic strategy in Ulcerative Colitis, particularly in induction and maintenance phases.

-Patients were objectively assessed using FC measurement ant their symptoms were evaluated using both an established disease activity score (SCCAI) and novel two-item patient reported outcomes (PRO2).

- An association between greater drug exposure and favourable treatment outcomes was observed.

- A week 6 threshold of 3.8µg/ml was identified as an SGC target for the achievement of both clinical remission and combined clinical-biochemical remission during induction

-Serum golimumab concentration thresholds of 2.4 µg/ml during maintenance therapy most closely associate with achievement of combined clinical-biochemical remission.

GO-LEVEL demonstrates a relationship between golimumab exposure and favourable treatment outcomes including remission in both clinical and biochemical activity during induction and maintenance.

GLM

UC

2019

COMPARISON OF IMMUNOASSAYS FOR MEASURING SERUM LEVELS OF GOLIMUMAB AND ANTIBODIES AGAINST GOLIMUMAB IN ULCERATIVE COLITIS: A RETROSPECTIVE OBSERVATIONAL STUDY

Berger AE*, Duru G, de Vries A, Marini JC, Aoucheta D, Cornillie F, Nancey S, Detrez I, Gils A, Roblin X, Paul S.

*Immunology and Immunomonitoring Laboratory, CHU Saint-Etienne, Saint-Etienne, France

ABSTRACT

BACKGROUND: Golimumab is a monoclonal anti-tumor necrosis factor alpha antibody, which is used in ulcerative colitis with an exposure-response relationship. The goal of this study was to compare results obtained with different immunoassays (golimumab and antigolimumab antibodies trough levels).

METHODS: This study was based on samples from 78 ulcerative colitis patients on golimumab treatment. Golimumab was quantified by either an anti-IgG detection antibody (Theradiag, Marne la Vallée, France) or an antibody directed against golimumab (Sanquin, Amsterdam, The Netherlands, KU Leuven, Leuven, Belgium, and Janssen R&D, San Diego, CA). Bridging drug-sensitive enzyme-linked immunosorbent assays (Theradiag, Janssen R&D, and KU Leuven), a bridging drug-tolerant enzyme-linked immunosorbent assay (Janssen R&D), and a radioimmunoassay (Sanquin) were used to quantify antidrug antibody.

RESULTS: Median serum golimumab levels were 4.5, 3.5, 4.9, and 2.4 mcg/mL with Theradiag, Sanquin, KU Leuven, and Janssen R&D assay, respectively ($P < 0.05$). Correlation coefficients between assays ranged from 0.9 to 0.97. When using the KU Leuven and Janssen R&D assays, 86% of samples were in the same quartile of distribution of values, and for Sanquin and Janssen R&D assays, this overlap was 80%. The concordance observed for the other pairs was 83% (Sanquin/KU Leuven R&D), 71% (Theradiag/KU Leuven), and 68% (Theradiag/Janssen R&D and Theradiag/Sanquin). The specificity of assays for golimumab was demonstrated. Antidrug antibodies were detected in 28.2% of the samples with the Janssen R&D drug-tolerant assay and in the same 2 patients by the 3 other assays.

CONCLUSIONS: Performances of these immunoassays were similar in terms of quality, but differences in the quantitative results point to the importance of using the same assay consistently to monitor a patient's treatment.

KEY POINTS

		Theradiag	Sanquin	KU Leuven	Janssen R&D
Mean GLM	µg/ml	5	4.1	5.4	3.4
Median GLM	µg/ml	**4.5**	**3.5**	**4.9**	2.4
25th percentile	µg/ml	2.4	1.6	2.4	1.1
75th percentile	µg/ml	7.3	4.7	6.9	3.9
Standard deviation		3.7	3.5	3.7	3.2
N		78	75	78	78

Table 2. Comparison of the four different assays to monitor Golimumab (GLM)treatment. For each assay, mean, median, 25th, 75th percentiles and standard deviation of GLM quantification are specified. N= number of measured samples.

- This study highlights the importance of using the same assay consistently to monitor a patient's treatment

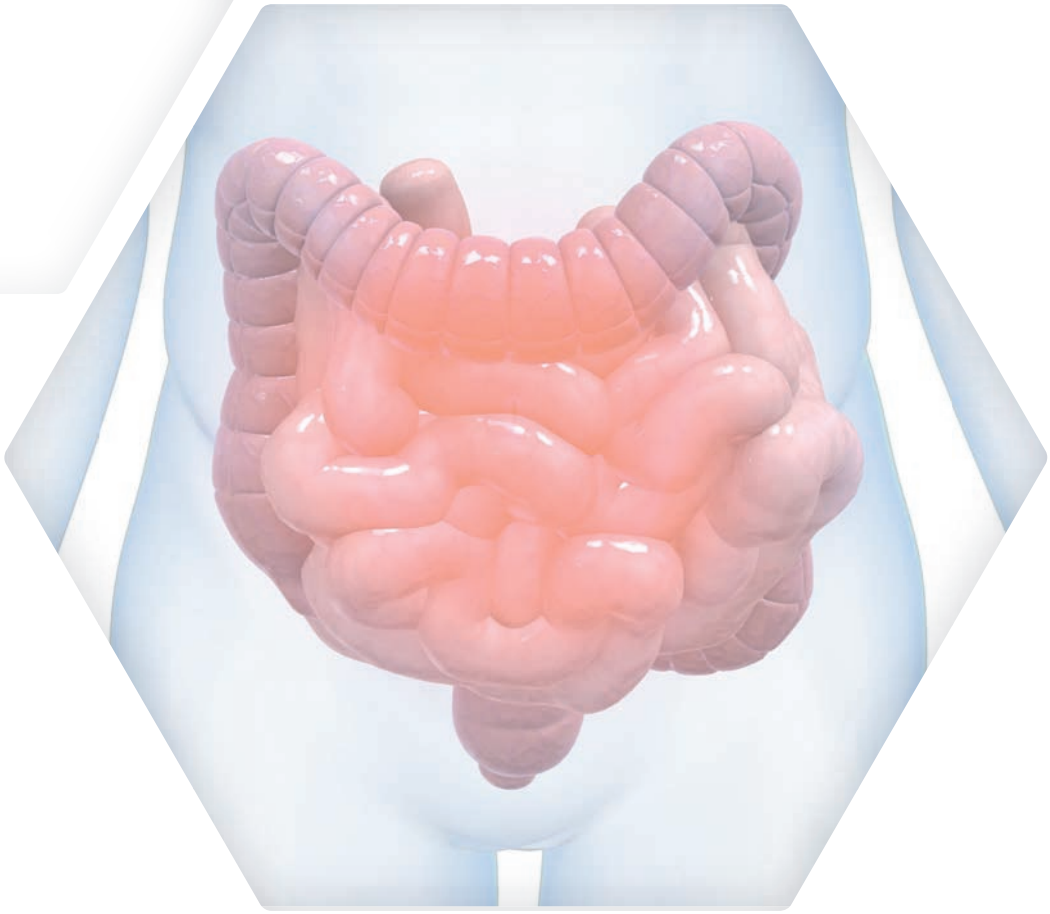
- Median serum golimumab levels were 4.5, 3.5, 4.9 and 2.4 µg/ml with Theradiag, Sanquin, KU Leuven and Janssen R & D assay, respectively ($p<0.05$)

- Golimumab was undetectable in 2 golimumab treated patients with 3 of the 4 assays (KU Leuven, Sanquin and Janssen) while golimumab was detected in all samples with the Theradiag assay

- Values of Golimumab obtained with Theradiag for these 2 patients were 0.21µg/ml and 1.09 µg/ml and anti-golimumab antibodies were detected in most of the assays for these two patients

- Golimumab antidrug antibodies were detected in the same proportion by the 4 different assays.

Our data may help to better understand and use Golimumab monitoring in treated patients



Anti-IL12/IL23

USTEKINUMAB

UST

CD

2020

USTEKINUMAB SERUM TROUGH LEVELS MAY IDENTIFY SUBOPTIMAL RESPONDERS TO USTEKINUMAB IN CROHN'S DISEASE

*Painchart C, Brabant S, Duveau N, Nachury M, Desreumaux P, Branche J, Gérard R, Prevost CLD, Wils P, Lambin T, Boualit M, Labalette M, Pariente B

*Gastroenterology Department, CHRU Lille, Université Lille, Lille, France.

ABSTRACT

BACKGROUND: The aim of this study was to evaluate the association between serum ustekinumab (UST) trough levels and response to induction and maintenance UST treatment in refractory Crohn's Disease (CD) patients.

METHODS: We performed a prospective study including CD patients who received UST from September 2015 to January 2017. Patients received 90 mg of UST subcutaneously at weeks 0, 4, and 12, then every 8 weeks. Two cohorts of patients were analyzed: an induction cohort and a maintenance cohort. We evaluated clinical, biological, and imaging/endoscopic response to UST treatment. UST trough levels and anti-UST antibodies were dosed at weeks 12 and 28 in the induction cohort, and at a single time point in the maintenance cohort

RESULTS: Forty-nine patients were enrolled in the maintenance cohort. Mean concentrations of UST were 1.88 ± 1.40 µg/mL. UST trough levels were not significantly different in patients with or without clinical, biological, or imaging/endoscopic responses to UST treatment ($p > 0.11$). Twenty-three consecutive patients were included in the induction cohort. At week 12, mean UST concentrations were 1.45 ± 1.15 µg/mL. Patients with a biological response to UST treatment had significant higher serum UST trough concentration (median 1.72 µg/mL) than non-responders (median 0.56 µg/mL, $p = 0.02$). A UST trough level ≥ 1.10 µg/mL at week 12 was associated with a biological response to UST treatment at 6 months

CONCLUSIONS: UST trough levels were associated with a biological response at the end of the induction phase. In patients with low levels of UST, optimization treatment may be necessary to obtain a sustained response.

KEY POINTS

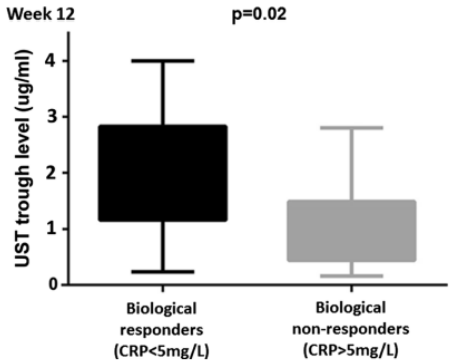


Figure 3. Serum UST trough levels at the end of induction phase (week 12) in the induction cohort according to the biological response to UST treatment. Bloxplot of serum UST trough levels in patients with (left box) or without (right box) biological response to UST therapy at week 12. The box represents the 25th-75th percentiles, and the whiskers correspond to the 5th -95th percentiles

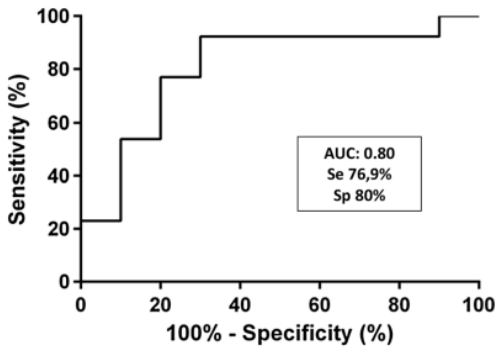


Figure 4. Receiver operating characteristic curve analysis of optimal serum UST thresholds at week 12 associated with biological response within the 6 months. The best ROC curve indicates a threshold of UST trough levelat week 12 of 1.10µg/ml (area under the curve 0.80, sensitivity 76.9% , and specificity 80% UST Ustekinumab ROC: receiver operating characteristic

- These results emphasize the need to monitor Ustekinumab concentrations during treatment to help physicians in patient management, by selecting who can benefit from early UST optimization at the end of the induction phase

- Early Ustekinumab trough levels are an objective predictive threshold and therapeutic target in CD patients

- An Ustekinumab trough level ≥1.10µg/mL at week 12 was associated with a biological response to Ustekinumab treatment at 6 months after Ustekinumab induction

- Ustekinumab treatment could be optimized in patients with a low residual level at the end of induction

- None of the patients in the authors' cohort developed anti-ustekinumab antibodies confirming the low immunogenicity of Ustekinumab

This study confirms that induction and maintenance phase UST treatment is effective in most patients with CD refractory to anti-TNF treatment

UST

CD

2019

CONCENTRATIONS OF USTEKINUMAB DURING INDUCTION THERAPY ASSOCIATE WITH REMISSION IN PATIENTS WITH CROHN'S DISEASE

Soufflet N*, Boschetti G, Roblin X, Cuercq C, Williet N, Charlois AL, Duclaux-Loras R, Danion P, Mialon A, Faure M, Paul S, Flourie B, Nancey S.

*Department of Gastroenterology, Lyon-Sud University Hospital, Hospices Civils de Lyon, Pierre Bénite, and University Claude Bernard Lyon 1, Lyon, France

ABSTRACT

ABSTRACT: Ustekinumab is approved for treatment of Crohn's disease (CD). Few data are available to assess the usefulness of monitoring inflammatory biomarkers and therapeutic drug monitoring to predict response to ustekinumab. We conducted a prospective study to assess the relationships between these parameters and the clinical outcome at week 16 in active CD patients receiving ustekinumab.

KEY POINTS

	AUROC	95% CI	*P* values	Optimal cut-off value	Sensitivity, %	Specificity, %	PPV, %	NPV, %
CRP								
Week 4	0.55	0.36–0.74	.53	3.9 mg/mL	51	58	46	77
Week 8	0.64	0.44–0.83	.18	5.4 mg/mL	55	77	28	47
Week 16	0.51	0.28–0.73	.90	9.5 mg/mL	58	50	31	61
fCal								
Week 4	0.62	0.41–0.84	.24	250 μg/g	41	75	50	72
Week 8	0.57	0.34–0.80	.50	250 μg/g	33	81	43	77
Week 16	0.55	0.25–0.85	.42	250 μg/g	53	80	33	90
Ustekinumab TL								
Week 4	0.62	0.39-0.85	.25	13.0 μg/mL	66	63	59	35
Week 8	0.75	0.53-0.96	.04	2.0 μg/mL	87	66	82	75
Week 16	0.77	0.57-0.98	.03	1.4 μg/mL	77	75	90	66

NOTE. Serum and fecal samples were available for analysis in all patients (n = 51) at each time point. *P* values were compared with baseline.
AUROC, area under the receiver operating characteristic curve; CRP, C-reactive protein; fCal, fecal calprotectin; TL, trough level; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

Table 1. AUROC, Sensitivities, Specificities and Positive and Negative Predictive values of Serum CRP, fCal, and Ustekinumab trough levels over time at weeks 4,8 and 16 after Ustekinumab infusion to distinguish between primary Non-Responders and Responders to Ustekinumab induction therapy

- This prospective study pointed out the relationship between therapeutic drug monitoring and inflammatory biomarkers monitoring and the clinical outcome at week 16 in active CD patients receiving ustekinumab

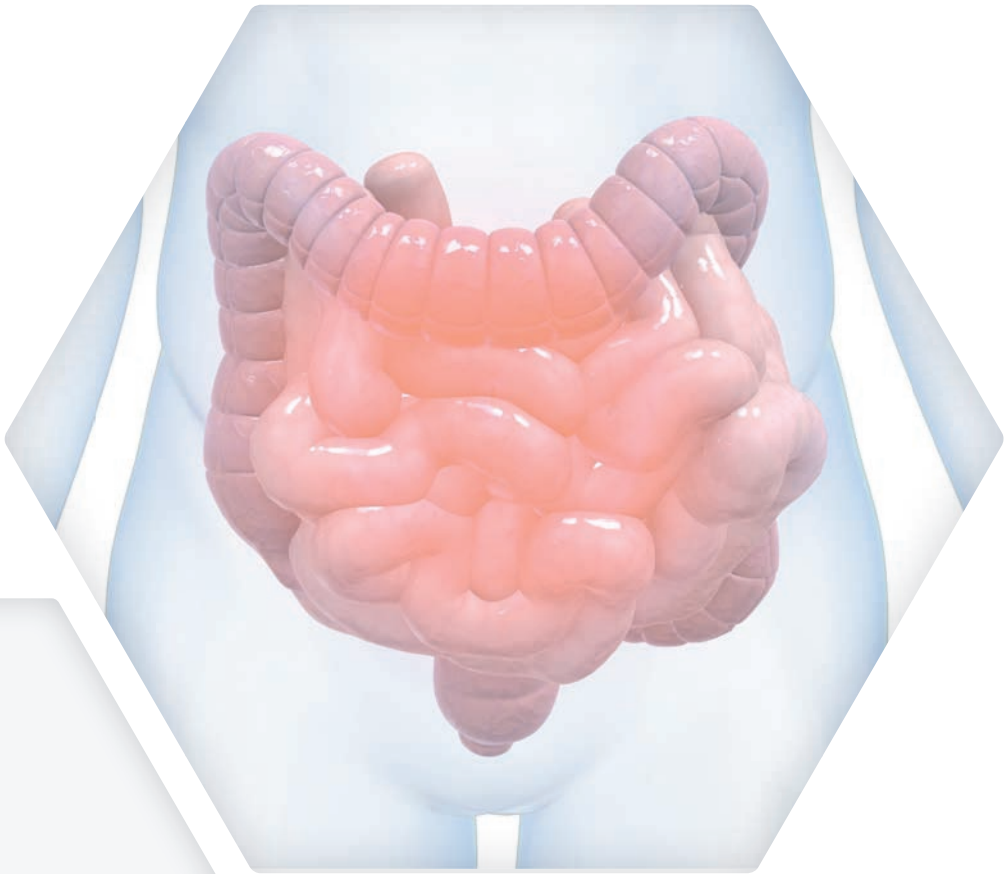
- All patients received an initial intravenous infusion of Ustekinumab according to their body weight, followed by subcutaneous injections of 90mg UST every 8 weeks

- Trough concentrations of Ustekinumab of 2.0µg/ml or greater at week 8 were associated with a response to induction therapy fCal decreased significantly over time exclusively in responders

- In contrast CRP level do not change significantly from weeks 0 to 16 in both responders and primary non responders

- The optimal drug TL greater than 2.0µg/ml measured at week 8 enabled a prediction of response to induction therapy at week 16

TDM is useful to identify early primary non responders CD patients during Ustekinumab induction therapy



Anti-α4-β7

VEDOLIZUMAB

VDZ

IBD

2019

EARLY VEDOLIZUMAB TROUGH LEVELS PREDICT TREATMENT PERSISTENCE OVER THE FIRST YEAR IN INFLAMMATORY BOWEL DISEASE

*Guidi L, Pugliese D, Tonucci TP, Bertani L, Costa F, Privitera G, Tolusso B, Di Mario C, Albano E, Tapete G, Gremese E, Papa A, Gasbarrini A, Rapaccini GL, Armuzzi

*UOC Medicina Interna e Gastroenterologia Columbus, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

ABSTRACT

BACKGROUND: Data from trials of vedolizumab for inflammatory bowel disease and from real-world studies suggest an exposure-response relationship, such that vedolizumab trough levels may predict clinical and endoscopic outcomes. The purpose of this study was to evaluate in a prospective observational study the utility of an early vedolizumab trough level assay for predicting the first-year vedolizumab therapy outcome.

METHODS: This prospective observational study included consecutive inflammatory bowel disease patients. We measured vedolizumab trough levels and anti-vedolizumab antibodies at weeks 6 and 14. Clinical outcome was assessed at weeks 6, 14, 22 and 54. The primary endpoint was the correlation between early vedolizumab trough levels and vedolizumab persistence over the first year of treatment, defined as the maintenance of vedolizumab therapy due to sustained clinical benefit.

RESULTS: We included 101 patients initiating vedolizumab. A cut-off vedolizumab trough level of 16.55 µg/ml at week 14 predicted vedolizumab persistence within the first year of therapy, with 73.3% sensitivity and 59.4% specificity (p = 0.0009). Week 14 vedolizumab trough level was significantly higher in patients with clinical remission at weeks 14, 22 and 54; and in patients achieving mucosal healing within 54 weeks.

CONCLUSIONS: High vedolizumab trough level at week 14 was associated with a higher probability of maintaining vedolizumab therapy over the first year due to sustained clinical benefit.

KEY POINTS

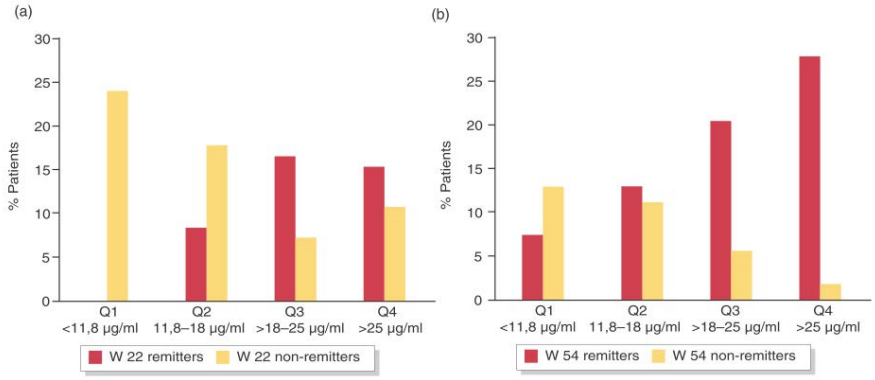


Figure 3. (a)Rates of clinical remission at week 22 by quartiles (Qs) of vedolizumab trough level (VTL) at week 14 (p<0.001); (b) rates of clinical remission at week 54 by Qs of VTL at week 14 (p=0.0076); .

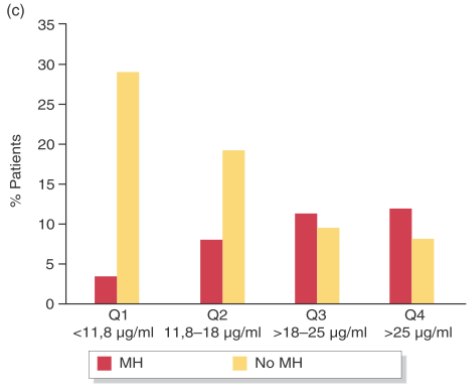


Figure 3. (c) Rates of mucosal healing (MH) by Qs of VTL at week 14 (p=0.013)

- This is the first real-world study identifying a correlation between early VDZ levels and treatment persistence at one year

- A Vedolizumab through level cut-off of >16.55 µg/ml at week 14 predicted VDZ persistence within the first year of therapy with a sensitivity of 73.3% and a specificity of 59.4% (p = 0.0009).

