Clinical Data TDM GOLIMUMAB

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Theradiag
INNOVATION FOR BIOTHERAPIES

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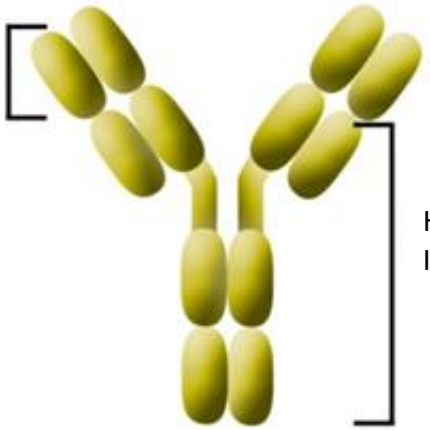
Introduction

Simponi® golimumab



Human

GOLIMUMAB (GLM):

- Human monoclonal antibody that binds and inhibits TNFα (Tumor Necrosis Factor)
- **Brand name:** Simponi®
- Marketed by MSD
- **Marketing authorization:** 2009/10/01
- About 15,000 treated patients (*data monitor 2018*)
- Patent expiry: In 2024 for Europe

GOLIMUMAB – Indications

Simponi® golimumab

- **Adult rheumatoid arthritis (RA),** alone or in combination with methotrexate. Moderate to severe active RA when response to background antirheumatic therapy, including methotrexate, has been inadequate

- **Adult psoriatic arthritis (PsA),** alone or in combination with methotrexate, when there has been an inadequate response to conventional disease-modifying therapy

- **Ankylosing spondylitis (AS),** in adults who have had an inadequate response to conventional disease-modifying therapies

- **Moderate to severe hemorrhagic recto colitis in adults (UC),** in case of failure or contraindication to conventional treatments (corticosteroids, azathioprine, 6-mercaptopurine)

- **Juvenile idiopathic polyarticular arthritis in children over 40 kg (JIpA),** in combination with methotrexate

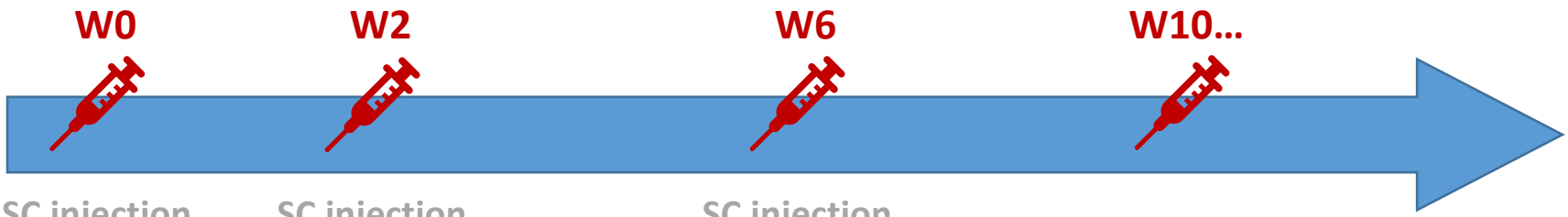
GOLIMUMAB – Dosages

Recommended dosage and schedule for GLM according to the FDA and EMA:

Indications	FDA recommandation	EMA recommandation
RA, PsA et AS	50 mg / month	50 mg / month if patient < 100 kg 100 mg / month if patient > 100 kg and no clinical response after 3 administrations of 50 mg
UC	200 mg week 0 100 mg week 2 100 mg every 4 weeks	200 mg week 0 100 mg week 2 50 mg every 4 weeks if patient < 80 kg 100 mg every 4 weeks if patient > 80 kg
JIpA		50 mg every 4 weeks