- Week 14 vedolizumab trough level was significantly higher in patients with clinical remission at weeks 14, 22 and 54; and in patients achieving mucosal healing within 54 weeks.

- VDZ trough levels at 6 weeks seemed to mainly predict clinical outcomes during the first six months, A VTL of >29.9 µg/ml at week 6 was indicative of remission at week 14 (AUROC, 0.641; p = 0.02), and a VTL of >29.3 µg/ml at week 6 was predictive of remission at week 22 (AUROC, 0.652; p = 0.01)

- Quartile analysis for VDZ TL at 6 weeks and 14 confirmed the dose-response relationship

Measurement of VDZ through levels at week 14 provides more information regarding drug persistence within the first year of therapy

VEDOLIZUMAB THROUGH LEVELS AND HISTOLOGICAL HEALING DURING MAINTENANCE THERAPY IN ULCERATIVE COLITIS

VDZ

UC

2019

Pouillon L*, Rousseau H, Busby-Venner H, De Carvalho Bittencourt M, Choukour M, Gauchotte G, Zallot C, Danese S, Baumann C, Peyrin-Biroulet L.

*INSERM U954 and Department of Hepato-Gastroenterology, University Hospital of Nancy, Lorraine University, Vandoeuvre-lès-Nancy, France.

ABSTRACT

BACKGROUND: Histological healing may be the ultimate therapeutic goal in ulcerative colitis [UC]. We investigated, for the first time, the association between vedolizumab trough levels and histological healing in UC.

METHODS: This is a single-centre retrospective cohort study including all consecutive UC patients on vedolizumab maintenance therapy who had a histological evaluation blindly to clinical data and underwent therapeutic drug monitoring, between June 2014 and March 2018. Per-event analysis was performed. Histological healing was defined as a Nancy histological index ≤1.

RESULTS: Thirty-five histological samples were analysed. Median [interquartile range] vedolizumab trough levels were higher in the group with histological healing (31.5 [25-49.1] µg/mL) compared with the group without histological healing (15 [9-26.6] µg/mL, p = 0.02). The higher vedolizumab trough level quartiles tended to be associated with greater rates of histological healing [p = 0.10]. A cut-off vedolizumab trough level of 25 µg/mL predicted histological healing with an accuracy of 74% and an area under the receiver operating curve of 0.62 [95% confidence interval 0.58-0.92, p = 0.004]. Bivariate analysis identified a vedolizumab trough level ≥25 µg/mL [p = 0.006], a partial Mayo score ≤1 [p = 0.008], C-reactive protein level <5 mg/L [p = 0.005] and a Mayo endoscopic subscore ≤1 [p = 0.0004] as factors associated with histological healing..

CONCLUSIONS: Histological healing was associated with higher vedolizumab trough levels during maintenance therapy in UC. A vedolizumab trough level threshold of 25 µg/mL proved most optimal to predict histological healing according to the Nancy histological index. Confirmation of these data in larger, independent cohorts is needed.

KEY POINTS

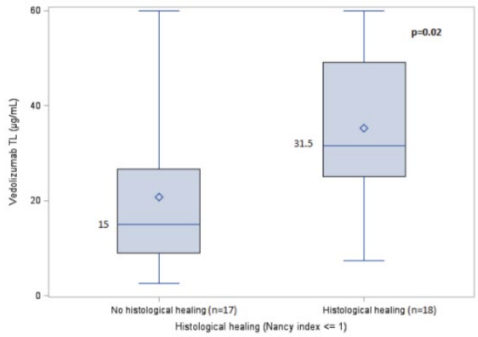


Figure 1. Distribution of serum vedolizumab through levels during maintenance therapy based on histological healing in UC patients (Legend TL= trough level)

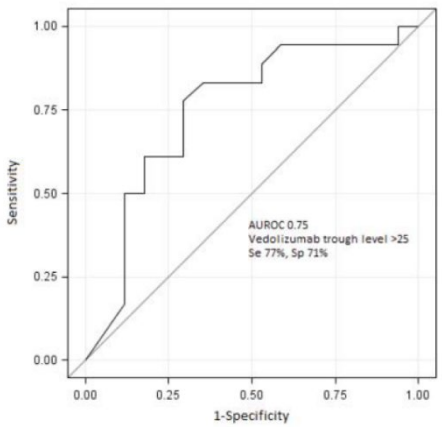


Figure 3. ROC analysis for serum Vedolizumab trough level during maintenance therapy, stratifying UC patients with and without histological healing

- This is the first study showing an association between histological healing and vedolizumab trough levels during maintenance therapy in UC patients

- Median vedolizumab trough levels were more than two times higher in patients with histological healing, compared with patients without histological healing

- A cut-off vedolizumab trough level of 25µg/ml predicted histological healing (sensitivity 77%; specificity 71%; AUROC 0.75) (p=0.006)

- Other factors associated with mucosal healing were a partial Mayo score ≤ 1(p=0.008), C-reactive protein level <5mg/L (p=0.005) and a Mayo endoscopic subscore ≤ 1(p=0.0004)

- Histological healing is now recognized as a major treatment goal in UC patients. The STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) guidelines acknowledge that histopathology is a sensitive measure of inflammation in UC

VDZ levels > 25µg/ml predict histological healing in maintenance therapy according to the Nancy histological index.

VDZ

IBD

2018

SOLUBLE MUCOSAL ADDRESSIN CELL ADHESION MOLECULE 1 AND RETINOIC ACID ARE POTENTIAL TOOLS FOR THERAPEUTIC DRUG MONITORING IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE TREATED WITHVEDOLIZUMAB: A PROOF OF CONCEPT STUDY

Stephane Paul*, Nicolas Williet, Thomas Di Bernado, Anne-Emmanuelle Berger*, Gilles Boschetti, Jerome Filippi, Emilie Del Tedesco, Stephane Nancey, Bernard Flourie, Xavier Roblin

* Department of Immunology, University Hospital of Saint-Etienne, Saint Etienne, France

ABSTRACT

BACKGROUND AND AIM: Vedolizumab [VDZ], a humanized monoclonal antibody targeting α4ß7 integrin, is effective in induction and maintenance therapy in patients with inflammatory bowel disease [IBD] who have not adequately responded to standard therapies, and high vedolizumab trough levels [VTLs] have been associated with clinical remission. The α4ß7 integrin binds to endothelial MAdCAM-1 and is upregulated by retinoic acid [RA]. The aim of this study was to determine the relationships between soluble MAdCAM-1 [sMAdCAM-1] and RA concentrations during clinical remission with VDZ maintenance therapy.

METHODS: In a retrospective study performed in IBD patients treated with VDZ, we measured VTL, sMAdCAM-1 and RA concentrations.

RESULTS: Among the **62 included patients [38 Crohn's disease]**, 24 relapsed and 38 stayed in remission from Weeks 10 to 30 after VDZ initiation. During this maintenance therapy, the median values of VTLs and RA were 15.4 µg/mL and 0.97 ng/mL, respectively, whereas sMAdCAM-1 was undetectable [<0.41 ng/mL] in 67.3% of samples. The positive predictive value [PPV] of undetectable sMAdCAM-1 for clinical remission was 80.0%, with a corresponding sensitivity of 74.6%. On multivariate analysis, undetectable sMAdCAM-1 and high VTLs [>19 µg/mL] were independently associated with clinical remission [OR = 7.5, p = 0.006 and OR = 2.2, p = 0.045, respectively]. **The combination of sMAdCAM-1 < 0.41 ng/mL and VTL > 19 µg/mL was the best pharmacokinetic profile, with a PPV of 95.2%**. Median values of sMAdCAM-1 and RA were significantly higher [p = 0.0001] before VDZ therapy than during the follow-up [sMAdCAM-1: 40.5 vs < 0.41 ng/mL; RA: 1.7 vs 0.97 ng/mL]. Only RA > 1.86 ng/mL before VDZ therapy was predictive of clinical remission during the follow-up (Area Under a Receiver Operating Characteristic curve [AUROC] = 80.7%).

CONCLUSIONS: **Undetectable sMAdCAM-1 appears strongly associated with clinical remission during VDZ maintenance therapy. Combination of undetectable sMAdCAM-1 with high VTL is also potentially interesting for therapeutic drug monitoring. Baseline RA concentrations are predictive of clinical remission. These findings need to be confirmed in further prospective studies.**

KEY POINTS

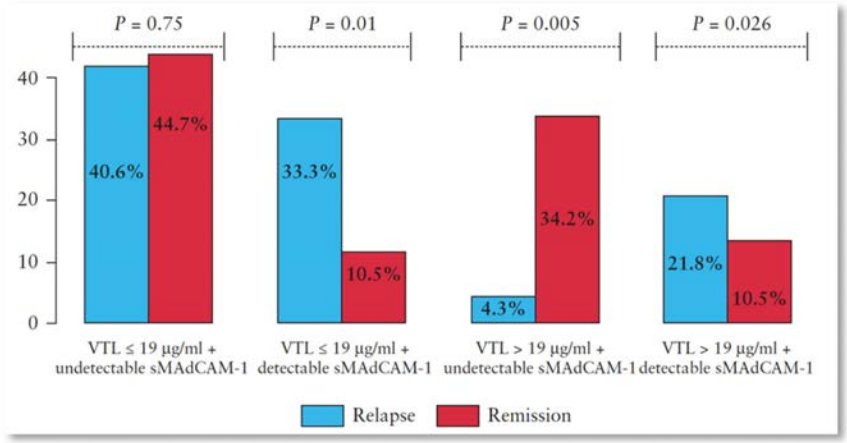


Figure 3. Comparison of pharmacokinetic profiles combining sMAdCAM-1 and vedolizumab trough levels in assays performed in clinical remission or at the time of relapse during vedolizumab maintenance therapy. VTL: vedolizumab trough levels; sMAdCAM-1: soluble mucosal addressin cell adhesion molecule-1.

	Threshold	Sensitivity	Specificity	Accuracy	PPV	NPV
Vedolizumab trough level	>19.0 µg/mL	47.5	65.0	0.50	72.1	39.7
sMAdCAM-1	<0.41 ng/mL [undetectable]	74.6	54.2	0.69	80.0	46.4
Retinoic acid	<1.05 ng/mL	59.0	65.6	0.57	78.3	52.0

sMAdCAM-1: soluble mucosal addressin cell adhesion molecule-1; NPV: negative predictive value; PPV: positive predictive value.

Table 2. Identification of optimal thresholds associated with clinical remission for vedolizumab trough levels, sMAdCAM-1 and retinoic acid by receiver operating characteristic [ROC] curves during vedolizumab maintenance therapy.

- In this restrospective study, results have shown that the pharmacokinetics of VDZ are quite complicated and involve different actors/molecules.
- To help decision-making and optimize clinical response during the maintenance therapy of VDZ treatment, authors propose with caution a new therapeutic strategy including the measurement of retinoic acid (RA) and the use of pharmacokinetic profiles combining values of vedolizumab trough levels (VTL) and sMAdCAM-1 levels.
- Low level of sMAdCAM-1 in responder patients reflects the decrease of inflammation. High concentration of RA induces higher expression of α4β7 integrin on lymphocyte surfaces.

sMAdCAM-1 is a unique surrogate marker to predict response to VDZ in IBD patients. RA appears as a key physiological factor. Further prospective studies will allow the elaboration of a new decisional algorithm to optimize VDZ treatment.

VDZ

IBD

2018

SAFETY, EFFICACY AND PHARMACOKINETICS OF VEDOLIZUMAB IN PATIENTS WITH SIMULTANEOUS EXPOSURE TO AN ANTI-TUMOUR NECROSIS FACTOR

S. Ben-Horin*, B. Ungar*, U. Kopylov*, A. Lahat*, M. Yavzori*, E. Fudim*, O. Picard*,Y. Peled, R. Eliakim*, E. Del Tedesco, S. Paul, X. Roblin

* Department of Gastroenterology, Sackler School of Medicine, Sheba Medical Center, Tel Aviv, Israel

ABSTRACT

BACKGROUND: Data on combination-biologic treatment in (IBD) are still scant.

AIM: To explore outcomes of patients co-exposed to anti-TNF and vedolizumab

METHODS: Patients starting vedolizumab having measurable anti-TNF levels after recently stopping adalimumab/infliximab ('VDZ-aTNF' group), were compared with control vedolizumab patients in a retrospective 1:2 matched case-control study.

RESULTS: **Seventy-five patients were included (25 VDZ-aTNF, 50 VDZ).** Adverse events were experienced by 9/25 VDZ-aTNF compared to 13/50 VDZ patients (P = 0.4, follow-up 14 weeks in all). Week 14 clinical remission was attained in 10/25 (40%) of VDZ-aTNF patients versus 23/50 (46%) of VDZ patients (OR = 0.8, 95% CI 0.3-2.1, P = 0.6) and clinical response in 19/25 (76%) versus 39/50 (78%) respectively (OR = 0.9, 95% CI 0.3-2.7, P = 0.8). Corticosteroid-free remission and corticosteroid-free response were experienced by 30% and 54%, respectively, of the entire cohort, and were similar between the two groups. **Vedolizumab drug concentrations at week 2, 6 and 14 were similar among VDZ-aTNF and VDZ patients (P > 0.5).** Multivariable analysis showed independent association of some vedolizumab drug-levels time-points with baseline albumin and weight, but not with anti-TNF co-exposure. In a prospective study of a separate cohort of patients starting infliximab (n = 12), the percentage of $\alpha 4\beta 7$+ memory T cells, slightly but nonsignificantly increased throughout weeks 0, 2 to 14 (26 ± 2.3%, 27.8 ± 2.9%, 29.5 ± 2.6% respectively, P = 0.06).

CONCLUSIONS: **Vedolizumab/anti-TNF co-exposure did not generate new safety signals during 14-weeks induction, nor did it reduce efficacy or alter vedolizumab pharmacokinetics. These observations may aid the design of future co-biologics trials and also suggest that a deliberate waiting-interval between anti-TNF cessation and subsequent vedolizumab initiation may not be warranted.**

KEY POINTS

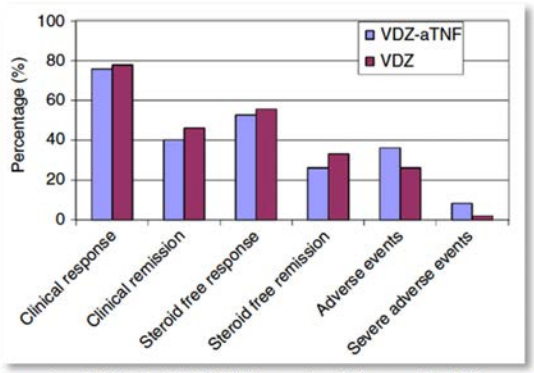


Figure 2. Main clinical outcomes by wk 14 in the VDZ-aTNF group (n = 25) versus the VDZ group (n = 50). VDZ-vedolizumab, aTNF—anti TNF.

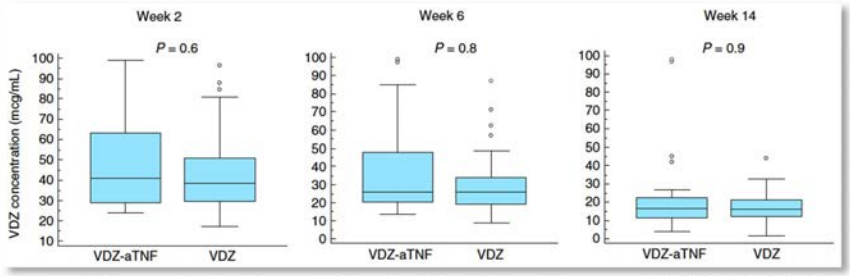


Figure 3. Serial consecutive trough concentrations of vedolizumab in patients co-exposed to VDZ and aTNF (VDZ-aTNF) compared to concentrations in patients with no concomitant exposure to aTNF (VDZ group). Median and 25%-75% IQRs are shown by the Box and median line within. aTNF, anti-TNF; VDZ, vedolizumab.

- Based on a relatively small size cohort of IBD patients, the study explores the impact of co-exposure to vedolizumab and anti-TNFs.
- Although limited to the 14 weeks induction time-frame, the follow up of patients did not show any warning signal or any alteration of vedolizumab pharmacokinetics, providing rational for further studies exploring possible benefits of the combination of VDZ and other anti-TNFs in IBD.
- Authors suggest that the impact of an opposite switch from VDZ to an anti-TNF would be worth to study.
- Control trials are also needed to confirm the benefit of a combined VDZ-aTNF regimen compared to a VDZ monotherapy.

With the view to obtain better clinical outcomes, combination of biologics appear as novel treatment strategies gaining interest in the management of IBD treated patients.

VDZ

IBD

2018

EARLY VEDOLIZUMAB TROUGH LEVELS PREDICT MUCOSAL HEALING IN INFLAMMATORY BOWEL DISEASE: A MULTICENTRE PROSPECTIVE OBSERVATIONAL STUDY

W. Yacoub*, N. Williet, L. Pouillon, Bittencourt, S. Nancey, A. Lopez, L. Peyrin-Biroulet*, T. Di-Bernado, M. De Carvalho, S. Paul, C. Zallot*, X. Roblin

* NSERM U954 and Department of Hepato-Gastroenterology, University Hospital of Nancy, Lorraine University, Vandoeuvre-le s-Nancy, France

Tracker

ABSTRACT

BACKGROUND: The correlation between vedolizumab trough levels during induction therapy and mucosal healing remains unknown.

AIM: **To compare early vedolizumab trough levels in patients with and without mucosal healing within the first year after treatment initiation.**

METHODS: We prospectively collected vedolizumab trough levels in all inflammatory bowel disease patients at weeks 2, 6 and 14 of vedolizumab treatment in three French referral centres between 1 June 2014 and 31 March 2017. Results of every patient that underwent mucosal assessment by magnetic resonance imaging and/or endoscopy in the first year after treatment initiation were analysed.

RESULTS: Median vedolizumab trough levels in the overall population (n = 82) were 27 μg/mL (interquartile range, IQR 21.2-33.8 μg/mL) at week 2, 23 μg/mL (IQR 15- 34.5 μg/mL) at week 6 and 10.7 μg/mL (IQR 4.6-20.4 μg/mL) at week 14. **Only median vedolizumab trough levels at week 6 differed between patients with and without mucosal healing within the first year after treatment initiation (26.8 vs 15.1 μg/mL, P = 0.035).** A cut-off trough level of 18 μg/mL at week 6 predicted mucosal healing within the first year after the start of vedolizumab with an area under the receiver operating curve of 0.735 (95% confidence interval 0.531-0.939). **A vedolizumab trough level above 18 μg/mL at week 6 was the only independent variable associated with mucosal healing within the first year of treatment** (odds ratio 15.7, 95% confidence interval 2.4-173.0, P = 0.01).

CONCLUSION: Early therapeutic drug monitoring might improve timely detection of vedolizumab-treated patients in need for an intensified dosing regimen.

KEY POINTS

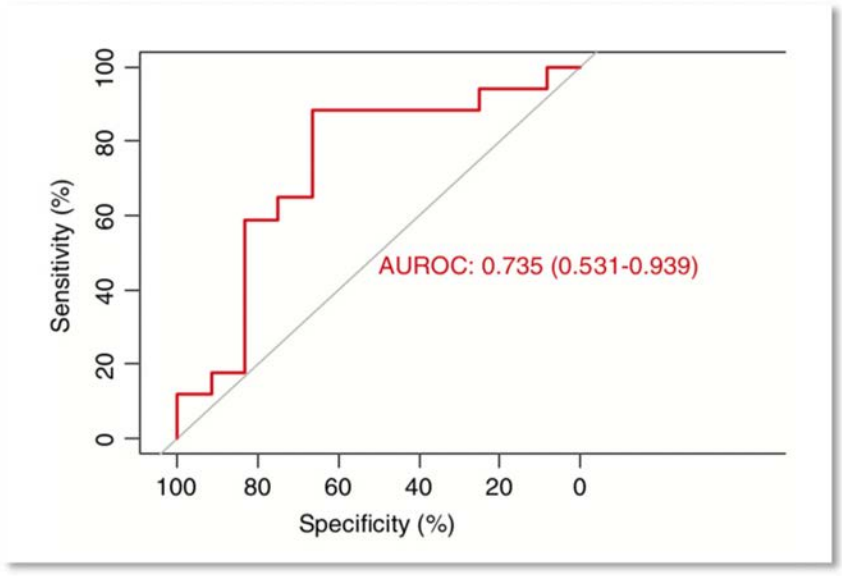


Figure 1. Area under the receiver operating curve for vedolizumab trough levels at week 6 stratifying patients with and without mucosal healing within 1 year after vedolizumab initiation. AUROC, area under the receiver operating curve

- Monitoring the trough level of vedolizumab during induction therapy allows better therapeutic decision in IBD patients
- A cut-off trough level of 18 μg/mL at 6 weeks predicts mucosal healing, within the first year after the first infusion of vedolizumab, with PPV and NPV of 78.9% and 80.0% respectively (AUROC 0.735)
- Cut-offs for therapeutic drug monitoring of vedolizumab-treated patients appear the same in patients with moderately to severely active CD and UC
- Results reveal no linear association between CRP and vedolizumab trough levels; however deep remission can be predicted at 6 weeks under a cut-off of 15,9 μg/mL and CRP < 5mg/mL (AUROC 0539)
- In this cohort, immunogenicity to vedolizumab represents 2.4%

First study showing a correlation between vedolizumab trough levels and mucosal healing during induction therapy in IDB treated patients

VDZ

IBD

2018

EARLY CHANGES IN THE PHARMACOKINETIC PROFILE OF VEDOLIZUMAB-TREATED PATIENTS WITH IBD MAY PREDICT RESPONSE AFTER DOSE OPTIMISATION

Célia Gouynou*, Lieven Pouillon*, Hélène Rousseau, Camille Zallot*, Cédric Baumann, Laurent Peyrin-Biroulet*

* Department of Gastroenterology, Nancy University Hospital, France.

ABSTRACT

LETTER

KEY POINTS

Table 1 The mean vedolizumab trough concentrations and change from baseline after dose optimisation in the group of responders versus the group of non-responders

	Responders (n=12)	Non-responders (n=11)	P value
Baseline			
Vedolizumab TC, µg/mL, mean (SD)	11.4 (9.0)	10.5 (11.1)	0.85
Month 3			
Vedolizumab TC, µg/mL, mean (SD)	34.3 (21.8)	21.5 (14.9)	0.13
Vedolizumab TC compared with baseline, Δ, µg/mL, mean (SD)	22.9 (19.3)	11 (7.3)	0.07

TC, trough concentration.

- In this retrospective study, authors report the analysis of vedolizumab patients with IBD having increased regimen following primary or secondary loss of response.

- The study is based on 23 patients (8 UC and 15 CD). Clinical remission was observed in 52,2% of patients (4/8 UC, 8/15 CD).

- Vedolizumab trough levels at baseline and at 3 months were measured: The mean change after dose optimisation was numerically higher in the group of responders (see table).

- Further prospectively collected data are needed to confirm such results.

There is no established correlation between the response to dose optimization and changes in pharmacokinetic profile of vedolizumab-treated patients. Therefore, early therapeutic drug monitoring after dose optimization might improve timely detection of patients with IBD in need for altered treatment regimen.

VDZ

IBD

2017

ASSOCIATION BETWEEN LOW TROUGH LEVELS OF VEDOLIZUMAB DURING INDUCTION THERAPY FOR INFLAMMATORY BOWEL DISEASES AND NEED FOR ADDITIONAL DOSES WITHIN 6 MONTHS

Nicolas Williet*, Gilles Boschetti, Marion Fovet*, Thomas Di Bernado*, Pierre Claudez*, Emilie Del Tedesco*, Camille Jarlot*, Leslie Rinaldi*, Anne Berger, Jean-Marc Phelip*, Bernard Flourie, Stéphane Nancey, Stéphane Paul, and Xavier Roblin*

*Department of Gastroenterology, University Hospital of Saint Etienne, France

ABSTRACT

BACKGROUND & AIMS: We investigated whether serum trough levels of vedolizumab, a humanized monoclonal anti- body against integrin a4b7, during the induction phase of treatment can determine whether patients will need additional doses (optimization of therapy) within the first 6 months.

METHODS: We conducted an observational study of 47 consecutive patients with Crohn's disease (CD; n [31) or ulcerative colitis (UC; n [16) who had not responded to 2 previous treatment regimens with antagonists of tumor necrosis factor and were starting therapy with vedolizumab at 2 hospitals in France, from June 2014 through April 2016. All patients were given a 300-mg infusion of vedolizumab at the start of the study, Week 2, Week 6, and then every 8 weeks; patients were also given corticosteroids during the first 4–6 weeks. Patients not in remission at Week 6 were given additional doses of vedolizumab at Week 10 and then every 4 weeks (extended therapy or optimization). **Remission at Week 6 of treatment was defined as CD ac- tivity score below 150 points for patients with CD and a partial Mayo Clinic score of <3 points, without concomitant corticosteroids, for patients with UC.** Blood samples were collected each week and serum levels of vedolizumab and antibodies against vedolizumab were measured using an enzyme-linked immunosorbent assay. Median trough levels of vedolizumab and interquartile ranges were compared using the nonparametric Mann-Whitney test. The primary objective was to determine whether trough levels of vedolizumab measured during the first 6 weeks of induction therapy associated with the need for extended treatment within the first 6 months.

RESULTS: Based on response to therapy at Week 6, extended treatment was required for 30 of the 47 patients (23 patients with CD and 7 patients with UC). At Week 2, trough levels of vedolizumab for patients selected for extended treatment were 23.0 mg/mL (interquartile range, 14.0–37.0 mg/mL), compared with 42.5 mg/mL in patients who did not receive extended treatment (interquartile range, 33.5–50.7; P [.15). At Week 6, trough levels of vedolizumab <18.5 mg/mL were associated with need for extended therapy (100% positive predictive value, 46.2%; negative predictive value; area under the receiver operating characteristic curve, 0.72) within the first 6 months. **Among patients who required extended treatment at Week 10, all of those with trough levels of vedolizumab <19.0 mg/mL at Week 6 had achieved clinical remission 4 weeks later (secondary responders).**

CONCLUSION: In a prospective study of patients with CD or UC receiving induction therapy with vedolizumab, **low trough levels of vedolizumab at Week 6 (<19.0 mg/mL) are associated with need for additional doses** (given at Week 10 and then every 4 weeks). **All patients receiving these additional doses achieved a clinical response 4 weeks later**.

KEY POINTS

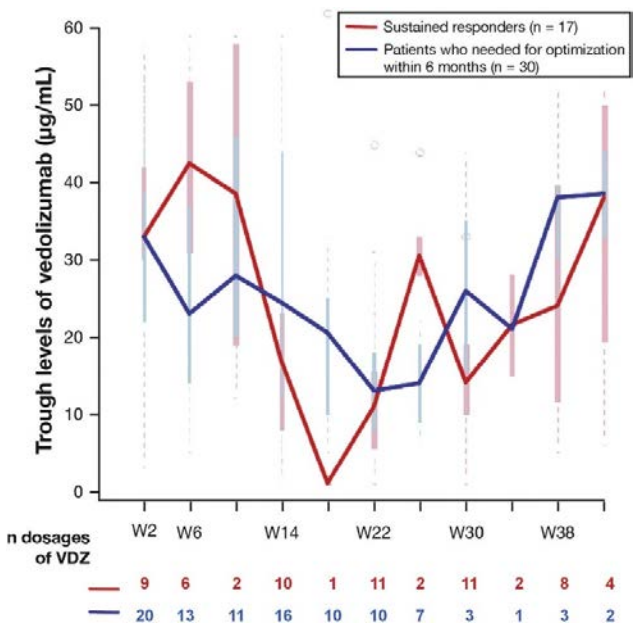


Figure 2. Trough levels of vedolizumab in patients with sustained response and in patients who needed drug optimization within 6 months.

- The study investigates the predictive value of the Vedolizumab trough levels during induction therapy in moderate to severe IBD patients under the specific French indication.The results show that 76,7% of the CD patients were classified in the drug-optimized subgroup.

- Vedolizumab trough level measured at Week 2 and ranging from 24.5 to 36 µg/mL was associated to the occurrence of a sustained remission in IBD patients at Week 24.

- no patients from this cohort has developed specific anti-vedolizumab antibody

This small prospective study conducted in a real-life basis shows that low levels of vedoluzimab at Week 6 could represent a novel surrogate pharmacologic marker of non-response and may help clinicians for better decision-making in drug optimization

Rheumatology

Anti-TNFα

GOLIMUMAB

Anti-TNFα

INFLIXIMAB

Anti-TNFα

CERTOLIZUMAB

Anti-TNFα

ADALIMUMAB

Anti-TNFα

ETANERCEPT

Anti-CD-20

RITUXIMAB

Anti-IL6-R

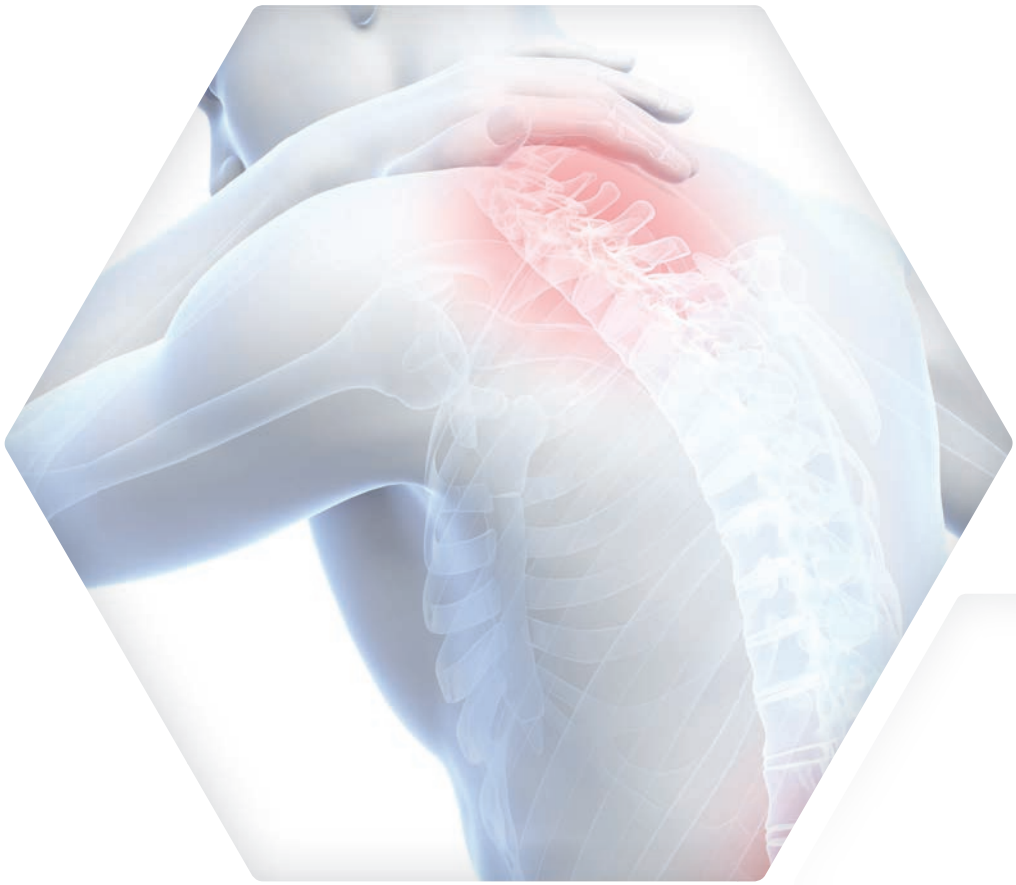
TOCILIZUMAB

Anti-IL17A

SECUKINUMAB

Anti-TNFα

INFLIXIMAB



IFX Biosimilars

IBD/RA/PsoA

2020

EFFECTS OF SUCCESSIVE SWITCHES TO DIFFERENT BIOSIMILARS INFLIXIMAB ON IMMUNOGENICITY IN CHRONIC INFLAMMATORY DISEASES IN DAILY CLINICAL PRACTICE

*Lauret A, Moltó A, Abitbol V, Gutermann L, Conort O, Chast F, Goulvestre C, Le Jeunne C, Chaussade S, Roux C, Batteux F, Dougados M, Allanore Y, Avouac J

*Paris Descartes University, Cochin Hospital, Rheumatology department, Paris, France

ABSTRACT

BACKGROUND: To determine whether the successive switches from innovator infliximab to a first then a second biosimilar infliximab, or from a first to a second infliximab biosimilar, increase the risk of immunogenicity during a 3-year observation period.

METHODS: This is a usual care study performed in the Rheumatology, Gastroenterology and Internal Medicine departments of Cochin Hospital, Paris, France. Two independent cohorts were constituted; Cohort 1 included 265 patients on maintenance therapy with the original treatment who successively switched to CT-P13 in October-December 2015 then to SB2 in December 2017. Cohort 2 included 44 biologic-naïve patients who received CT-P13 starting from November 2015 before being switched to SB2 in December 2017.The end of the observation period was December 2018. Immunogenicity was defined by the detection of positive anti-drug antibodies (ADA >10 ng/mL), at least at two consecutive time points.

RESULTS: Cohort 1 consisted on 265 patients on maintenance therapy with innovator infliximab who switched to CT-P13. Then, 140 patients switched to SB2, 26 remained treated with CT-P13, and innovator infliximab was re-established in 55 patients. 30 patients (16 females) had positive ADA at baseline visit (11.3%), before the switch to CT-P13. These patients were more likely to have a BMI >30 (45% vs. 17%, p< 0.001) and received less innovator infliximab infusions (28±20 vs. 40±25 infusions, p=0.012) than patients without ADA. Among the 235 ADA-free patients at baseline, 20 patients developed ADA during the observation period, corresponding to a rate of 3 for 100 patient years. The mean time to positive ADA detection was 21±14 months (range: 1-37 months). Kaplan Meyer curve illustrating immunogenicity-free survival showed no influence of the number of biosimilars infliximab received on immunogenicity (Figure 1A). Cohort 2 consisted of 44 biologic-naïve patients who initiated CT-P13. Among these patients, 29 switched to SB2, 4 remained treated with CT-P13 and 11 discontinued the treatment before the second switch. 11/44 (25%) patients developed ADA during the observation period, corresponding to a rate of 14 for 100 patients years. Only a single patient developed ADA after the switch to SB2. The mean time to positive ADA detection was 13±11 months (range: 1-31 months). The risk of treatment discontinuation was significantly higher in patients with positive ADA in both cohorts (cohort 1: Hazard Ratio, HR: 2.37, 95% CI 1.38-4.05, p=0.002 and cohort 2: HR: 2.79, 95% CI 1.04-7.52, p=0.042) (Figure 1B-C).Predictors of immunogenicity were only identified in cohort 2: a BMI >30 at baseline visit and mean infliximab through levels < 2 mg/mL from baseline visit to ADA detection were predictive of the development of ADA with HR (95% CI) of 5.54 (1.30-23.65) and 5.53 (1.30-23.43), respectively. The retention rate of infliximab was 58% (154/265) in cohort 1 and 66% (29/44) in cohort 2 at the end of observation period (Figure 1D-E).

CONCLUSIONS: Immunogenicity was not favored by switches to biosimilars infliximab in our study. Thus, immunogenicity does not constitute a barrier to interchangeability between biosimilars infliximab in chronic inflammatory diseases.

KEY POINTS

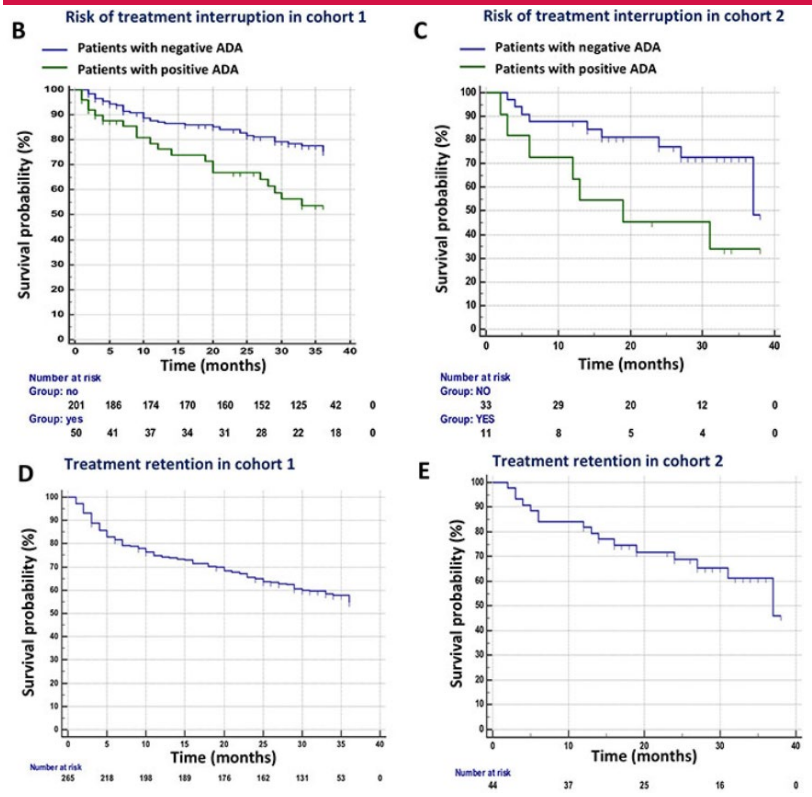


Figure 1. Kaplan Meyer survival Analyses. Risk of immunogenicity according to the number of biosimilars infliximab received :risk of treatment interruption according to the presence of anti-drug antibodies -ADA- in cohort 1 -B- and 2-C-; and treatment retention within the observation period in cohort 1 -D- and 2 -E-.

- This study allows the demonstration of a comparable immunization rate regardless the number of biosimilars received over a 3-year period

- Among the 235 ADA negative patients at baseline who received innovator infliximab during maintenance therapy (cohort 1), 8,5% developed ADA during the 3-year observation period. The incidence of ADA development was 11% in AxSpA, 3.5% in IBD, 8% in RA and 10% in PsA

- The rate of ADA seroconversion was 25% in infliximab-naïve patients (cohort2) who received biosimilars infliximab during the observation period. The incidence of ADA development was 20% in AxSpA, 22% in IBD,44% in RA and 25% in PsA

- In the two cohorts the risk of treatment discontinuation was significantly higher in patients with positive ADA at baseline visit or during follow-up compared to patients without ADA

- Patients who did not developed ADA within a long exposition period upon innovator infliximab may have a lower probability of further having ADA, given that ADA seroconversion usually occurs during the first months of treatment.

First study including the inclusion of patients that received 3 different infliximab molecules

IFX Biosimilars

RA/SpA/PsA

2019

EFFICACY, IMMUNOGENICITY AND COST ANALYSIS OF A SYSTEMATIC SWITCH FROM ORIGINATOR INFLIXIMAB TO BIOSIMILAR CT-P13 OF ALL PATIENTS WITH INFLAMMATORY ARTHRITIS FROM A SINGLE CENTER

Valido A*, Silva-Dinis J, Saavedra MJ, Iria I, Gonçalves J, Lopes JP, Fonseca JE

*Serviço de Reumatologia e Doenças Ósseas Metabólicas, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal

ABSTRACT

BACKGROUND: Biosimilar drugs are intended to be as effective as the originator product but with a lower cost to healthcare systems. In our center we promoted a switch from originator infliximab (IFXor) to biosimilar infliximab (CT-P13). We analyzed efficacy, safety, immunogenicity and cost savings of switching.

METHODS: Eligible patients were adults with the diagnosis of rheumatoid arthritis (RA), spondyloarthritis (SpA) and psoriatic arthritis (PsA) on therapy with IFXor for at least 6 months and with stable disease activity. Efficacy was measured considering change from baseline in Disease Activity Score in 28 joints (DAS28) for RA and PsA and in Ankylosing Spondylitis Disease Activity Score (ASDAS) for SpA. Disease worsening was considered when an increase of 1.2 from baseline in DAS28 or an increase of 1.1 in ASDAS occurred. Serum IFX levels (sIFX) were dichotomized as therapeutic (between 3-6 µg/mL), low (< 3 µg/mL), and high (> 6 µg/mL). Anti-drug antibody (ADA) levels were dichotomized into detectable (> 10 ng/ml) or non-detectable (< 10 ng/ml). A cost analysis was done based on the purchasing prices of the 2 drugs at our center. During a period of 1 year switch to CT-P13 was performed in 60 patients for non-medical reasons. We had a total of 36 patients with SpA, 16 with RA and 8 with PsA. Disease activity was stable over the observation period and similar to the values observed with IFXor.

RESULTS: Median follow-up time was 15 months during which 5 patients stopped CT-P13. Forty two switchers had blood samples collected before and after switch. A total of 27 patients had unaltered sIFX levels and ADA status during follow up. Three patients had detectable ADA at baseline, with low sIFX levels. After switch, ADAs became negative in 2 of those patients, and the other patient kept detectable ADA levels. ADAs became positive in 5 patients after switch. The switch to CT-P13 represented a 26.4 % reduction of costs in the use of IFX therapy in these patients.

CONCLUSIONS: The switch in routine care of a group of RA, SpA and PsA patients from IFXor to CT-P13 did not affect efficacy, safety, immunogenicity and reduced costs in 26.4%. The observed changes in blood samples were not associated with higher disease activity and did not lead to stopping IFX therapy.

KEY POINTS

TABLE V. ADA AND sIFX CONCENTRATION AT BASELINE AND AFTER SWITCH

	RA (n=13)			PsA (n=2)			SpA (n=27)			Total (n=42)		
	Baseline	After switch (3-9 m)	After switch (≥ 12 m)	Baseline	After switch (3-9 m)	After switch (≥ 12 m)	Baseline	After switch (3-9 m)	After switch (≥ 12 m)	Baseline	After switch (3-9 m)	After switch (≥ 12 m)
IFX serum concentration* (µg/mL)	11.5 (9.7)	9.6 (8.9)	7.4 (4.2)	6.9 (2.3)	6.7 (2.3)	6.7 (1.8)	6.1 (3.9)	6.2 (8.1)	5.4 (3.7)	7.6 (6.8)	7.9 (8.9)	6.1 (3.9)
Positive ADA, n/total	2/13	1/13	1/13	0/2	0/2	0/2	1/27	5/27	5/27	3/42	6/42	6/42

ADA: Anti-drug antibody; IFX: Infliximab; PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis; SpA: Spondyloarthritis; m: months. *mean values (SD)

Table V. Proportions of patients with various CT-P13 trough concentration cut-offs in 333 patients treated with CT-P13 maitenance therapy measured between week 14 and week 54 according to the type of inflammatory disease.

TABLE VI. PATIENTS SHOWING VARIATION IN ADA AND SIFX CONCENTRATION AT BASELINE AND AFTER SWITCH

	Baseline			3-9 months			12 months		
	sIFX (µg/mL)	ADA (ng/mL)	Nab (%)	sIFX (µg/mL)	ADA (ng/dL)	Nab (%)	sIFX (µg/mL)	ADA (ng/mL)	Nab (%)
Patient 1	1.5	100	30	5.1	10	0	4.6	10	0
Patient 2	0.4	180	50	1.0	250	70	0.7	200	80
Patient 3	1.7	80	30	3.2	10	0	5.3	10	0
Patient 4	8.8	10	0	1.6	70	0	3.0	10	0
Patient 5	6.51	10	0	6.9	80	0	7.4	120	0
Patient 6	5.6	10	0	0.6	280	80	1.1	320	40
Patient 7	4.8	10	0	0.6	360	50	0.6	250	70
Patient 8	5.8	10	0	41.4	214	0	10.2	260	0
Patient 9	3.0	10	0	0.03	10	0	1.1	50	0
Patient 10	5.1	10	0	1.8	10	0	2.3	10	0

ADA: Anti-drug antibody; sIFX: serum infliximab concentration; Nab: Neutralize antibody

Table 3. The predictors associated with therapeutic infliximab trough concentration (>3µg/mL) between week 14 and week 54 in 203 patients with Crohn's disease with CT-P13.