Harzallah et al – 2017 – Therapeutic Advances in Gastroenterology

GOLIMUMAB : Simponi® - Administration protocol - UC

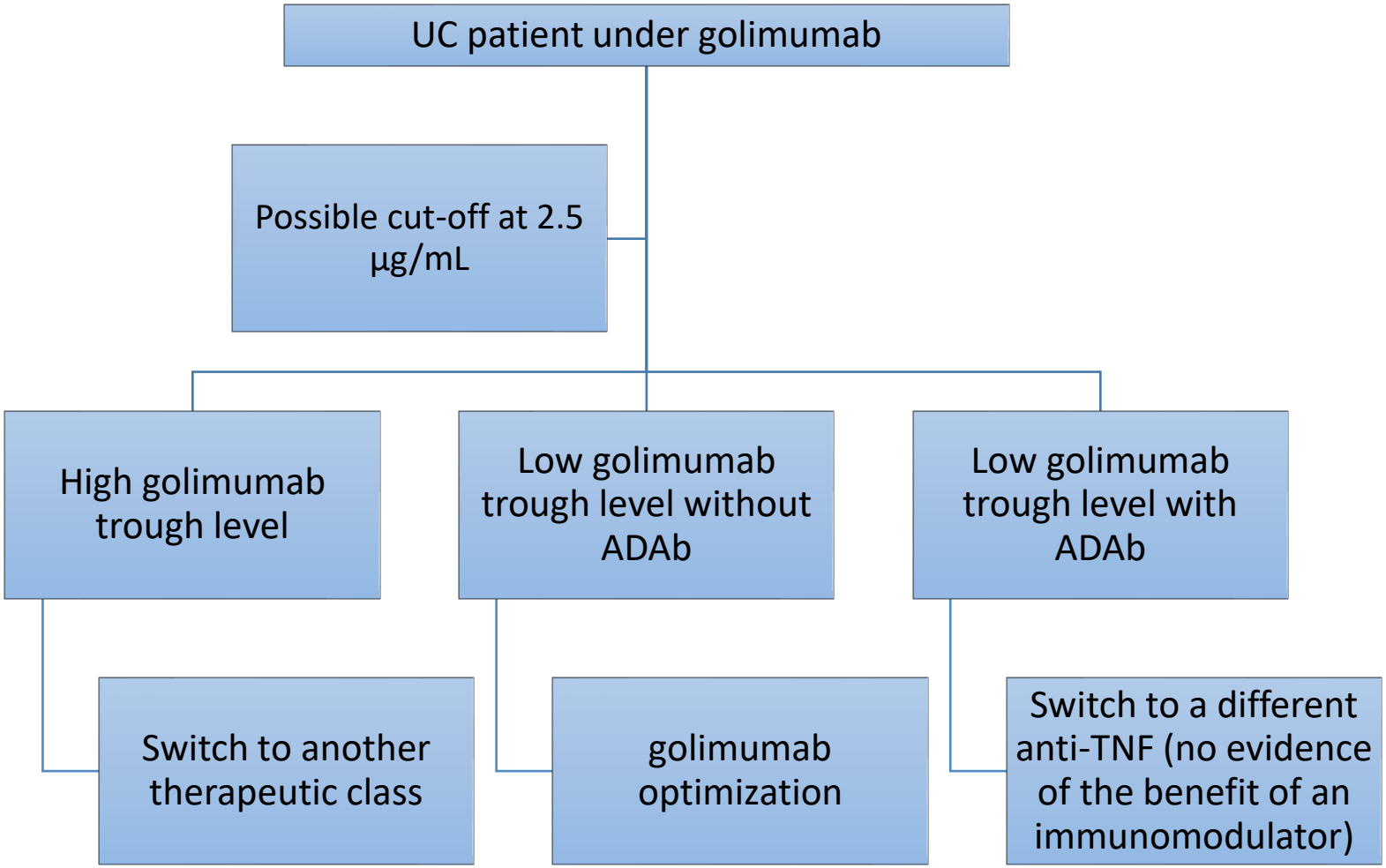


SC injection
200 mg
(2 x 100 mg)

SC injection
100 mg

SC injection
50 mg (<80 kg)
100 mg (≥80 kg)

Treatment algorithm for GLM in patients with clinically relapsed ulcerative colitis



Harzallah et al - 2017 - Therapeutic Advances in Gastroenterology

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Clinical trials - Gastroenterology

Therapeutic thresholds for golimumab serum concentrations during induction and maintenance therapy in Ulcerative Colitis: results from the GO-LEVEL study

- **Aims:** To identify optimal serum golimumab concentration thresholds during induction and maintenance treatment with golimumab.

- **Methods:** GO-LEVEL was an open label; phase IV study that included a prospective cohort of 42 UC patients commencing golimumab, as well as a cross-sectional cohort receiving maintenance treatment. Serum golimumab concentrations were measured using commercially available ELISA (LISA TRACKER, Theradiag).