- This study reinforces that the real life switch from Infliximab originator to CT-P13 does not affect efficacy, safety or immunogenicity. The switch from infliximab originator to CT-P13 promoted a cost reduction of 26,4%

- Switch to a biosimilar drug reduced the financial burden of treating patients with inflammatory arthritis (cost saving of 26,4%) similarly to what has been reported in previous studies such as the NOR-SWITCH (cost saving of 39%)

- Patients with detectable antidrug antibody and low serum Infliximab levels who changed to non-detectable ADA, with normalization of sIFX (CT-P13), had no variation in disease activity

- Moreover, patients who maintained antidrug antibodies ADA after switch did not show differences in the amount of IgG1-lambda or IgG4, which may indicate that the transition from originator to CT-P13did not alter the immunogenic status of the patient.

First study assessing real-world use of TDM in RA, SpA and PsA patients treated with CT-P13

Anti-TNF drugs

RA

2018

CORRELATION BETWEEN HLA HAPLOTYPES AND THE DEVELOPMENT OF ANTIDRUG ANTIBODIES IN A COHORT OF PATIENTS WITH RHEUMATIC DISEASES

Maurizio Benucci*, Arianna Damiani*, Francesca Li Gobbi*, Francesca Bandinelli*, Maria Infantino*, Valentina Grossi, Mariangela Manfredi, Guillaume Noguier, Francesca Meacci

* Rheumatology Unit, Azienda Sanitaria, USLToscana Centro, Hospital S. Giovanni di Dio, Florence, Italy;

ABSTRACT

INTRODUCTION: The aim of this study was to investigate the correlation between human leukocyte antigen (HLA) haplotypes and the development of antidrug antibodies (ADAs) in a cohort of patients with rheumatic diseases.

PATIENTS AND METHODS: **We evaluated the presence of ADAs in 248 patients with inflammatory rheumatic diseases after 6 months of treatment with anti-TNF drugs**: 26 patients were treated with infliximab (IFX; three with rheumatoid arthritis [RA], 13 with ankylosing spondylitis [AS], 10 with psoriatic arthritis [PsA]); 83 treated with adalimumab (ADA; 24 with RA, 36 with AS, 23 with PsA); 88 treated with etanercept (ETA; 35 with RA, 27 with AS, 26 with PsA); 32 treated with certolizumab (CERT; 25 with RA, two with AS, five with PsA); and 19 treated with golimumab (GOL; three with RA, seven with AS, nine with PsA). Serum drug and ADA levels were determined using Lisa-Tracker Duo, the ADA-positive samples underwent an inhibition test, and the true-positive samples underwent genetic HLA typing. To have a homogeneous control population, we also performed genetic HLA typing of 11 ADA-negative patients.

RESULTS: After inhibition test, the frequency of ADAs was 2/26 patients treated with IFX (7.69%), 4/83 treated with ADA (4.81%), 0/88 treated with ETA (0%), 4/32 treated with CERT (12.5%), and 1/19 treated with GOL (5.26%). The frequency of HLA alleles in the examined patients was HLA-DRß-11 0.636, HLA-DQ-03 0.636, and HLA-DQ-05 0.727. **The estimated relative risks between the ADA-positive patients and the ADA-negative patients were HLA-DRß-11 2.528 (95% CI 0.336-19.036), HLA-DQ-03 1.750 (95% CI 0.289-10.581), and HLA-DQ-05 2.424 (95% CI 0.308-15.449)**.

CONCLUSION: This is the **first study that shows an association between HLA and genetic factors associated with the occurrence of ADAs in patients with rheumatic diseases**, but the number of samples is too small to draw any definite conclusion.

KEY POINTS

Frequency of HLA-DRβ1-11	Frequency of HLA-DQ-03	Frequency of HLA-DQ-05
Patients with ADAs		
0.636	0.636	0.727
Patients without ADAs		
0.182	0.363	0.454
RR		
2.528	1.750	2.424
95% CI		
0.336–19.036	0.289–10.581	0.308–15.449

Abbreviations: ADAs, antidrug antibodies; RR, relative risk.

Table 3. HLA frequency in rheumatic patients with and without ADAs.

- Using High-resolution HLA class I and II typing, the authors identified 3 HLA class II alleles associated with the development of antidrug antibodies (ADAs), Table 3.

- Authors indicate that the ADA frequencies observed in the study are in lign with numbers reported in the literature. However, variations observed in the literature may occur due to the different dosage methods used (ELISA, RIA,antigen-biding test, PH-shift anti-idiotype) as well as the underlying disease and/or with the concomitant use of immunosuppressive treatments.

- Further comparative studies are needed to investigate rheumatic patients who do not develop ADAs versus healthy subjects, and non-ADA patients and healthy subjects.

Within the many factors that can affect immunogenicity and lead to the development of antidrug antibodies, genetic background appears as an important factor.

IFX

RA

2017

METHOTREXATE REDUCED TNF BIOACTIVITY IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH INFLIXIMAB

Delphine Dénarié*, Mélanie Rinaudo-Gaujous, Thierry Thomas*, Stéphane Paul, and Hubert Marotte*

* Department of Rheumatology, CHU Saint-Etienne, Saint-Etienne, France

ABSTRACT

OBJECTIVES: To evaluate methotrexate effect on tumor necrosis factor (TNF) alpha bioactivity during infliximab (IFX) therapy in rheumatoid arthritis (RA) patients and to correlate TNF bioactivity with antibody towards IFX (ATI) development and RA clinical response.

METERIALS & METHODS: Thirty-nine active women RA patients despite conventional synthetic disease modifying antirheumatic drugs (csDMARDs) requiring IFX therapy were enrolled, and clinical data and blood samples were recorded at baseline (W0) and at 6 weeks (W6), W22, and W54 of IFX treatment. TNF bioactivity as well as IFX trough and ATI concentrations were assessed on blood samples.

RESULTS: TNF bioactivity decreased from W0 to W54 with a large range from W22 at the time of ATI detection. From W22, TNF bioactivity was lower in presence of methotrexate as csDMARD compared to other csDMARDs. IFX trough concentration increased from W0 to W54 with a large range from W22, similarly to TNF bioactivity. **Methotrexate therapy prevented ATI presence at W22 and reduced TNF bioactivity compared to other csDMARDs (p=0.002).**

CONCLUSION: **This suggests that methotrexate plays a key role in TNF bioactivity and against ATI development**.

KEY POINTS

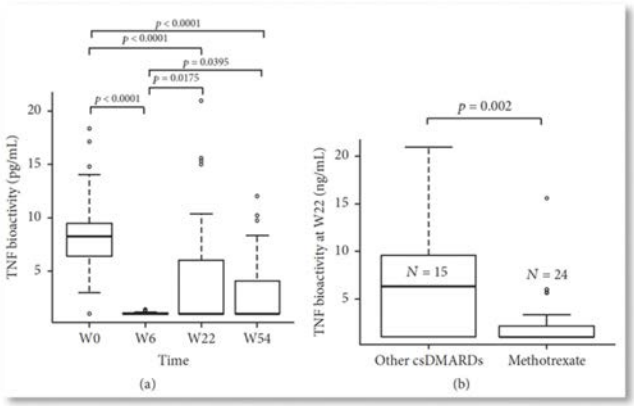


Figure 1. TNF bioactivity (a) decreased strongly at W6 with a sight increase afterwards. TNF bioactivity was lower in patients with methotrexate compared to patients with other csDMARDs (b).

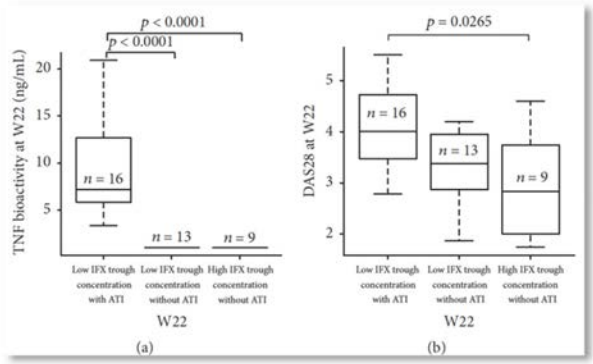


Figure 2. High TNF bioactivity was observed in the group "Low IFX trough concentration with ATI", but not in the groups "Low IFX trough concetration without ATI" and "High IFX trough concentration withour ATI"(a). Kruskal-Wallis rank sum test; p<0.0001). DAS28 was higher in the "Low IFX trough concentration with ATI" group compared to the two others (b), Kruskal-Wallis rank sum test; p=0,0266).

- This small study shows that although heterogenous during IFX therapy, TNF bioactivity strongly correlated with DAS28 and reflected clinical response.

- Authors explored TNF bioactivity in 3 groups according to IFX trough levels and ATI positivity at W22.

- Discrepant results between TNF bioactivity and low IFX trough levels (<2µg/mL) in presence or absence of ATI (cut-off at 20ng/mL) are reported.

- Authors also noticed that the development of ATI was 40% more frequent in RA patients than in SpA patients.

First report to show a Major role of methotrexate on ATI concentration and function in RA patients compared to other csDMARDs.

IFX & Biosimilar

SPA

2017

SAFETY, EFFICACY AND IMMUNOGENICITY OF SWITCHING FROM INNOVATOR TO BIOSIMILAR INFLIXIMAB IN PATIENTS WITH SPONDYLOARTHRITIS: A 6-MONTH REAL-LIFE OBSERVATIONAL STUDY

Maurizio Benucci*, Francesca Li Gobbi*, Francesca Bandinelli*, Arianna Damiani*, Maria Infantino, Valentina Grossi, Mariangela Manfredi, Simone Parisi, Enrico Fusaro, Alberto Batticciotto, Piercarlo Sarzi-Puttini, Fabiola Atzeni, Francesca Meacci.

*Rheumatology Unit, S. Giovanni do Dio Hospital, Florence, Italy.

ABSTRACT

BACKGROUND: Biosimilar infliximab (INX) was recently approved by the European Medicine Agency for the treatment of rheumatoid arthritis, ankylosing spondylitis (AS), Crohn's disease, ulcerative colitis, psoriatic arthritis (PsA), and psoriasis on the grounds that its pharmacokinetics, safety, and efficacy were comparable to those of innovator INX.

AIM: The aim of this study was to investigate the real-life efficacy, safety, and immunogenicity of switching from innovator to biosimilar INX in patients with spondyloarthritis (SpA).

METHODS: **Forty-one patients attending three Italian rheumatology centres with a previous diagnosis of SpA** and clinically inactive or moderate disease activity (ASDAS-CRP\ 2.1; 22 with AS, five with enteropathic arthritis, 10 with PsA, and four with undifferentiated SpA), who had been treated for more than 6 months with innovator INX in accordance with the ASAS/EULAR guidelines, were switched to biosimilar INX for pharmaco-economic reasons (Tuscany Law No. 450 of 7 April 2015) and followed up for 6 months. A record was kept of their BASDAI, BASFI, ASDAS-CRP, DAS28-CRP (in the presence of peripheral disease), MASES, VAS pain scores, the duration of morning stiffness, and adverse events (AEs).

RESULTS: At the time of the switch, the patients had a median age of 50.9 years (range 23–80), a median disease duration of 124.5 months (range 14–372), and a median duration of treatment with innovator INX of 73.7 months (range 6–144). After 6 months of biosimilar INX therapy, there were no statistical differences in their median BASDAI (2.73 ± 1.5 vs. 2.6 ± 1.3, p = .27), BASFI (2.34 ± 1.3 vs. 2.17 ± 1.2, p = 0.051), ASDAS-CRP (1.35 ± 0.3 vs. 1.28 ± 0.2, p = 0.24), DAS28-CRP (2.66 ± 0.67 vs. 2.67 ± 0.35, p = 0.92), MASES (0.35 ± 0.7 vs. 0.17 ± 0.4, p = 0.08), or VAS pain scores (18 ± 14.7 vs. 16.7 ± 11.3, p = 0.55), whereas the median duration of morning stiffness had significantly decreased (7.2 ± 6.9 vs. 5.8 ± 6, p = 0.02). Furthermore, **there was no change in circulating INX (4.22 ± 2.89 vs 4.84 ± 2.86 l g/mL, p = 0.80) or anti-INX antibody levels (27.76 ± 17.13 vs 27.27 ± 17.28 ng/mL, p = 0.98**).

CONCLUSION: The switch from innovator to biosimilar INX in this Italian multicentre SpA cohort was not associated with any statistically significance differences in efficacy, adverse events or anti-drug antibody level.

KEY POINTS

Parameters	Baseline	After 6 months	*p* value
BASDAI	2.73 ± 1.5	2.6 ± 1.3	0.27
BASFI	2.34 ± 1.3	2.17 ± 1.2	0.051
ASDAS-CRP	1.35 ± 0.3	1.28 ± 0.2	0.92
DAS28-CRP	2.66 ± 0.67	2.67 ± 0.35	0.24
MASES	0.35 ± 0.7	0.17 ± 0.4	0.08
VAS pain	18 ± 14.7	16,7 ± 11.3	0.55
Morning stiffness	7.2 ± 6.9	5.8 ± 6	0.02
Infliximab levels ug/mL	4.22 ± 2,89	4.84 ± 2.86	0.80
ADA Infliximab ng/mL	27,76 ± 17.13	27.27 ± 17.28	0.98

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *ASDAS-CRP* Ankylosing Spondylitis Disease Activity Score, disease activity score (DAS28)-CRP (in the presence of peripheral disease), *MASES* Maastricht Ankylosing Spondylitis Enthesitis Score, *VAS* visual analogic scale, pain scores; *ADA* anti-drug antibody

Table 1. Clinical and laboratory data at baseline and after 6 months of biosimilar INX.

- This paper provides the first real-life data showing that there is no immunogenic changes appear after switching from innovator INX to biosimilar INX in a cohort of 41 patients with spondyloarthritis. Results demonstrate that the switch is safe and efficacious.

- Authors also indicate that the reason to switch from iINX to bINX was motivated by governmental law to help sustainability of their national healthcare system. Considering the potential cost savings, it is of particular interest to determine whether newly diagnosed patients as well as those already under reference drugs can be effectively and safely treated with a particular biosimilar.

Careful assessment of the adverse events and immunogenicity of the switch from innovator to biosimilar biologics is needed as there is still limited evidence and no guidelines.

IFX

Inflamm Dis

2015

HIGH LEVEL OF ANTI-DRUG ANTIBODIES AFTER INTRA-ARTICULAR INJECTION OF ANTI-TNF

Pascal Zufferey*, Mathieu Perreau and Alexander So*

* Service de rhumatologie, Centre hospitalier universitaire vaudois, Lausanne, Switzerland

ABSTRACT

LETTER

KEY POINTS

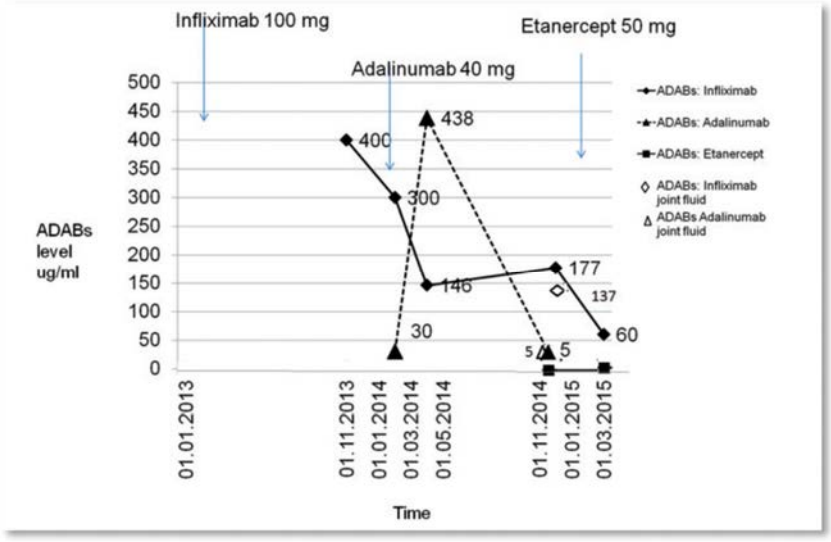


Figure 1. Evolution of blood and joint fluid anti-drug antibodies against the different agents injected into the knee ADABs cut-off for infliximab, adalimumab and etanercept: <10 μg/ml. ADAB: anti-drug antibodies.

- The Authors report data on the induction of anti-drug antibodies (ADABs) after intra-articular injection (100mg of IFX) in a 35-year-old patient with non-specific inflammatory mono-arthritis of the right knee that did not respond to 3 consecutive intra-articular steroid injections.
- Quantification of ADABs before the next infusion (9 months later) showed high levels of ADABs to IFX. ADABs diffused from joint to the blood and vice-versa.
- A single intra-articular exposure to a second anti-TNF agent was followed by the appearance of ADABs directed against the new monoclonal agent (40 mg Adalimumab).
- Authors suggested that the route of administration as well as long intervals between the injections/ low dose of IFX could be responsible for the rapid appearance of ADABs leading to a loss of response after repeated injections.

Anti-drug antibodies against anti-TNF monoclonal agents can appear even after single intra-articular infiltration. Such clinical observation support the monitoring of ADABs when isolated intra-articular injections of anti-TNF blocker are used.

Anti-TNFα

INFLIXIMAB

Anti-TNFα

ADALIMUMAB

Seminars in Arthritis and Rheumatism, Volume X, Number X, xxx 2018 – Abirisk Consortium

IFX & ADA

RA

2018

INCIDENCE AND RISK FACTORS FOR ADALIMUMAB AND INFLIXIMAB ANTI-DRUG ANTIBODIES IN RHEUMATOID ARTHRITIS : A EUROPEAN RETROSPECTIVE MULTICOHORT ANALYSIS

Jocelyn Quistrebert*, Signe Hässler*, Delphine Bachelet*, Cyprien Mbogning*, Anne Musters, Paul Peter Tak, Carla Ann Wijbrandts, Marieke Herenius, Sytske Anne Bergstra, Gülşah Akdemir, Martina Johannesson, Bernard Combe, Bruno Fautrel, Sylvie Chollet-Martin, Aude Gleizes, Naoimh Donnella, Florian Deisenhammer, Julie Davidson, Agnes Hincelin-Mery, PierreDönnes, Anna Fogdell Hahn, Niek De Vries, Tom Huizinga, Imad Abugessaisa, Saedis Saevarsdottir, Salima Hacein-Bey Abina, Marc Pallardy, Philippe Bröet, Xavier Mariette, on behalf of the ABIRISK Consortium.

* CESP, INSER MUMR1018, Faculty of Medicine, Paris-Sud University, Paris-Saclay University, UVSQ, Villejuif, France.

ABSTRACT

OBJECTIVE: To evaluate the incidence of anti-drug antibody (ADA) occurrences and ADA-related risk factors under adalimumab and infliximab treatment in rheumatoid arthritis (RA) patients.

METHODS: The study combined retrospective cohort from the ABIRISK project totaling 366 RA patients treated with adalimumab ($n = 240$) or infliximab ($n = 126$), 92.4% of them anti-TNF naive ($n = 328/355$) and 96.6% of them co-treated with methotrexate ($n = 341/353$) with up to 18 months follow-up. ADA positivity was measured by enzyme-linked immunosorbent assay. The cumulative incidence of ADA was estimated, and potential bio-clinical factors were investigated using a Cox regression model on interval-censored data.

RESULTS: ADAs were detected within 18 months in 19.2% ($n = 46$) of the adalimumab-treated patients and 29.4% ($n = 37$) of the infliximab-treated patients. **The cumulative incidence of ADA increased over time**. In the adalimumab and infliximab groups, respectively, the incidence was 15.4% (5.2–20.2) and 0% (0–5.9) at 3 months, 17.6% (11.4–26.4) and 0% (0–25.9) at 6 months, 17.7% (12.6–37.5) and 34.1% (11.4–46.3) at 12 months, 50.0% (25.9–87.5) and 37.5% (25.9–77.4) at 15 months and 50.0% (25.9–87.5) and 66.7% (37.7–100) at 18 months. **Factors associated with a higher risk of ADA development were: longer disease duration** (1–3 vs. < 1 year; adalimumab: HR 3.0, 95% CI 1.0–8.7; infliximab: HR 2.7, 95% CI 1.1–6.8), **moderate disease activity (**DAS28 3.2–5.1 vs. < 3.2; adalimumab: HR 6.6, 95% CI 1.3–33.7) **and lifetime smoking** (infliximab: HR 2.7, 95% CI 1.2–6.3).

CONCLUSION: **The current study focusing on patients co-treated with methotrexate for more than 95% of them found a late occurrence of ADAs not previously observed, whereby the risk continued to increase over 18 months. Disease duration, DAS28 and lifetime smoking are clinical predictors of ADA development.**

KEY POINTS

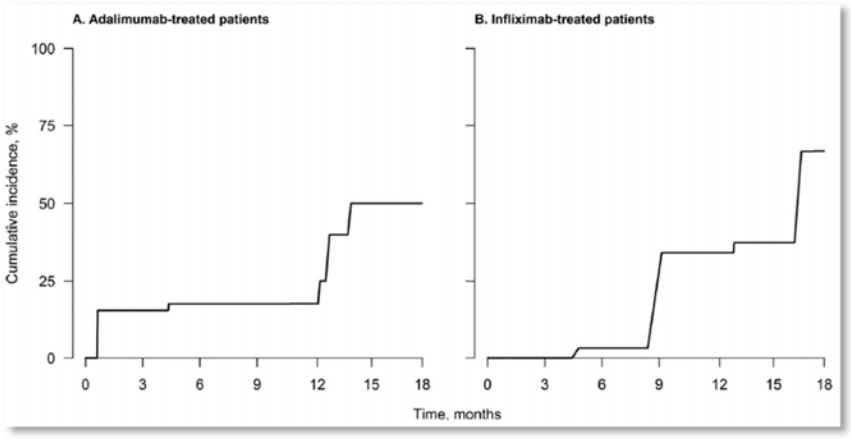
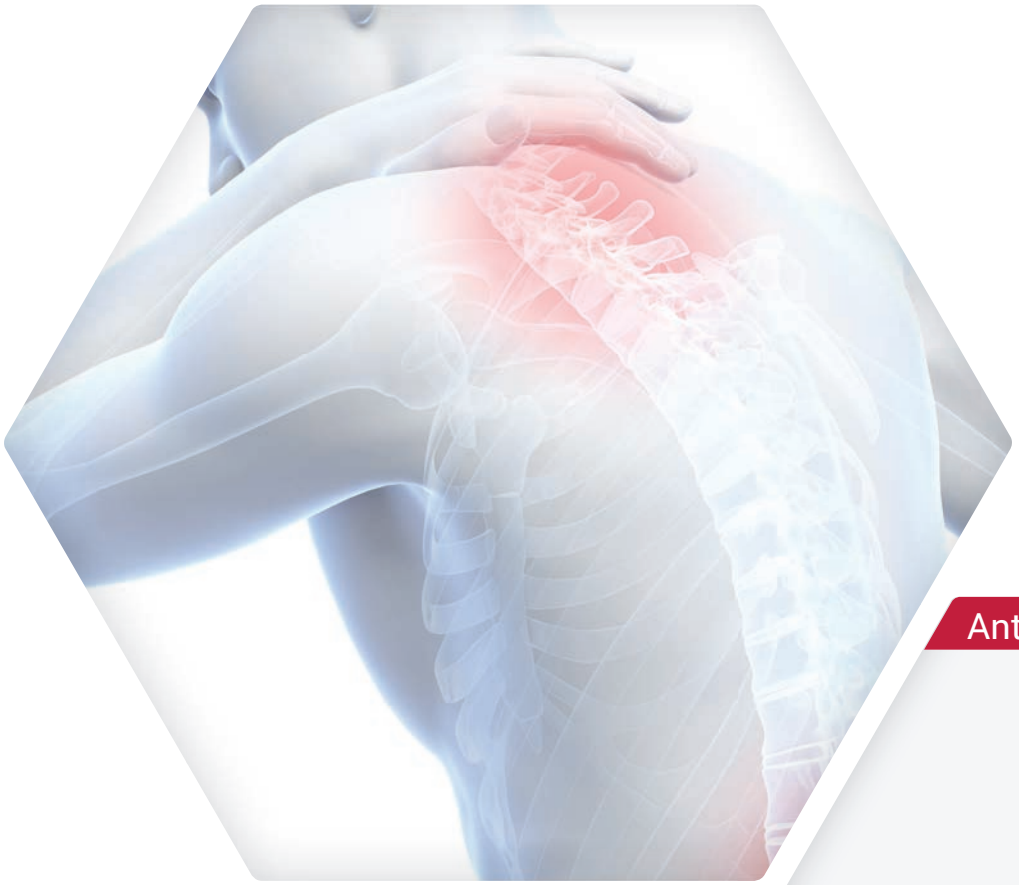


Figure 2. Cumulative incidence of anti drug antibody (ADA). Cumulative incidence of ADA over a maximum of 18 months follow-up in 240 adalimumab-treated patients (A) and 126 infliximab-treated patients (B).

Mean concentrations	adalimumab treated patients	infliximab-treated patients
ADA positive patients	6.7 µg/mL	0.8 µg/mL
ADA negative patients	10.6 µg/mL	15.9 µg/mL

- This study explores the immunogenicity of adalimumab and infliximab in 3 heterogenous populations of RA patients (IMPROVED/Amsterdam, n=62+92; ESPOIR, n=68; EIRA, n=18).
- Results showed ADA occurrence in 20-30% of RA patients treated and confirmed the association between ADA positivity and a low drug levels for both anti-TNF treatments.
- The median time to ADA occurrence was 4.5 months versus 13 months in adalimumab and infliximab-treated patients respectively.

The study provides results from real life clinical practice with the assessment of trough samples where ADA positivity appeared as a delayed phenomenon and was associated with a lower probability of clinical response for anti-TNF-treated patients.



Anti-TNFα

ETANERCEPT

ETA

RA

2012

ETANERCEPT CONCENTRATION IN PATIENTS WITH RHEUMATOID ARTHRITIS AND ITS POTENTIAL INFLUENCE ON TREATMENT DECISIONS: A PILOT STUDY

Claire Immediato Daïen, Vincent Daïen, Ermis Parussini *, Anne-Marie Dupuy, Bernard Combe and Jacques Morel.

Departement of Rhumatology, Hospital of Lapeyronie and Montpellier I University; *BMD, France

ABSTRACT

OBJECTIVES: For patients with rheumatoid arthritis (RA), recommendations are inconclusive about whether tumor necrosis factor-a (TNF-a)-blocker therapy should be evaluated at 3 or 6 months. Biomarkers are needed to predict at 3 months which patients would benefit from further treatment because of nonoptimal response. Our objective was to investigate whether serum etanercept (ETN) concentrations and anti-ETN antibodies at 3 months are predictors of clinical response to ETN at 6 months in patients with RA in terms of European League Against Rheumatism criteria and Disease Activity Score in 28 joints (DAS28).

METHODS: Between 2009 and 2010, we included 19 women with active RA who were candidates for ETN therapy. Response criteria were evaluated at 3 and 6 months. **Serum concentrations of ETN and anti-ETN antibodies were measured by ELISA at baseline and at 3 and 6 months**.

RESULTS: **Eighteen patients completed follow up**. Three-month ETN concentrations were lower for 6-month nonresponders than responders ($p = 0.03$). Three-month ETN levels correlated significantly with change in DAS28 between baseline and 6 months ($r = -0.62$, $p = 0.006$). **The best predictor of response at 6 months was observed with an ETN threshold of 3.1 µg/ml at 3 months. No anti-ETN antibodies were found**.

CONCLUSIONS: **ETN concentrations at 3 months predict response to ETN therapy at 6 months. Low ETN concentrations could explain the absence of response to ETN, suggesting that patients with low ETN levels could benefit from increased ETN dose or earlier interruption of treatment.**

KEY POINTS

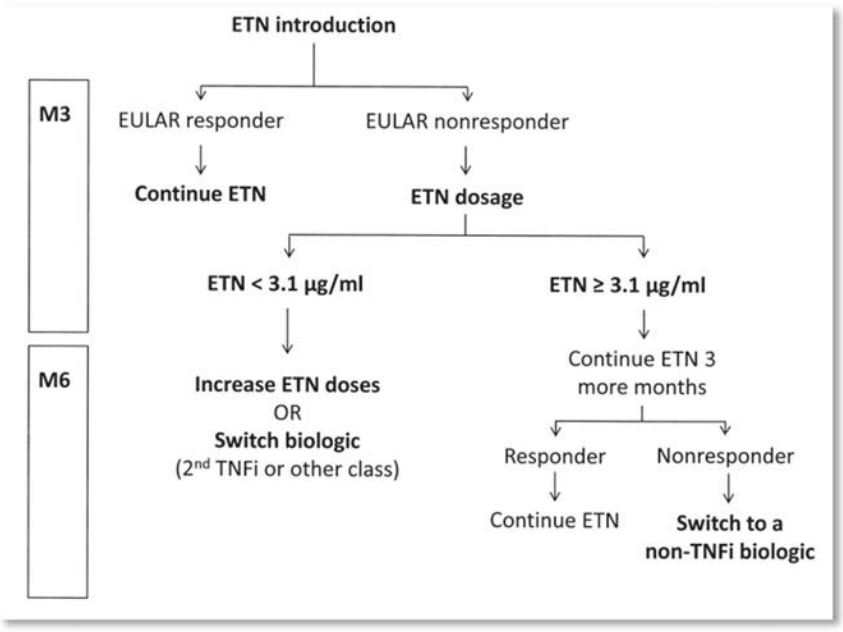


Figure 4. Proposed decision algorithm for the management of RA with etanercept (ETN). TNFi: TNF inhibitor; European League Against Rheumatism.

- The authors report clinical utility of ETN serum concentration assessment in a small cohort of patients.

- An ETN threshold of 3,1µg/ml was associated with a sensitivity of 87% and a specificity of 67%. And the DAS28 at 6 months was significantly higher in patients with low than in those with high median 3-month ETN concentrations.

- The impact of ETN dosage increase deserves more investigations to propose new strategies of anti-TNF drug dosage according to disease activity and clinical remission. Validation studies on larger cohorts are needed.

- The authors question the benefit of switching to another TNF inhibitor in case of nonresponse despite optimal ETN concentration and suggest to switch to another class of biologics.

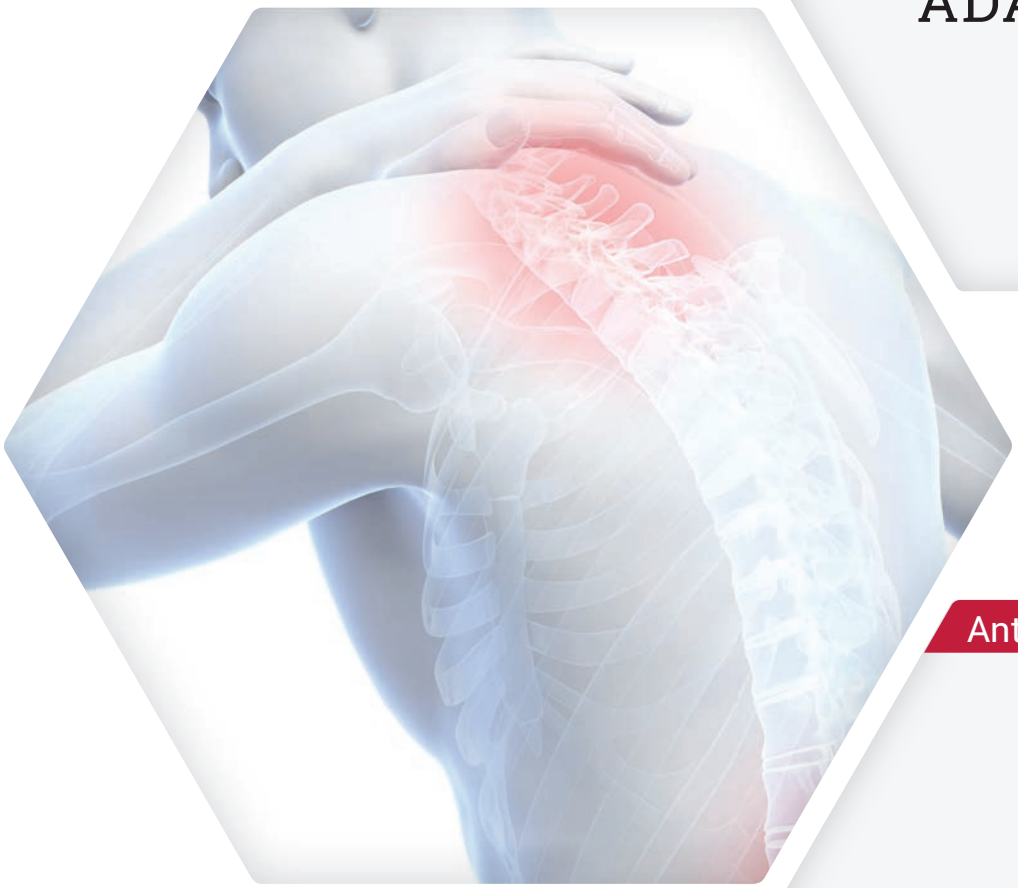
The study proposes a decision algorithm to be used in daily practice based on clinical response and optimal thresholds of biomarkers predictors.

Anti-TNFα

INFLIXIMAB

Anti-TNFα

ADALIMUMAB



Anti-TNFα

ETANERCEPT

ADA/ETN

RA

2019

TAPERING WITHOUT RELAPSE IN RHEUMATOID ARTHRITIS PATIENTS WITH HIGH TNF BLOCKER CONCENTRATIONS: THE STRASS STUDY

*Marrotte H, Rinaudo-Gaujous M, Petiet C, Fautrel B, Paul S

*Rheumatology Department, CHU Saint-Etienne, Saint-Etienne, France

ABSTRACT

BACKGROUND: At the time of personalised medicine, prediction of the absence of relapse during tapering strategy is a huge challenge to improve this approach. Furthermore, EULAR recommendations proposed in RA patients in remission without glucocorticoids to first step down the bDMARDs.We investigated the interest of TNF blocker blood concentration assessment in order to predict the absence of relapse during tapering in the STRASS study. The STRASS study demonstrated the feasibility of step-down therapeutic strategy compared with maintenance strategy in RA patients in clinical remission treated with adalimumab or etanercept. In contrast to l'Ami study, which performed a single tapering, successive tapering step every 3 months in RA patient still in remission was performed.

METHODS: Among the 137 patients included in STRASS study, 132 serum samples were collected solely at baseline without other blood collections and assessed by ELISA with Lisa Tracker (adalimumab or etanercept kit by Theradiag, Marne-La-Vallee, France). We defined high level of TNF blocker, by concentration higher or equal to upper detection limits in serums (8 µg/mL for adalimumab and 5 µg/mL for etanercept). For adalimumab, this definition was similar to the definition of high trough concentrations defined by l'Ami.

RESULTS: Overall, in STRASS study, no clear effect was observed between high blood levels of TNF blockers at baseline and persistence of remission over 24 months. However, when focusing at 6 months (that means two first steps-down in the spacing arm), the proportion of patients without relapse was higher in case of high TNF blockers concentration at baseline (x^2=6.22; p=0.01; figure 1). In the l'Ami study, adalimumab trough concentration decreased under the high concentration level at 12 and 24 weeks after only one tapering. This could explain the increased rate of relapse after the third tapering in STRASS (figure 1). Furthermore, no data with etanercept on tapering are available to date. Difference pattern of flares between RA patients treated by adalimumab or etanercept could be due to the absence of cut-off previously reported for etanercept

CONCLUSIONS: Our data suggest to perform a drug monitoring before each tapering, in order to avoid the situation with low TNF blockers blood trough concentration leading to clinical relapse. Furthermore, to reduce the high TNF blockers trough concentration could be also benefit for the RA patients in remission since high TNF blockers trough concentration was reported to be associated with a strong risk of infection. The clinical utility of TNF blockers monitoring and determination of specific cut-offs in predicting clinical remission had already been explored especially in inflammatory bowel diseases.5 Here, we claim the monitoring of trough concentrations in order to improve successful tapering strategy In conclusion, we confirmed that tapering is feasible without an increased rate of relapse in RA patients with clinical remission and high TNF blocker blood concentration. Furthermore, since the initial concentration of STRASS study will be predictive of RA relapse in case of TNF blocker injection spacing, we propose to assess trough TNF blocker concentration before each tapering step in order to maintain remission and avoid a relapse in RA patients with clinical remission. Finally, we proposed an algorithm to manage step-down strategy (figure 2), which should be confirmed in a prospective study.

KEY POINTS

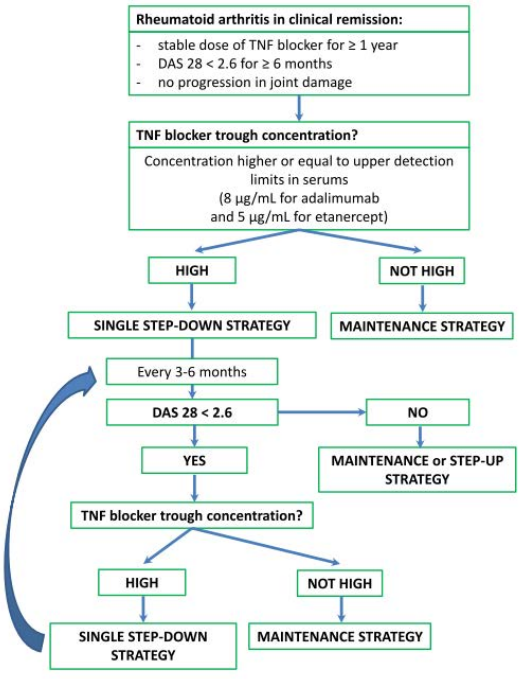


Figure 1: . Proposed algorithm based on therapeutic drug monitoring to improve tapering strategy.

- This study suggests the value of monitoring through concentrations before each tapering in RA patients to avoid the situation with low TNF-blockers blood concentration leading to clinical relapse.

-Reducing high TNF blocker can also benefit for RA patients in remission to adjust the treatment and reduce the risk of infection.

-High level of TNF blocker was defined by concentration higher or equal to upper detection limits in serums (8 µg/ml for adalimumab and 5 µg/ml for etanercept)

- An algorithm to manage step-down strategy in accordance with TNF blocker trough concentration has been proposed.

Tapering driven by TDM is feasible and does not lead to an increased rate of relapse in RA patients with clinical remission and high TNF blocker concentration.

IFX, ADA & ETN

RA & AS

2016

EFFECT OF SERUM ANTI-TUMOUR NECROSIS FACTOR(TNF) DRUG TROUGH CONCENTRATIONS AND ANTIDRUG ANTIBODIES (ADAB) TO FURTHER ANTI-TNF SHORT-TERM EFFECTIVENESS AFTER SWITCHING IN RHEUMATOID ARTHRITIS AND AXIAL SPONDYLOARTHRITIS

Fabien Bernard Vincent*, Stephan Pavy*, Roman Krzysiek, Thierry Lequerrée, Jérémie Sellam, Yassine Taoufik, Xavier Mariette*, Corinne Miceli-Richard *

* Department of rheumatology, Hôpital Bicêtre, France

ABSTRACT

LETTER TO THE EDITOR

KEY POINTS

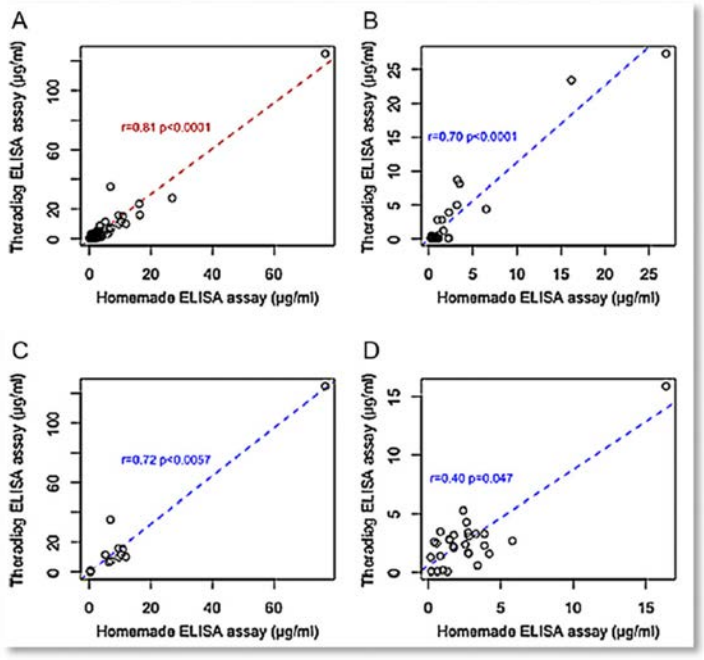


Figure 1. Correlation between homemade and commercial Theradiag ELISAs for serum anti-TNF drug levels (µg/mL) quantification in patients with RA and AS. Correlation between homemade and commercial Theradiag ELISAs for serum anti-TNF drug levels quantification in the whole cohort (A), and in subsets of patients with IFX (B), ADA (C), and ETN (D).

- In this multi-centre study, authors report the levels of serum trough levels and anti-drugs antibodies (when a failure decision was taken and before the drug switch) in a cohort of 44 RA patients and 31 AS patients.
- **Authors show that homemade and commercial ELISAs, were significantly correlated in the whole cohort in IFX and ADA subsets, whereas ETN drugs levels were weakly correlated**.
- Serum drug trough concentrations were significantly higher in RA patients without detectable ADAb (n=20) compared to those with ADAb (n=16). This was not observed in AS patients.
- Either the presence of ADAb to the failed TNF inhibitor or serum TNF levels quantified before the switch were not associated to the clinical response of the subsequent anti-TNF drug.

Serum trough concentration may be a predictive biomarker to assess short-term effectiveness of a further anti-TNF therapy after switching in RA and AS.

Anti-TNFα

CERTOLIZUMAB

CTZ

RA

2020

EXPOSURE-RESPONSE RELATIONSHIP OF CERTOLIZUMAB PEGOL AND ACHIEVEMENT OF LOW DISEASE ACTIVITY AND REMISSION IN PATIENTS WITH RHEUMATOID ARTHRITIS

Paul S*, Marotte H, Arthur Kavanaugh A, Goupille P, Kvien TK, de Longueville M, Mulleman D,Sandborn WJ, Vande Casteele N

*Department of Immunology, CIC1408, GIMAP EA3064, Université Jean Monnet, Saint Étienne, France.

ABSTRACT

BACKGROUND: Anti-tumor necrosis factor (anti-TNF) drugs are often prescribed for the treatment of rheumatoid arthritis (RA) and other immune-mediated inflammatory diseases. Although this treatment has been shown to be effective in many patients, up to 40% of patients do not achieve disease control. Drug concentration in plasma may be a factor affecting the observed variability in therapeutic response. In this study, we aimed to identify the plasma concentrations of the anti-TNF certolizumab pegol (CZP), associated with improvement in disease activity in patients with RA. Data were pooled from three randomized, controlled clinical trials with a combined total of 1,935 patients analyzed. Clinical outcomes of low disease activity (LDA) and remission were defined as Disease Activity Score in 28 joints with C-reactive protein (DAS28(CRP)) ≤ 2.7 and < 2.3, respectively. Quartile analysis results indicated that there may be an exposure–response relationship between CZP concentration and LDA/remission outcomes at weeks 12

METHODS: In this study, we aimed to identify the plasma concentrations of the anti-TNF certolizumab pegol (CZP), associated with improvement in disease activity in patients with RA. Data were pooled from three randomized, controlled clinical trials with a combined total of 1,935 patients analyzed. Clinical outcomes of low disease activity (LDA) and remission were defined as Disease Activity Score in 28 joints with C-reactive protein (DAS28(CRP)) ≤ 2.7 and < 2.3, respectively.

RESULTS: Quartile analysis results indicated that there may be an exposure–response relationship between CZP concentration and LDA/remission outcomes at weeks 12 and 24; the association was strongest for LDA ($P < 0.05$). Receiver operating characteristic (ROC) analysis showed that CZP concentrations ≥ 28.0 µg/ml at week 12, and ≥ 17.6 µg/ml at week 24, were associated with a greater likelihood of achieving LDA/remission outcomes. Although confirmatory studies are warranted to define the optimal CZP therapeutic range at weeks 12 and 24, these data indicate that CZP concentrations may be associated with improvement of disease activity

CONCLUSIONS: CZP concentrations may be associated with improvement of disease activity

KEY POINTS

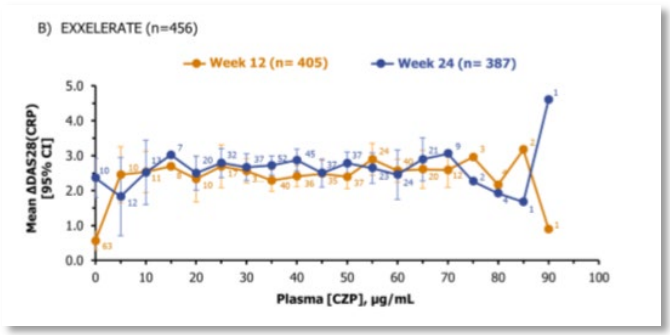


Figure 1. Exposure-response curve of CZP-versus change from baseline in DAS28(CRP) at weeks 12 and 24.