- **Results:**

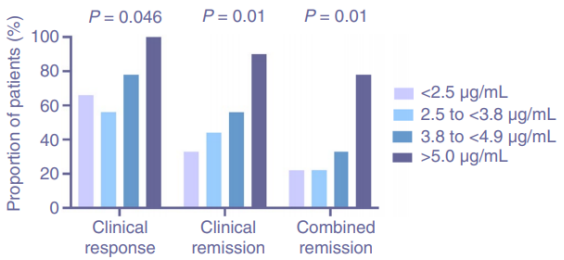


FIGURE 1 Proportion of patients in clinical response, clinical remission and combined clinical-biochemical remission according to serum golimumab concentration quartile at week 6

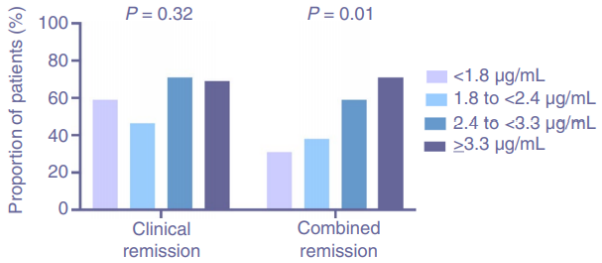


FIGURE 2 Proportion of patients in clinical remission and combined clinical-biochemical remission according to serum golimumab concentration quartile during maintenance

- Relationship between golimumab exposure and favorable treatment outcomes including reductions in both clinical and biochemical disease activity, during both induction and maintenance therapy
- Serum golimumab concentration thresholds of **3.8 µG/ML** at week 6 and **2.4 µG/ML** during maintenance are closely associated with achievement of combined clinical-biochemical remission

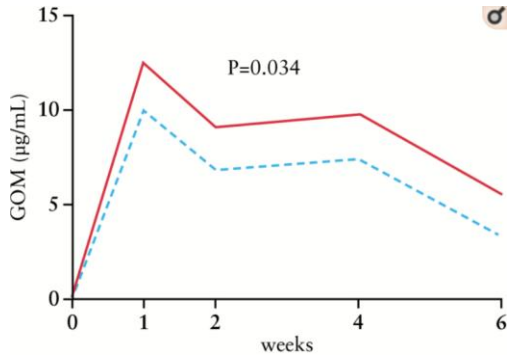
Samaan et al - 2020 - Aliment Pharmacol Ther

Variability in Golimumab Exposure: A 'Real-Life' Observational Study in Active Ulcerative Colitis

- **Aims:** To investigate whether a low golimumab serum concentration and/or a positive anti-golimumab antibody status reduces the efficacy of this drug in patients with UC.

- **Methods:** Serum samples of 21 patients with moderate-to-severe UC were collected during the first 14 weeks of golimumab therapy. For measurement of golimumab serum concentrations, both a TNF-coated ELISA and a sandwich-type ELISA were developed. Anti-golimumab antibodies were measured using a bridging ELISA and a newly-developed drug-tolerant immunoassay. Clinical response and mucosal healing were assessed 14 weeks after start of treatment.

- **Results:**



Drug exposure as defined by median area under the curve (AUC [Week 0–6]) of GLM was significantly greater for partial clinical responders (solid line) than non-responders (dashed line) [p = 0.034].

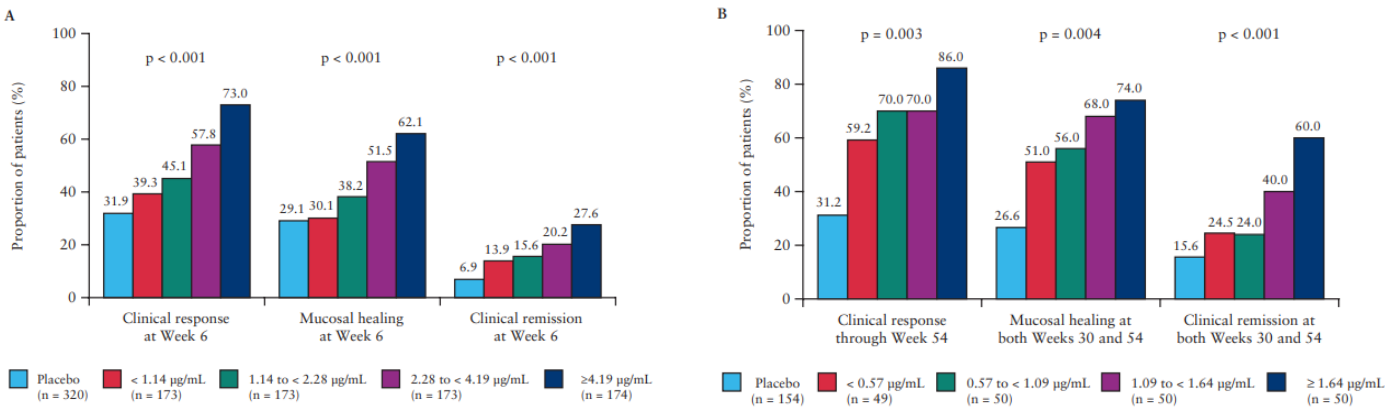
- Adequate exposure to golimumab drives clinical response. A worse disease at baseline influences clinical response rate negatively
- The response to golimumab treatment is related to serum golimumab concentrations and shows a large variation between patients