Outcome	Week	AUROC (95% CI)	CZP cut-off point[a] (µg/mL)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
DAS28(CRP) remission	12	0.58 (0.51, 0.64)	28.0	86.0	20.2	36.4	73.0
DAS28(CRP) LDA	12	0.54 (0.47, 0.60)	30.4	80.0	24.2	58.6	47.4
DAS28(CRP) remission	24	0.59 (0.53, 0.65)	23.2	89.6	19.7	51.2	66.7
DAS28(CRP) LDA	24	0.57 (0.51, 0.64)	17.6	93.3	17.0	69.2	55.9

Table 3. Summary of ROC analyses in EXXELERATE (CZP-randomised patients).

- This publication supports the argument that the clinical effect of anti-TNFs may be concentration-dependent for some patients, and therefore some non-responders who have sub-therapeutic drug concentrations may benefit from a change in dosage rather than an immediate switch to a different biologic

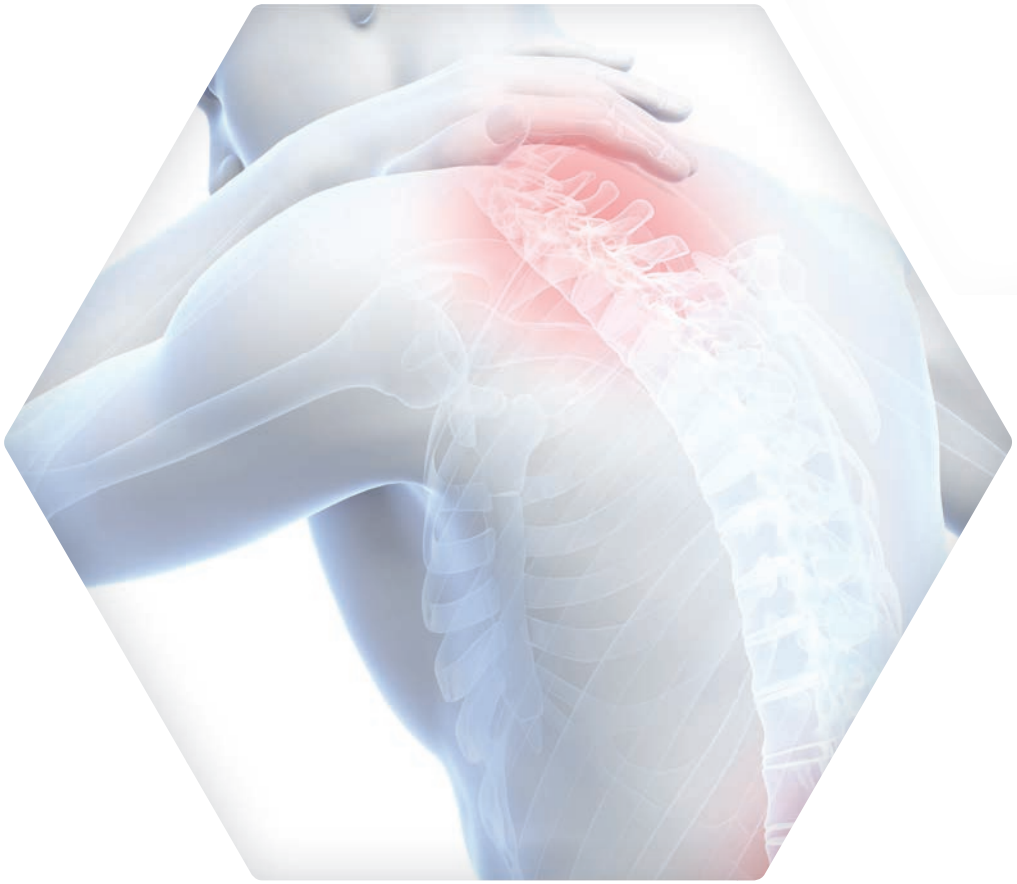
- Based on the ROC analysis of EXXELERATE data, CZP concentrations ≥28.0µg/mL at week 12 were associated with a greater likelihood of achieving DAS28(CRP) LDA and remission outcomes

- CZP concentrations ≥ 17.6µg/mL at week 24 were associated with LDA and remission outcomes

- Plasma CZP concentrations <10µg/mL were generally associated with smaller improvement from baseline in DAS28 (CRP) compared to patients with higher CZP

- Authors suggest that CZP concentrations cut-offs are associated with the likelihood of achieving DAS28(CRP) LDA and remission

Monitoring Plasma CZP concentration may help to guide treatment strategies and potentially achieve better clinical outcomes for patients with Rheumatoid Arthritis



Anti-IL6-R

TOCILIZUMAB

TCZ

RA

2018

FIXED DOSING OF INTRAVENOUS TOCILIZUMAB IN RHEUMATOID ARTHRITIS. RESULTS FROM A POPULATION PHARMACOKINETIC ANALYSIS

Bastida Carla*, Ruiz-Esquide Virginia, Pascal Marion, de Vries Schultink Aurelia H M, Yagüe Jordi, Sanmartí Raimon, Huitema Alwin D R, Soy Dolors*

* Pharmacy Department, Hospital Clinci Barcelona, of Gastroenterology, Spain

ABSTRACT

AIM: Intravenous tocilizumab is currently dosed on body weight although a weak correlation between body weight and clearance has been described. The aim of the study was to assess the current dosing strategy and provide a scientific rational for dosing using a modeling and simulation approach.

METHODS: Serum concentrations and covariates were obtained from intravenous tocilizumab treated subjects at a dose of 4, 6 or 8 mg every 28 days. A population pharmacokinetic analysis was performed using nonlinear mixed effects modeling. The final model was used to simulate tocilizumab exposure to assess a dosing strategy based on body-weight or fixed dosing, using as target a cumulative area under the curve at 24 weeks of treatment above 100 · 103 µg·h/mL..

RESULTS: A one-compartment disposition model with parallel linear and nonlinear elimination best described the concentration-time data. The typical population mean values for clearance, apparent volume of distribution, maximum elimination rate and Michaelis-Menten constant were 0.0104 L/h, 4.83 L, 0.239 mg/h and 4.22 µg/mL, respectively. Interindividual variability was included for clearance (17.0%) and volume of distribution (30.8%). Significant covariates for clearance were patient body weight and C-reactive protein serum levels. An estimated exponent for body weight of 0.360 confirms the weak relationship with tocilizumab clearance. **Simulations demonstrate that patients with lower weights are at risk of underdosing if the weight-based dosing approach is used. However, fixed-dosing provides a more consistent drug exposure regardless of weight category.**

CONCLUSIONS: **Our study provides evidence to support fixed dosing of intravenous tocilizumab in rheumatoid arthritis patients since it reduces variability in tocilizumab exposure among weight categories compared to the current weight-based dosing approach.**

KEY POINTS

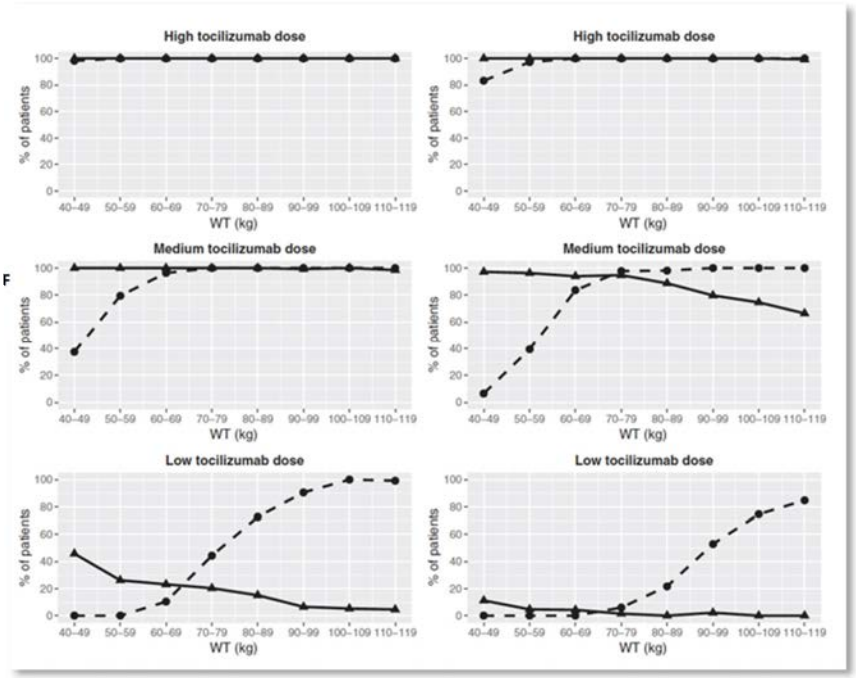


Figure 3. Percentage of patients reaching the efficacy target (cumulative area under the curve at 24 weeks of treatment with intravenous tocilizumab above 100 x 10^3 µg h ml^{-1}) with intravenous tocilizumab at different doses: high dose, 560 mg and 8 mg kg^{-1}; medium dose, 420 mg and 6 mg kg^{-1}; low dose, 280 mg and 4 mg kg^{-1} along a weight (WT) range, using two different dosing approaches: fixed dosing (solid line) vs. body-weight based dosing (dashed line). Results from 1000 simulations, without considering the effect of CRP (left column) and considering a CRP of 2.8 mg dl^{-1} (right column).

- Authors investigate quantitative relationships between the PK parameters and physiological and/or demographic features of 35 subjects with RA disease treated with iv TCZ. Serum concentration was measured at trough, 7, 14 and 21 days after infusion.

- No anti-drug antibodies could be detected in all patients tested showing TCZ levels below 1µg/ml thus supporting the low incidence of ADA formation in RA patients treated with TCZ.

- Results show that the distribution of cAUC values among weight groups after fixed dosing is much more uniform than after weight dosing.

- Interestingly, authors reported a significant effect of CRP on TCZ clearance.

With no linear correlation between body weight and exposure to TCZ, fix-dosing approach appears appropriate in adult RA patients. Routine measurement of specific parameters may help predicting treatment response and optimal dose.

TCZ

RA

2016

CORRELATIONS BETWEEN IMMUNOGENICITY, DRUG LEVELS, AND DISEASE ACTIVITY IN AN ITALIAN COHORT OF RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOCILIZUMAB

Benucci M*, Meacci F, Grossi V, Infantino M, Manfredi M, Bellio E, Bellio V, Li Gobbi F*, Bazzichi L, Moscato P, Caputo D, Saviola G, Talotta R, Sarzi-Puttini P, Atzeni F.

*Rheumatology Unit, S. Giovanni do Dio Hospital, Florence, Italy.

ABSTRACT

AIM: The aim of this study was to evaluate the real-life immunogenicity of anti-drug antibodies, drug levels, and disease activity in an Italian cohort of rheumatoid arthritis patients treated with tocilizumab (TCZ).

METHODS: We evaluated **126 TCZ-treated patients with rheumatoid arthritis** (16 males and 110 females; mean age 59±12 years, range 26–83; mean disease duration 11±5 years) with inadequate 12-week response to any synthetic and biological disease-modifying anti-rheumatic drugs, in a retrospective analysis. One-hundred and seven patients were treated with methotrexate mean dose 12.6±1.3 mg/week in combination with TCZ, 13 received TCZ monotherapy, and six received leflunomide 20 mg/day plus TCZ; all patients were treated with prednisone mean dose 6.4±1.2 mg/day. They had a 28-joint Disease Activity Score (DAS28) of >3.2, an erythrocyte sedimentation rate (ESR) of >30 mm/hour, and CRP levels of >1.0 mg/dL. We evaluated at baseline and after 6 months of treatment: DAS28; rheumatoid factor (RF) IgM, IgA, and IgG; anti-citrullinated peptide antibody; ESR; CRP; TNF-α; and IL-6. **TCZ and anti-TCZ antibodies were detected using LISA-TRACKER Duo TCZ.** TCZ levels of <10 µg/mL were considered low and >10 µg/mL high.

RESULTS: After 6 months of treatment only one patient was positive for anti-TCZ antibodies. **There were correlations between DAS28, ESR, and CRP and IL-6 levels in all patients.** Comparison of the 84 patients with TCZ levels of <10 µg/mL and the 42 with TCZ levels of >10 µg/mL showed the following differences: DAS28: 3.09±1.32 vs 2.78±1.32, *P*=0.0005; ESR: 27±14.8 vs 14±12 mm/hour, *P*=0.0001; CRP: 1.47±1.05 vs 0.65±0.80 mg/dL, *P*=0.0086; TNF-α: 10.2±1.2 vs 9.9±1.1 pg/mL, *P*=0.999; IL-6: 3.65±4.75 vs 3.62±4.41 pg/mL, *P*=0.97; anti-citrullinated peptide antibody: 85.2±93.7 vs 86.7±90.3 IU/mL, *P*=0.94; RF IgM: 72.4±62.7 vs 68.3±61.6 IU/mL, *P*=0.754; RF IgA: 41.7±36.4 vs 47.8±42.1 U/mL, *P*=0.449; and RF IgG: 46.4±46.1 vs 59.3±58.2 U/mL, *P*=0.212.

CONCLUSION: These findings show that the occurrence of anti-drug antibodies against TCZ is very rare and that there are statistically significant correlations between TCZ levels of >10 µg/mL and ESR, CRP levels, and DAS28.

KEY POINTS

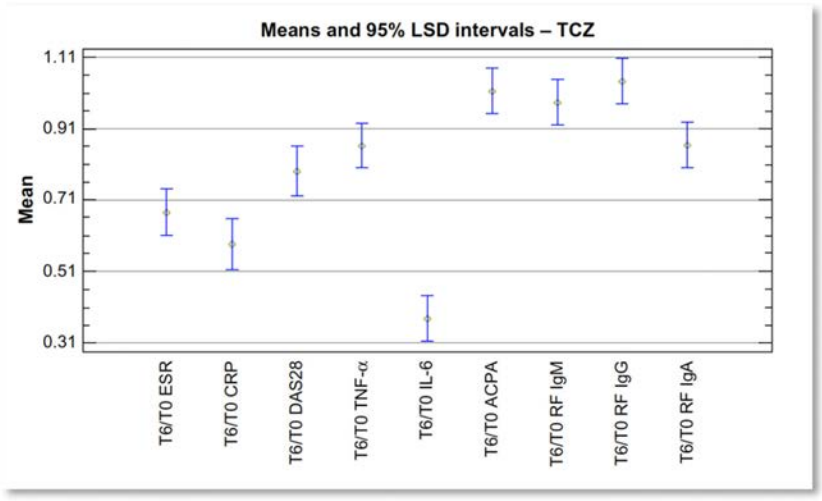


Figure 1. Correlation between level of TCZ and clinical and laboratory parameters.
Note: T0, baseline; T6, after 6 months of treatment.
Abbreviations: LSD, least significant difference; RF, rheumatoid factor; TCZ, tocilizumab; ESR, erythrocyte sedimentation rate; DAS28, 28-joint Disease Activity Score; ACPA, anti-citrullinated peptide antibody.

- As reported in other studies, the authors confirm the low immunogenicity of the TCZ biologic with the scarce occurrence of transient or neutralizing antibodies in TCZ treated patients.

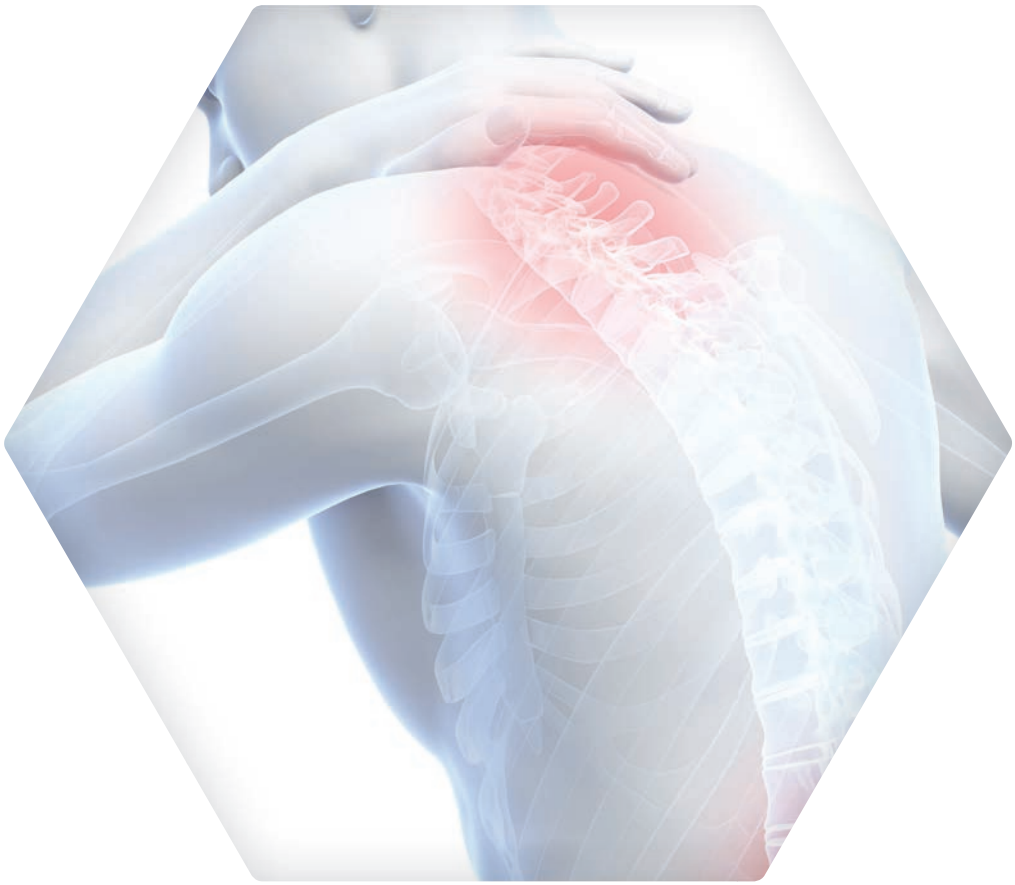
- The authors indicate that the low prevalence of TCZ ADAs could be a consequence of TCZ-induced IL-6 blockade acting on Tfh CD4 T cells and/or B cells at their different stages of differentiation and maturation since it was shown that IL-6 induces antibody production indirectly.

-Results show statistically significant correlation of TCZ levels of >10mg/mL with several clinical and biological parameters.

Therapeutic drug monitoring appears useful to assess biological parameters and disease activity in RA patients treated with TCZ.

Anti-CD-20

RITUXIMAB



RTX

RA/sAID

2020

IMMUNIZATION TO RITUXIMAB IS MORE FREQUENT IN SYSTEMIC AUTOIMMUNE DISEASES THAN IN RHEUMATOID ARTHRITIS: OFATUMUMAB AS ALTERNATIVE THERAPY

Combier A*, Nocturne G, Henry J, Belkhir R, Pavy S, Le Tiec C, Descamps E, Seror R, Mariette X

*Department of Rheumatology, Hôpitaux Universitaires Paris-Sud, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris-Sud, INSERM UMR1184 Le Kremlin Bicêtre, France

ABSTRACT

BACKGROUND: The frequency and consequences of anti-drug antibodies to rituximab (RTX-ADA) are not well known in RA and even less in other systemic auto-immune diseases (sAID). We aimed to evaluate the frequency, consequences and predictive factors of RTX-ADA in RA and sAID

METHODS: All patients presenting with RA or other sAID treated with RTX from 2012 to 2017 in our tertiary reference centre for sAID were retrospectively studied. Patients who were tested for RTX-ADA were identified.

RESULTS: One hundred and ninety-nine patients were treated with RTX (RA: 124, other sAID: 75). Among 62/199 (31.1%) tested for RTX-ADA, 14 were positive: 3/35 RA (8.6%) and 11/27 (40.7%) other sAID, (P = 0.0047). Among the whole RTX-treated populations, the frequency of RTX-ADA was 2.4% and 14.7% (P = 0.0026) in RA and sAID, respectively. Most of the immunized patients had infusion reactions to second or subsequent RTX cycles (11/14) and loss of efficacy (2/14). Predictive factors of immunization were sAID vs RA (78.6% vs 21.4%, P = 0.026, adjusted odds ratio (OR) = 5.35[1.43—54.75]) and African ethnicity (57.1% vs 4.2%, P < 0.001, adjusted OR = 9.25 [5.08—302.12]). Associated immunosuppressive therapy did not protect against immunization. Three patients with pSS immunized against RTX were treated with ofatumumab with complete remission of their disease.

CONCLUSIONS: Immunization against RTX is more frequent in other sAID than in RA. Testing for RTX-ADA must be performed in patients with infusion reactions or loss of efficacy especially if they are of African origin. Immunized patients might be treated efficiently and safely with ofatumumab. This alternative should be further evaluated for sAID

KEY POINTS

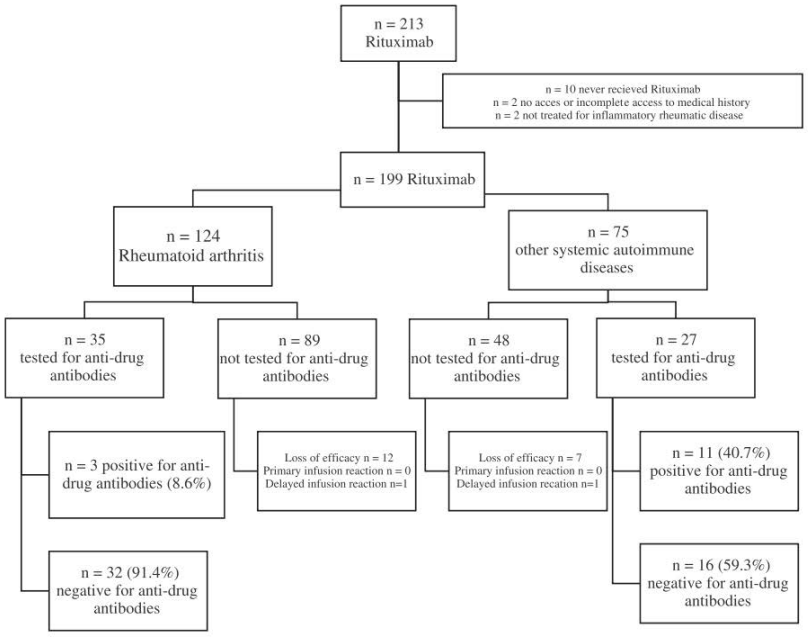


Figure 1. Flow chart

- Among the whole RTX-treated populations, the rate of RTX-ADA is higher in patients with Systemic Autoimmune Diseases sAID (40.7%) compared with patients with RA (8.6%)

- Immunization against RTX is an event leading to loss of efficacy, absence of B-cell depletion and delayed infusion reactions.

- It is appropriate to have Anti-drug antibody concentrations measured in patients presenting with one of these three features

- Infusion reactions are well-known side effects of rituximab and may be prevented by steroid premedication

- Genetic factors may be associated with Anti-drug antibody formation and some polymorphisms in the BAFF gene increasing B-cell activity or in the NCR3 gene increases immune response.

-Young age was also identified as another predictive factor of immunization against RTX

In case of immunization, pursuing rituximab may be dangerous and Ofatumumab, a fully humanized mAb represents an alternate anti-CD20 therapy in rituximab-immunized patients

Dermatology

Anti-TNFα

CERTOLIZUMAB

Anti-TNFα

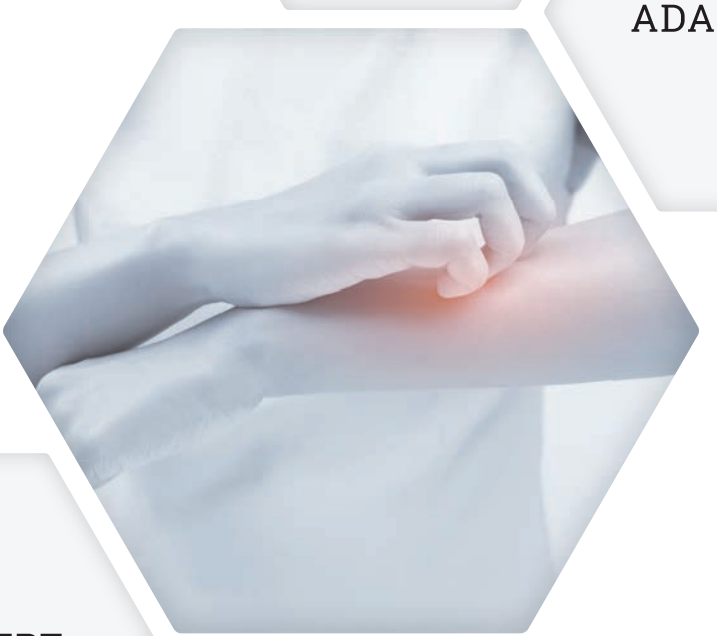
GOLIMUMAB

Anti-TNFα

INFLIXIMAB

Anti-TNFα

ADALIMUMAB



Anti-TNFα

ETANERCEPT

Anti-IL12/IL23

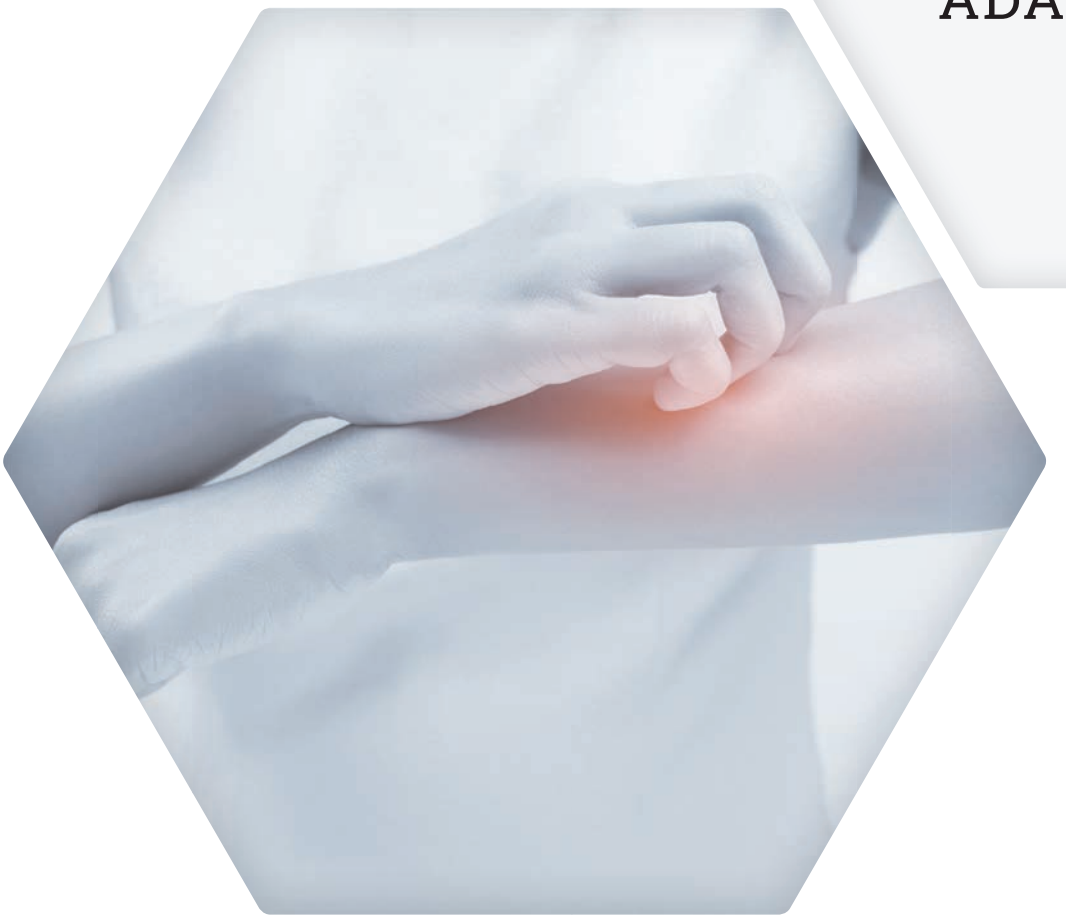
USTEKINUMAB

Anti-IL17A

SECUKINUMAB

Anti-TNFα

ADALIMUMAB



ADA

PSO

2017

IMPORTANCE OF IMMUNOGENICITY TESTING FOR COST-EFFECTIVE MANAGEMENT OF PSORIASIS PATIENTS TREATED WITH ADALIMUMAB

Fernando Mota*, Esmeralda Neves, José Carlos Oliveira, Manuela Selores*, Tiago Torres*

*Department of Dermatology, Porto Central Hospital, Porto, Portugal

ABSTRACT

INTRODUCTION: Up to 30% of patients treated with anti-tumor necrosis factor drugs do not respond adequately, and up to 50% lose response over time. Immunogenicity is now known to be one of the main causes of this loss of response.

METHODS: Serum levels of adalimumab and anti-drug antibodies (ADAs) were measured in 19 patients with psoriasis.

RESULTS: Eighty-nine percent of the patients were responders (Psoriasis Area Severity Index (PASI) > 75) and 11% were partial responders (PASI 50–75). The serum levels of adalimumab were lower than the cutoff in both of the partial responders and the ADAs were high, whereas the other 17 patients had adalimumab levels above the cutoff and low ADA levels. Both partial responders were obese and none of them were taking methotrexate. Both patients switched to ustekinumab, and a PASI 90 response was observed after 16 weeks.

CONCLUSION: Immunogenicity is a risk of biological drugs. **In this work, the detection of low levels of adalimumab and high levels of ADAs using a sandwich ELISA correlated with loss of clinical response. Testing immunogenicity and the drug pharmacokinetics of biological drugs in psoriasis patients will probably be part of the daily management of these patients in the future**.

KEY POINTS

Partial responder characteristics	PR 1	PR 2
Age, years	67	46
Sex	Male	Female
Body mass index	35	39
Psoriatic arthritis	No	Yes
Co-treatment w/ MTX	No	No
Duration of treatment w/ adalimumab, months		
Total	13	24
w/ partial response*	6	6
Duration of dose optimization, months**	0	2
Adalimumab levels (µg/ml)	0.1	0.7
Cutoff › 4.9 µg/ml		
ADA levels (µg/ml)	27.6	9.6
Cutoff › 10 µg/ml		

*From worsening until biologic switch
**Duplication of standard dose regimen

Table 2. Partial responder (PR) characteristics. MTX = methotrexate, ADA = anti-drug antibody.

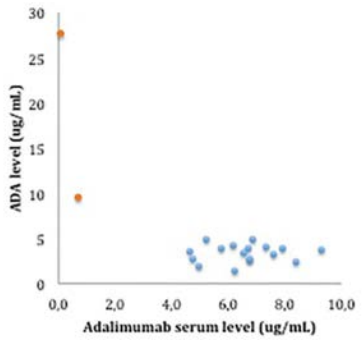


Figure 1. Distribution of adalimumab and ADA serum levels. Orange dots = partial responders (PASI 50–75), blue dots = responders (PASI > 75), ADAs = anti-drug antibodies.

- The study presents data from the real life clinical practice for psoriasis patients treated with adalimumab.

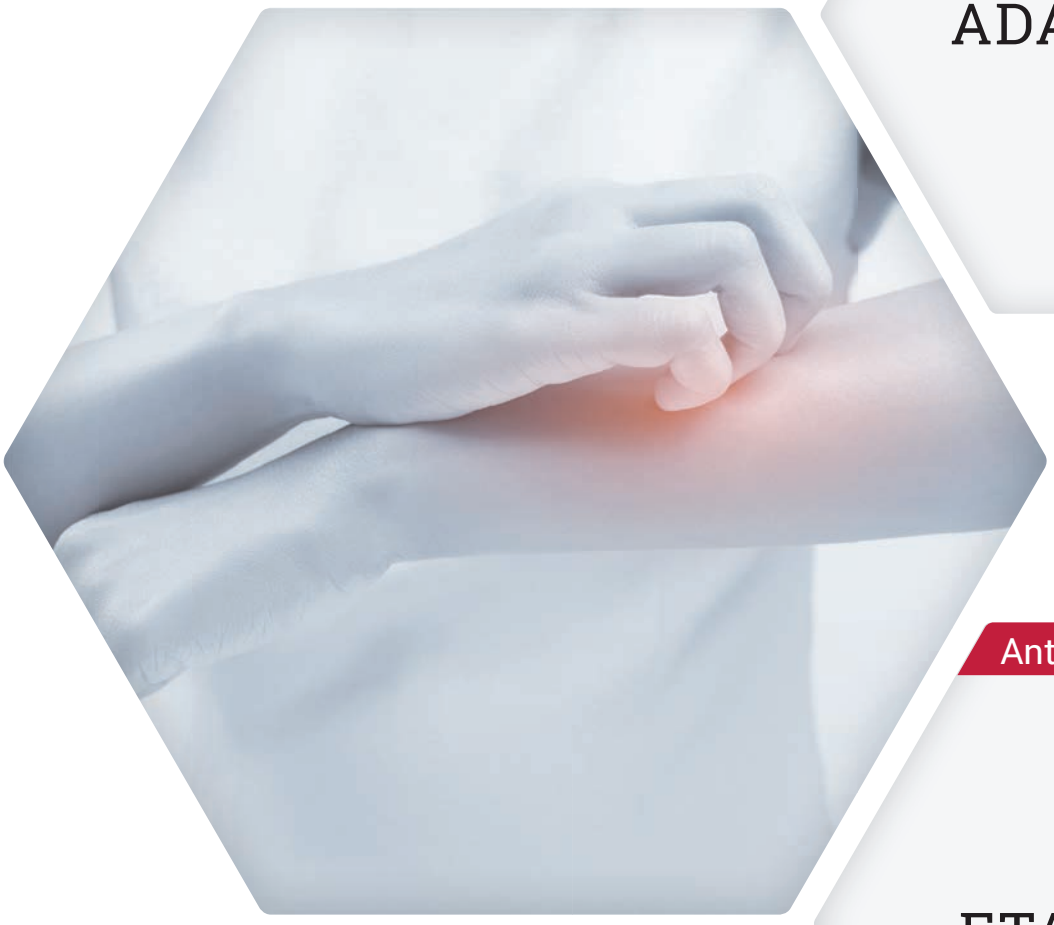
- The authors confirm the observation that the presence of high titers of anti-drug antibobies (cutoff level of 10 µg/mL) correlates with low adalimumab concentration (cutoff level of 4.9 µg/mL) and a lack of clinical response.

- The authors are in favour of the use of TDM in psoriasis patients to help clinicians optimizing the dose or interval of administration while maintaining efficacy and allowing possible cost savings.

Despite the absence of statistical significance due to the small size of the cohort, the study reports that monitoring immunogenicity in psoriasis patients appears as a powerful approach that should be taken into account alongside with clinical efficacy, safety profile and the impact on comorbidities.

Anti-TNFα

ADALIMUMAB



Anti-TNFα

ETANERCEPT

ADA & ETA

PSO

2013

PREDICTING TREATMENT RESPONSE IN PSORIASIS USING SERUM LEVELS OF ADALIMUMAB AND ETANERCEPT: A SINGLE-CENTRE,COHORT STUDY

S.K. Mahil*, Z. Arkir, G. Richards, C.M. Lewis, J.N. Barker* and C.H. Smith*

*St John's Institute of Dermatology, Division of Genetics and Molecular Medicine, King's College London, U.K.

ABSTRACT

BACKGROUND: A substantial proportion of patients with psoriasis do not respond, or lose initial response to tumour necrosis factor-α antagonists. One possible mechanism relates to subtherapeutic drug levels due to an immunogenic antibody response.

OBJECTIVES: To investigate the association between serum adalimumab and etanercept levels, antidrug antibody levels and clinical response in a cohort of patients with psoriasis using a commercially available enzyme-linked immunoassay.

METHODS: **In a single-centre cohort of 56 adults** with chronic plaque psoriasis initiated on adalimumab or etanercept monotherapy between 2009 and 2011, drug and antidrug antibody levels were measured at the patients' routine clinic reviews (4, 12 and 24 weeks of treatment and the last available observation). Patients' responses at 6 months were stratified into responders [75% reduction in Psoriasis Area and Severity Index from baseline (PASI 75) or Physician's Global Assessment score of 'clear' or 'nearly clear'] and nonresponders (failure to achieve PASI 50).

RESULTS: After 4 weeks, **adalimumab levels were significantly higher in responders compared with nonresponders** (P = 0,003) and these higher levels were sustained at 12 and 24 weeks. **Anti adalimumab antibodies were detected in 25% of nonresponders** (two of eight patients, average 22,5 weeks' follow-up) and none of the responders (n = 23, average 26,1 weeks' follow-up). **There was no significant association between etanercept levels and clinical response at 4 weeks (P = 0,317) and no anti etanercept antibodies were detected.** Lack of serum trough levels may have resulted in underestimation of the prevalence of antidrug antibodies.

CONCLUSIONS: **Early adalimumab drug level monitoring at 4 weeks may be useful in predicting treatment response and potentially reduce drug exposure** (and associated cost) with earlier review of treatment in those with low levels. **No conclusions about the value of etanercept drug monitoring can be made due to the paucity of data. Larger studies are now required to assess the clinical utility and cost-effectiveness of these assays in personalizing therapy in psoriasis**.

KEY POINTS

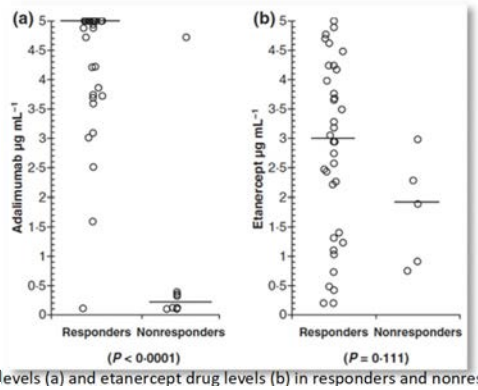


Figure 2. Adalimumab drug levels (a) and etanercept drug levels (b) in responders and nonresponders at weeks 4, 12 and 24. Each data point represents a single serum sample. Horizontal bars represent median serum drug levels.

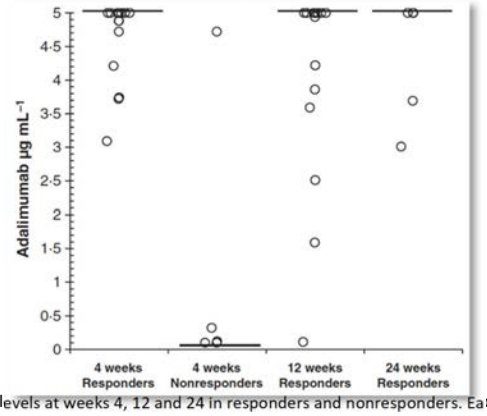


Figure 3. Adalimumab drug levels at weeks 4, 12 and 24 in responders and nonresponders. Each data point represents a single serum sample. Horizontal bars represent median serum adalimumab levels. There were insufficient data for nonresponders at 12 and 24 weeks to make any comparison with responders.

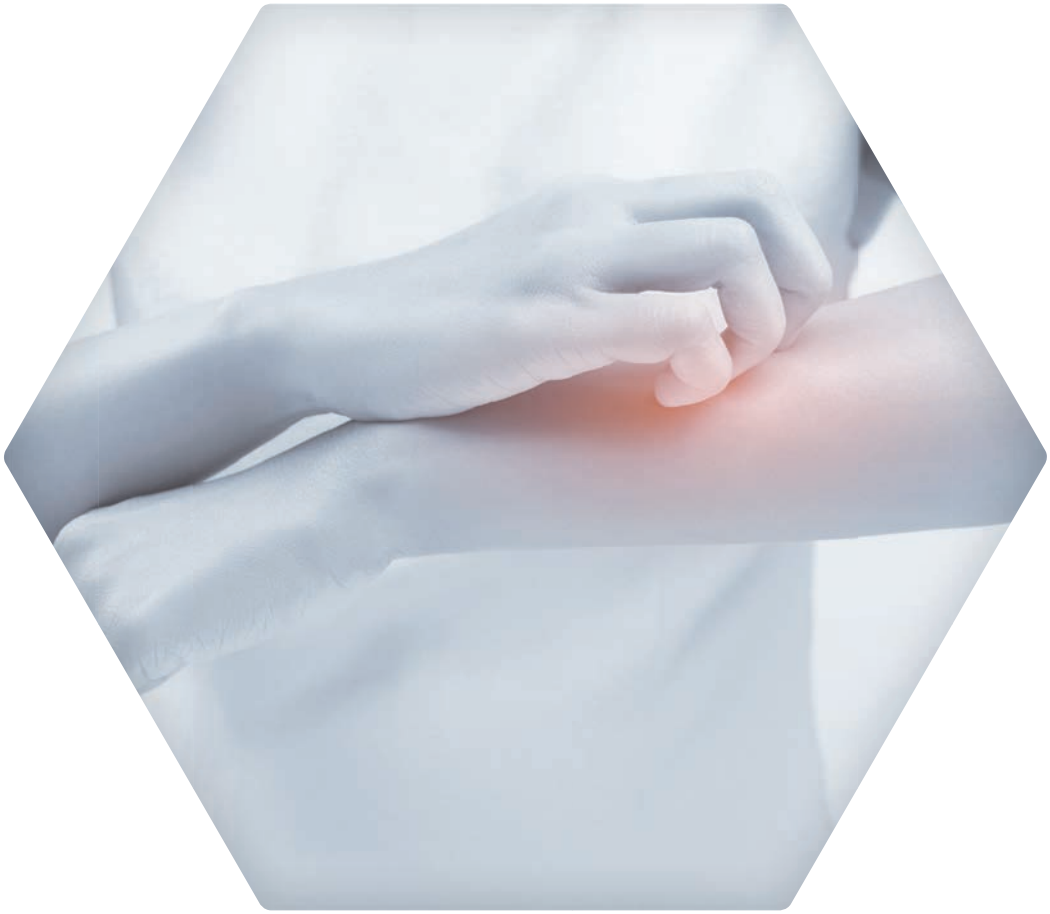
- In this small study, 74% of patients (23 out of 31) who received adalimumab showed a clinical response. 68% of patients (17 out of 25) under etanercept were responsive.

- First study to demonstrate that adalimumab drug levels at 4 weeks predict response at 6 months, with low or absent levels associated with failure to achieve 50% improvement in PASI values.

- Results show that anti adalimumab antibodies are associated with nonresponse.

- Large-scaled studies along with drug and anti-drug assay standardization are needed to further explore therapeutic thresholds drug concentrations.

Personalized approach to therapy by quantifying drug levels using ELISA tests may enable early assessment of immunogenicity status, pharmacokinetics parameters and prediction of treatment responses.



Anti-IL12/IL23

USTEKINUMAB

UST

PSO

2018

USEFULNESS AND CORRELATION WITH CLINICAL RESPONSE OF SERUM USTEKINUMAB LEVELS MEASURED AT 6 WEEKS VERSUS 12 WEEKS

M. Toro-Montecinos*, F. Ballescá*, C. Ferrandiz*, A. Teniente-Serra, E. Martinez-Caceres & J. M. Carrascosa*

* Department of Dermatology, Hospital Universitario Germans Trias i Pujol, Barcelona, Spain.

ABSTRACT

BACKGROUND: Monitoring serum drug levels has been proposed as a useful tool for improving and personalizing the management of psoriasis. However, in the case of ustekinumab the usefulness of such monitoring was not demonstrated when drug levels were measured at week 12.

OBJECTIVE : To evaluate the correlation of serum ustekinumab levels measured at weeks 6 and 12 with clinical response.

METHODS: In a prospective cohort study, we enrolled patients with psoriasis treated with ustekinumab 45mg every 12 weeks for at least 24 weeks. We measured serum ustekinumab levels at weeks 6 and 12 in each patient. Using the absolute PASI score, response to treatment was defined as optimal (≤1), excellent (≤3), appropriate (>3 and ≤5), or inappropriate (>5).