Detrez et Al - 2016 - J Crohns Colitis

Pharmacokinetics and exposure-response relationship of golimumab in patients with moderately-to-severely active Ulcerative Colitis: results from phase 2/3 PURSUIT induction and maintenance studies

- **Aims:** To assess golimumab pharmacokinetics (PK) and exposure-response (ER) in adults with moderate-to-severe UC from the PURSUIT studies.
- **Methods:** Induction analyses evaluated serum golimumab concentration and efficacy data through week 6 following subcutaneous doses at week 0 and 2; maintenance analyses assessed data through week 54 following 4-weekly dosing.
- **Results:**

Proportions of patients achieving clinical response, mucosal healing, and clinical remission during induction by SGC quartile at Week 6 [A], and during maintenance by SGC quartile at Week 44 [B], in PURSUIT.



- Positive association between serum golimumab concentrations and efficacy outcomes in patients with UC was confirmed during both induction and maintenance
- Factors related to the distribution of serum golimumab concentrations, as well as optimal concentration thresholds for efficacy outcomes in UC, were identified

Omoniyi J. Adedokun - 2017

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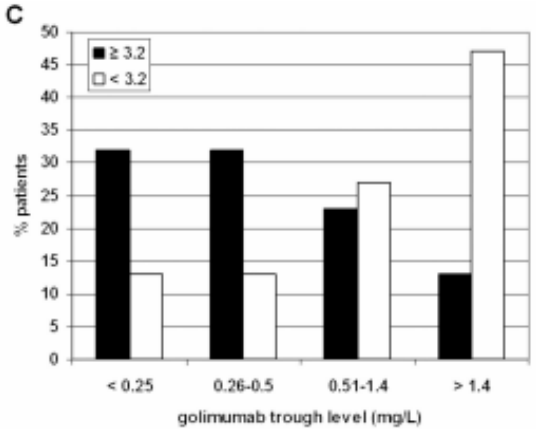
Clinical trials - Rheumatology

Golimumab trough levels, antidrug antibodies and clinical response in patients with rheumatoid arthritis treated in daily clinical practice

- **Aims:** To evaluate the relationship between golimumab level, immunogenicity and response in RA.
- **Methods:**
  - Prospective observational cohort consisted of 37 consecutive adult patients with RA, in whom golimumab 50 mg subcutaneously once monthly was initiated.
  - Clinical measurements and trough-level sera were collected at baseline and 4, 16, 28 and 52 weeks (The Netherlands), or half yearly (Spain).
- **Results:**



Percentage of patients with DAS28 <3.2 and ≥3.2 stratified according to the golimumab level at 52 weeks of treatment.

- **Responders had a significantly higher golimumab trough level at 1 year of treatment. ESR and CRP were statistically significantly inversely associated with golimumab level over time**

ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein

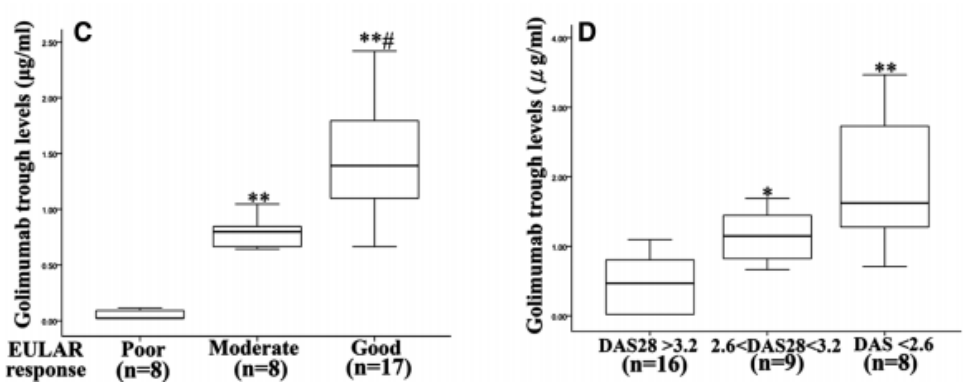
Kneepkens et al - 2014 - Ann Rheum Dis

Immunogenicity, drug trough levels and therapeutic response in patients with rheumatoid arthritis or ankylosing spondylitis after 24-week golimumab treatment

- **Aims:** To evaluate the relations among ADAb, serum drug trough levels, therapeutic response and methotrexate (MTX) dosage in golimumab-treated patients.