RESULTS: About 54 serum samples from 27 patients were analyzed. **No correlation was found between serum drug levels and absolute PASI at week 12. At week 6, an inverse linear correlation was found (p=.0001). Moreover, serum levels at week 6 were higher in patients with optimal, excellent and appropriate responses than in patients with an inappropriate response.**

CONCLUSION: **Assessment of ustekinumab serum levels at week 6 could provide useful information in routine clinical practice.**

KEY POINTS

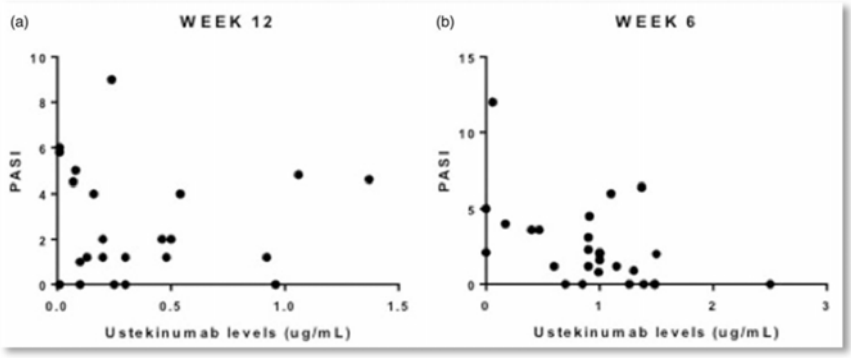


Figure 1. Correlation between serum ustekinumab levels and absolute PASI at week 12 (a), and at week 6 (b).

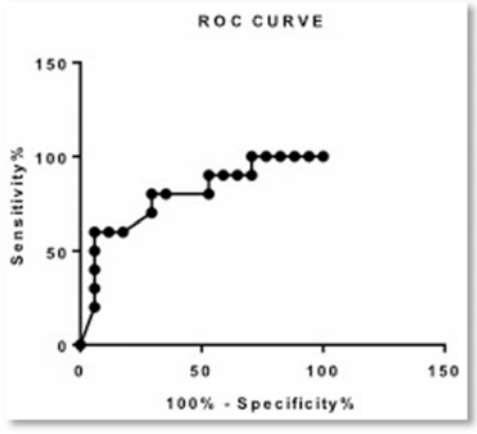


Figure 3. Receiver operating characteristic (ROC) curve for sensitivity and specificity to determine the lower limit value of the therapeutic range of the cohort.

- This observational study has shown a statistically significant linear correlation between absolute PASI and measurement of ustekinumab serum levels at week 6.
- Authors emphasize the observed persistence of the effects of the drug in the cutaneous immune system at week 6 in clinical pratice.
- The cut-off value of 0.95 µg/mL (sensibility 80%, specificity 71%) was chosen at the lower end of the range. The upper limit of the therapeutic range was set at 1.8 µg/mL because no improvement in PASI was detected above this value.
- Interestingly no relationship was observed between patient weight and serum drug levels.
- Further confirmation is needed on a larger number patients.

Measurement of serum drug levels at week 6 may provide more information for the TDM of ustekinumab. Authors support the use of analytical tools that can facilitate better and more personalized monitoring of patients and even help to predict response to biologic therapies.

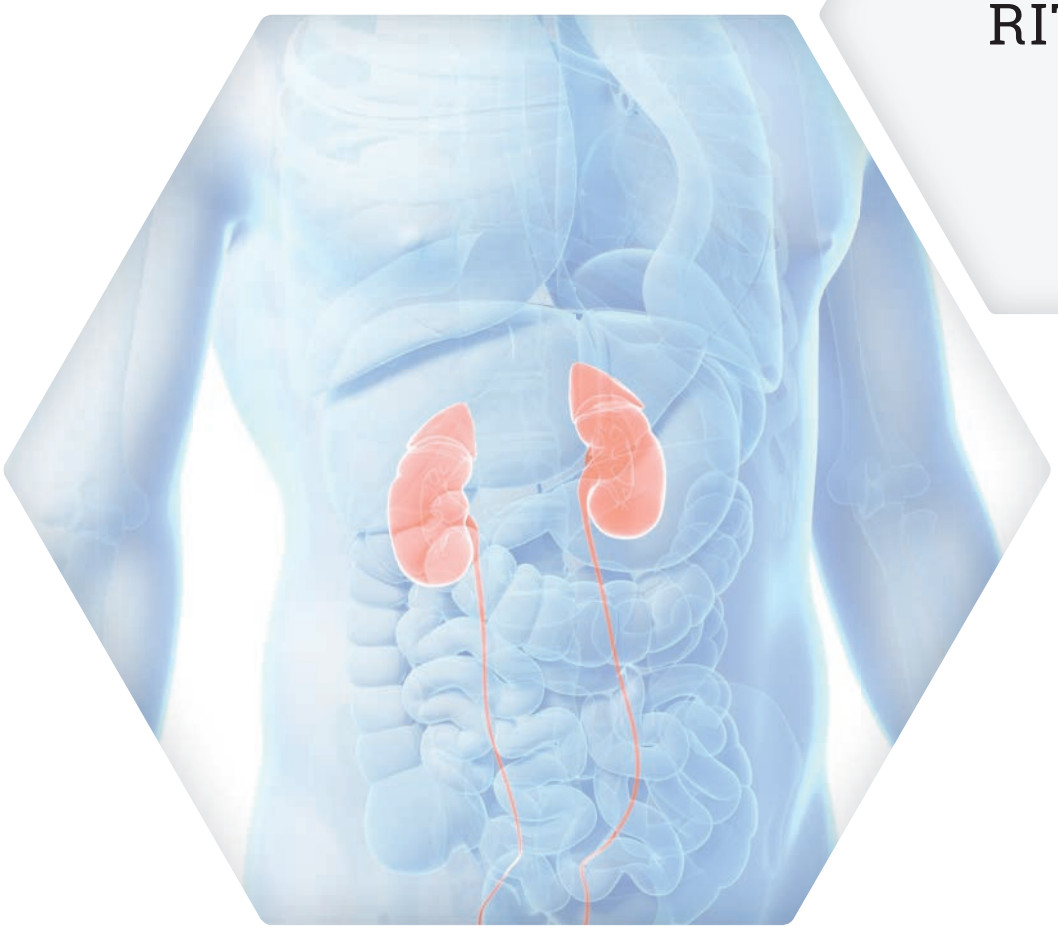
Nephrology

Anti-CD-20

RITUXIMAB

Anti-CD-20

RITUXIMAB



HIGH-DOSE RITUXIMAB AND EARLY REMISSION IN PLA2R1-RELATED MEMBRANOUS NEPHROPATHY

RTX

MN

2020

Seitz-Polski B, Dahan K, Debiec H, Rousseau A, Andreani M, Zaghrini C, Ticchioni M, Rosenthal A, Benzaken S, Bernard G, Lambeau G, Ronco P, Esnault VLM.

*Department of Immunology, Hôpital l'Archet, Centre Hospitalier Universitaire de Nice, Nice, France

ABSTRACT

BACKGROUND: Different rituximab protocols are used to treat membranous nephropathy. We compared two rituximab protocols in patients with membranous nephropathy.

METHODS: Twenty-eight participants from the NICE cohort received two infusions of 1-g rituximab at 2-week intervals, whereas 27 participants from the Prospective Randomized Multicentric Open Label Study to Evaluate Rituximab Treatment for Membranous Nephropathy (GEMRITUX) cohort received two infusions of 375 mg/m2 at 1-week interval. We measured serum rituximab levels and compared remission at month 6 and before any treatment modification and analyzed factors associated with remission and relapses.

RESULTS: Remissions occurred in 18 (64%) versus eight (30%) from the NICE and GEMRITUX cohort (P=0.02) at month 6, respectively, and in 24 (86%) versus 18 (67%) participants (P=0.12) before treatment modification, respectively. Median time to remission was 3 [interquartile range (IQR), 3-9] and 9 [IQR, 6-12] months for NICE and GEMRITUX cohorts respectively (P=0.01). Participants from the NICE cohort had higher circulating level of rituximab and lower CD19 counts (3.3 µg/L [IQR, 0.0-10.8] versus 0.0 [IQR, 0.0-0.0] P<0.001 and 0.0 [IQR, 0.0-2.0] versus 16.5 [IQR, 2.5-31.0] P<0.001) at month 3, lower level of anti-PLA2R1 antibodies at month 6 (0.0 [IQR, 0.0-8.0] versus 8.3 [IQR, 0.0-73.5] P=0.03). In the combined study population, lower epitope spreading at diagnosis and higher rituximab levels at month 3 were associated with remissions at month 6 (13/26 (50%) versus 22/29 (76%) P=0.05 and 2.2 µg/ml [IQR, 0.0-10.9] versus 0.0 µg/ml [IQR, 0.0-0.0] P<0.001 respectively). All non-spreaders entered into remission whatever the protocol. Eight of the 41 participants who reached remission had relapses. Epitope spreading at diagnosis (8/8 (100%) versus 16/33 (48%) P=0.01) and incomplete depletion of anti-PLA2R1 antibodies at month 6 (4/8 (50%) versus 5/33 (9%) P=0.05) were associated with relapses.

CONCLUSIONS: Our work suggests that higher dose rituximab protocol is more effective on depletion of B-cells and lack of epitope spreading is associated with remission of membranous nephropathy

KEY POINTS

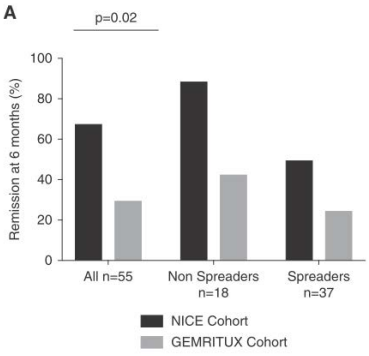


Figure 4. Remission of membranous nephropathy in the NICE and GEMRITUX cohorts at 6 months according to epitope spreading and rituximab protocol received .

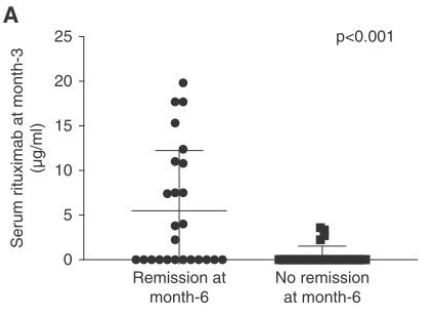


Figure 3. Comparison of serum infliximab concentrations according to remission (n=26) or absence of remission (n=29) at month 6 in the pooled NICE and GEMRITUX cohorts

- Rituximab induced clinical remission in 60%-80% of patients with primary membranous nephropathy

- A single low dose of rituximab (375mg/m^2) was poorly effective in patients with membranous nephropathy

- There is a large interindividual rituximab pharmacokinetics variability which could explain differences in the clinical response.

- Higher cumulative doses of rituximab (2g in NICE cohort versus 1.4g in GEMRITUX) combined with different timing of infusion (2-week intervals instead of 1-week intervals) induce earlier remission and higher rate of remission with more complete remission at 6 months

- A shorter time to remission is clinically meaningful to reduce the risk of complications of nephrotic syndrome, particularly venous thromboembolic disease. These findings are associated with higher residual serum levels at month 3 and lower CD19 counts at month 3 and month 6, and with a greater decline in anti-PLA2R1 antibodies titer at month 6.

Clinical remission at 6 months is associated with lower rate of epitope spreading and higher serum rituximab levels at month 3 (2.2µg/ml)

RITUXIMAB BIOAVAILABILITY IN PRIMARY MEMBRANOUS NEPHROPATHY

RTX

MN

2019

*Boyer-Suavet S, Andreani M, Cremoni M, Brglez V, Benzaken S, Bernard G, Nachman P, Esnault V, Seitz-Polski B

* Service de Néphrologie-Dialyse-Transplantation, CHU de Nice, Université Côte d'Azur, Nice, France

ABSTRACT

No abstract Available.

KEY POINTS

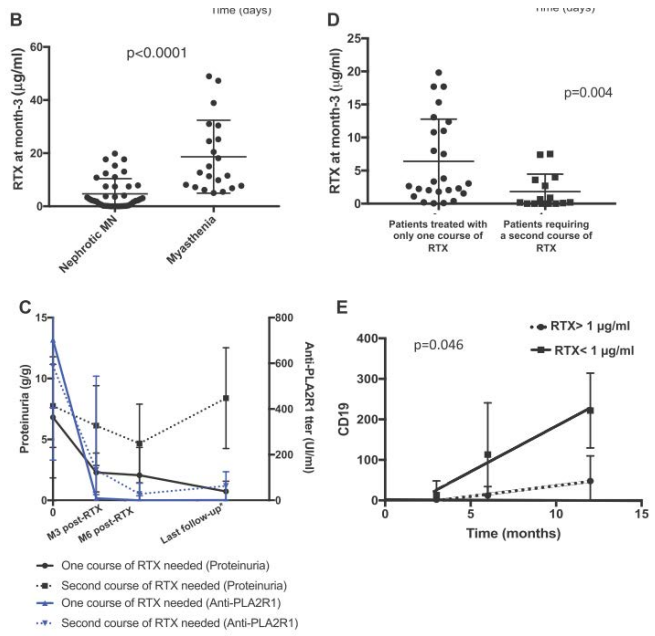


Table 2. Bioavailability of rituximab in idiopathic MN. (A) Residual-free rituximab level measured by ELISA (LISA-TRACKER Duo Rituximab, Theradiag(c) Croissy-Beaubourg, France) in two MN patients matched for age, weight and proteinuria. (B) Residual rituximab level at Months 3 in the MN cohort compared with a cohort of myasthenia gravis patients with no proteinuria. Patients with nephrotic syndrome have lower rituximab level at Month 3: 12.7 (7.45-27.84) versus 2.27(0.19-7.5) µg/ml, p<0.0001. (C) Clinical and immunological outcome for MN patients according to the need or not of a second course of RTX: patients who required a second RTX course exhibited an increase in proteinuria and anti-PLA2R1 antibodies titre before retreatment. M3: 3 months after rituximab; M6: 6 months after rituximab; last follow-up: last value timepoint of follow-up for patients treated with only one course of rituximab and for patients who required a second course, values before re-treatment. (D) Residual rituximab serum level at month 3 in MN patients treated with only one course of rituximab versus those requiring a second course after resistant MN or relapse: 0.20 (0.00-3.59) versus 3.05 (1.67-11.70), p=0.004. (E) Count of CD-19 at months 3,6 and 12 in two groups of MN patients according to their residual rituximab level at month 3. In patients with low residual rituximab level (<1µg/ml), B-cells re-emerged more quickly (slope 5.23 versus 22.45, p=0.0465)

- This study shows a large inter-individual variability among MN patients treated with the same schedule of rituximab that was independent of age, weight and proteinuria

- Residual rituximab levels at month 3 were significantly lower in MN patients compared to myasthenia gravis patients with no proteinuria treated with a similar treatment regimen(p<0.001)

- Residual serum rituximab levels were high at 1 month after infusion and still detected at month 3, but became undetectable at month 6

- Nephrotic patients have a shorter exposure to rituximab compared with a population with no proteinuria, due to rituximab wasting in the urine

- Internalization and destruction of rituximab by target B cells could also contribute to low residual rituximab levels

- Higher residual serum rituximab concentration at month 3 significantly correlated with higher B-cell depletion

-Undetectable serum Rituximab at month 3 might be an useful biomarker for patients with persistently high anti-PLA2R1 activity, and active disease which can predict resistance to rituximab and correlates with clinical outcomes.

Rituximab monitoring at 3 months is relevant to predict clinical outcomes in primary membranous nephropathy

RTX

MN

2019

NEUTRALIZING ANTI-RITUXIMAB ANTIBODIES AND RELAPSE IN MEMBRANOUS NEPHROPATHY TREATED WITH RITUXIMAB

*Boyer-Suavet S, Andreani M, Lateb M, Savenkoff B, Brglez V, Benzaken S, Bernard G, Nachman PH, Esnault V, Seitz-Polski B

*Service de Néphrologie-Dialyse-Transplantation, CHU de Nice, Université Côte d'Azur, Nice, France

ABSTRACT

BACKGROUND: Membranous Nephropathy (MN) is an autoimmune disease associated with antibodies against podocyte proteins: M-type phospholipase A2 receptor (PLA2R1) or thrombospondin type-1 domain-containing 7A (THSD7A) in 70 and 3% of patients, respectively. Antibody titer is correlated with disease activity: rising during active disease and decreasing before remission. Therefore, decreasing PLA2R1-Antibodies titer has become an important goal of therapy. Rituximab a chimeric monoclonal antibody induces remission in 60–80% of primary MN patients. All monoclonal antibodies such as rituximab can elicit antidrug antibodies, which may interfere with therapeutic response.

METHODS: We aim to analyze the relevance of anti-rituximab antibodies on the outcome of MN after a first course of rituximab. Forty-four MN patients were included and treated with two 1 g infusions of rituximab at 2-weeks interval. Anti-rituximab antibodies, CD19 count, and clinical response were analyzed. Then, we (i) analyzed the association of anti-rituximab antibodies at month-6 with response to treatment: remission, relapse and the need for another rituximab course; (ii) confirmed if anti-rituximab antibodies could neutralize rituximab B-cells depletion; and (iii) tested whether anti-rituximab antibodies could cross-inhibit new humanized anti-CD20 therapies. Anti-rituximab antibodies were detected in 10 patients (23%). Seventeen patients received a second rituximab course after a median time of 12 months (7–12), following nine cases of resistance and eight relapses.

RESULTS: Anti-rituximab antibodies were significantly associated with faster B-cell reconstitution at month-6 (75 [57–89] vs. 2 [0–41] cells/μl, p = 0.006), higher proteinuria 12 months after rituximab infusion (1.7 [0.7; 5.8] vs. 0.6 [0.2; 3.4], p = 0.03) and before treatment modification (3.5 [1.6; 7.1] vs. 1.7 [0.2; 1.7] p = 0.0004). Remission rate 6 months after rituximab was not different according to anti-rituximab status (p > 0.99) but the rate of relapse was significantly higher for patients with anti-rituximab antibodies (p < 0.001). These patients required more frequently a second course of rituximab infusions (7/10 vs. 10/34, p = 0.03). Anti-rituximab antibodies neutralized rituximab activity in 8/10 patients and cross-reacted with other humanized monoclonal antibodies in only two patients. Three patients with anti-rituximab antibodies were successfully treated with ofatumumab.

CONCLUSIONS: Anti-rituximab antibodies could neutralize rituximab B cells cytotoxicity and impact clinical outcome of MN patients. Humanized anti-CD20 seems to be a satisfying therapeutic alternative for patients with anti-rituximab antibodies and resistant or relapsing MN.

KEY POINTS

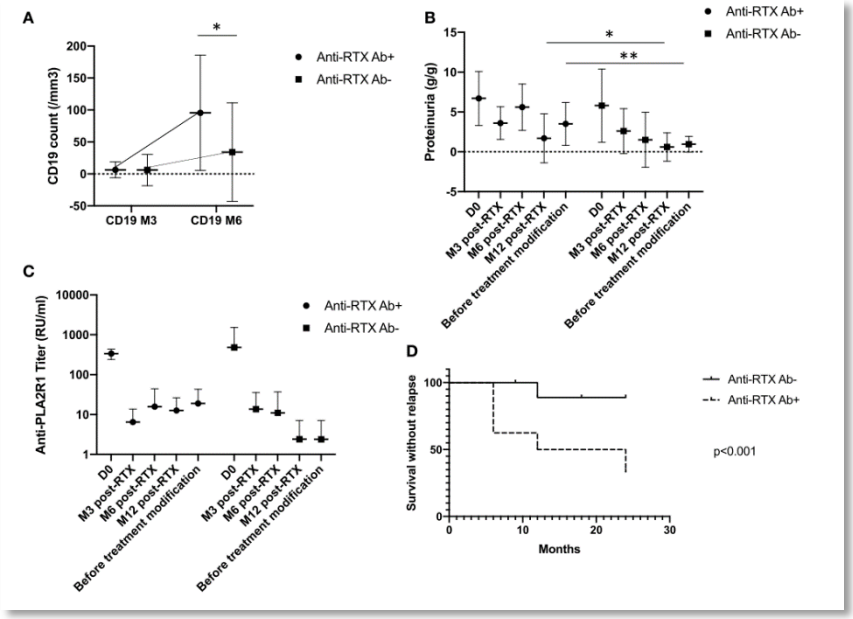


Figure 2. Anti-rituximab antibodies and outcomes (A) C19+ B-cells evolution according to anti-rituximab antibodies status: initial CD19+ B-cells depletion was seen in all patients. But for patients who developed anti-rituximab antibodies , B-cells recovered earlier. *p=0. 006 (B) Proteinuria evolution according to anti-rituximab antibodies status: proteinuria stopped decreasing or increased in patients who developed anti-rituximab antibodies *p=0.03.**p=0.004. (C) Anti-PLA2R1 antibodies titer evolution according to anti-rituximab antibodies status: anti-PLA2R1 antibodies levels did not decrease or increased following rituximab in patients who developed anti-rituximab antibodies. Before treatment modification anti-PLA2R1 titer tended to be higher in patients with anti-rituximab antibodies (p=0.09). (D) Renal survival without relapse within 2 years after rituximab therapy according to anti-rituximab antibody status: patients with anti-rituximab antibodies exhibited more relapsed within 2 years after rituximab therapy (p<0.001)

- This study suggests the value of immune-monitoring in adapting the therapeutic strategy in MN, particularly in resistant or relapsing cases

- Serum residual levels at month 3 were associated with remission

- Anti-rituximab antibodies were detected in 23% of patients treated with rituximab for idiopathic MN and were associated with the need for at least two courses of rituximab for resistant MN or relapses

- Neutralizing anti-rituximab antibodies are not rare and their presence at month 6 is associated with subsequent relapses

- Between month 3 and month 6, anti-rituximab antibodies could block B-cell depletion and might be associated with relapse or incomplete response to treatment

- Patients with non-neutralizing anti-rituximab antibodies showed a favourable outcome after two courses of rituximab

Anti-rituximab antibodies are not rare in MN patients and their presence at month-6 is associated with subsequent relapses

Theradiag
INNOVATION FOR BIOTHERAPIES

14 rue Ambroise Croizat
CS 90136 Croissy Beaubourg
F-77435 MARNE LA VALLEE CEDEX 2 France
Tel : +33 (0) 1 64 62 10 12 - Fax : +33 (0) 1 64 62 09 66
info@theradiag.com - www.theradiag.com

TB-V.08/2020 - UK

Read carrefully the instruction for use of the product insert