- **Methods:**
  - 78 biologic-naïve patients were enrolled and started golimumab therapy at a dosage of 50 mg given subcutaneously once a month
  - Serum ADAb levels and drug trough levels were determined at week 24 of golimumab therapy by bridging ELISA and capture ELISA

- **Results:**



Comparison of drug trough levels among patients with RA with different EULAR responses (C) and disease activity status achieved at week 24 of golimumab therapy (D).

- **The positive correlation between drug levels and therapeutic response indicates that drug monitoring could be useful for optimizing the dosing of biologics in a personalized therapy strategy**

Chen et Al - 2015 - Ann Rheum Dis

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Clinical trials - Dermatology

The GOLMePsA study protocol: an investigator-initiated, double-blind, parallel-group, randomised, controlled trial of GOLimumab and methotrexate versus methotrexate in early diagnosed psoriatic arthritis using clinical and whole body MRI outcomes

- **Aims:** To compare the clinical efficacy of a treatment strategy in newly diagnosed, treatment naïve PsA subjects, using the combination of golimumab, methotrexate and steroids versus standard care (MTX monotherapy plus steroids).

- **Methods:** Eighty-eight PsA patients, diagnosed within 24 months prior to screening and treatment naïve, were randomized at baseline to receive: (arm 1) the combination of intramuscular/intra-articular prednisolone, MTX and GOL or (arm 2) the combination of intramuscular/intra-articular prednisolone, MTX and placebo for 24 weeks (interventional period). Primary outcome measure is clinical improvement (at least 1 unit difference) in the Psoriatic Arthritis Disease Activity Score (PASDAS) composite index.

- **Discussion:** The hypothesis underlining this study is that very early treatment with first-line GOL reduces disease activity in PsA, in comparison to conventional therapy.

De Marco et Al – 2017 – BMC Musculoskelet Disord

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Ongoing clinical trials

Golimumab in UC patients with loss of response followed by dose optimization (GOLILOR)

Tracker

- **Outcomes:**
  - Primary: Correlation between concentration of golimumab and clinical response according to treatment (from baseline to 8 weeks).
  - Secondary:
    1. Number of patients with antibodies to golimumab (day 1).
    2. Correlation between concentration of antibodies to golimumab and clinical response according to treatment (from baseline to 8 weeks).
    3. Number of patients with Infectious diseases or Neuropathies or Injection site pain or fever (up to 8 weeks).

- **Methods:** 80 patients
  - Patients treated at 50 mg of golimumab every 4 weeks (less than 80 kg) will have an increase dose of golimumab: 100 mg every 4 weeks for 8 weeks.
  - Patients treated at 100 mg of golimumab every four weeks (more than 80 kg) will have an increase dose of golimumab: treated at 100 mg every 2 weeks for 4 weeks.

- **Estimated study completion date:** May 30, 2022

CHU Saint-Etienne - MSD - Lisa Tracker

Intensive treatment to reach the target with golimumab in UC (In-TARGET)

Tracker

- **Objective:** To determine the proportion of patients with Continuous Clinical Response (CCR) and endoscopic remission after one year of golumimab at week 54.

- **Methods:**
  - Multicenter, open-label, uncontrolled trial
  - Adults with moderate to severe UC who failed corticosteroids and immunosuppressive therapy or are intolerant to immunosuppressors. All included patients will be naïve to anti-TNF therapy. Active disease at golimumab treatment initiation defined as a MAYO score ≥6 and with an endoscopic sub score ≥ 2
  - Increase or decrease interruption dose of golimumab depending on CCR or relapse

- **Estimated study completion date:** October 2022

GETAID - Lisa Tracker

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Guidelines

Current National and International Guidelines / Consensus on Therapeutic Drug Monitoring in Inflammatory Bowel Disease (extract)

Guideline / Consensus	Country / Region	Organization	Published Date	Applicable Disease	Related Drug	Recommendation Statement for TDM Utilization	Reference
Best practices on immunomodulators and biologic agents for ulcerative colitis and Crohn's disease in Asia	Asia	Asia Pacific Association of Gastroenterology (APAGE) working group on Inflammatory Bowel Disease and Asian Organization for Crohn's and Colitis	May 2019	Inflammatory Bowel Disease	Infliximab Adalimumab	In responders and In patients in primary and secondary loss of response to guide treatment management	Intest Res,May 31, 2019
Appropriate Therapeutic drug Monitoring of Biologics Agents for patients with inflammatory Bowel diseases	USA	Expert consensus Development Meeting consisting of members of the BRIDGe group	March 2019	Inflammatory Bowel Disease	Infliximab Adalimumab Certolizumab Golimumab Vedolizumab Ustekinumab	In responders at the end of induction and during maintenance treatment for all anti-TNF In patients in primary and secondary loss of response to guide treatment management	Clinical Gastroenterology and Hepatology, 24 March 2019
New Zealand Society of Gastroenterology Guidelines on Therapeutic Drug Monitoring in Inflammatory Bowel Disease	New Zealand	New Zealand Society of Gastroenterology	March 2019	Inflammatory bowel disease	Infliximab Adalimumab	In patients in primary and secondary loss of response , proactively at the end of induction	N Z Med J. 2019 Mar 8;132(1491):46-62
Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care—An Evidence-based Guideline	Europe	European Crohn's and Colitis Organisation (ECCO) and European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)	August 2018	Ulcerative colitis	Infliximab Adalimumab Golimumab Vedolizumab	In patients in primary and secondary loss of response , proactively at the end of induction	J Pediatr Gastroenterol Nutr. 2018 May 30.
Management of Paediatric Ulcerative Colitis, Part 2: Acute Severe Colitis—An Evidence-based Consensus Guideline	Europe	ECCO and ESPGHAN	August 2018	Ulcerative colitis	Infliximab	In patients in primary and secondary loss of response , proactively at the end of induction	J Pediatr Gastroenterol Nutr. 2018 May 30.
ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications	Europe	ECCO and European Society of Gastrointestinal and Abdominal Radiology (ESGAR)	August 2018	Inflammatory bowel disease (Pediatrics)	Anti-TNFa	In patients in primary and secondary loss of response to Anti-TNFa treatment	Journal of Crohn's and Colitis, 2018, 1–32
Clinical Guideline: Management of Crohn's Disease in Adults	USA	American College of Gastroenterology (ACG)	March 2018	Crohn's disease	Anti-TNFa	In patients in primary and secondary loss of response to Anti-TNFa treatment	Am J Gastroenterol 2018; 113:481–517

TDM is supported by new guidelines: Appropriate therapeutic drug monitoring of biologic agents for patients with Inflammatory Bowel Diseases

Appropriate Therapeutic Drug Monitoring of biologic agents for patients with Inflammatory Bowel Diseases (IBD)

- **Aims:** To evaluate the clinical utility of TDM for biologic therapies in IBD.
- **Methods:** A comprehensive literature review was performed regarding the use of TDM of biologic therapy in IBD and presented to international IBD specialists.
- **Results:** For anti-TNF therapies, proactive TDM was found to be appropriate after induction and at least once during maintenance therapy. Reactive TDM was appropriate for all agents both for primary non-response and secondary loss of response.
- **Conclusion:** Consensus was achieved towards the utility of TDM of biologics in IBD, particularly anti-TNF therapies.

- The minimum drug concentration at week 6 for golimumab should at least be **2.5 µg/mL**
- During maintenance the minimum trough concentration for golimumab for patients in remission should be greater than **1 µg/mL**

Papamichael et Al – 2019 – Clin Gastro Hepato

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Take home messages

Summary

- ✓ **Golimumab or Simponi® →** Human monoclonal antibody that binds and inhibits TNFα
- ✓ **Indications →** rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), moderate to severe ulcerative colitis (UC), juvenile idiopathic polyarticular arthritis (JIpA)
- ✓ **Dosages**

Indications	FDA recommandation	EMA recommendation
RA, PsA et AS	50 mg / month	50 mg / month if patient < 100 kg 100 mg / month if patient > 100 kg and no clinical response after 3 administrations of 50 mg
UC	200 mg week 0 100 mg week 2 100 mg every 4 weeks	200 mg week 0 100 mg week 2 50 mg every 4 weeks if patient < 80 kg 100 mg every 4 weeks if patient > 80 kg
JIpA		50 mg every 4 weeks

- ✓ **Cut-off → 3.8 µg/mL** at week 6 and **2.4 µg/mL** during maintenance (GO-LEVEL)
  → at least **2.5 µg/mL** at week 6 and greater than **1 µg/mL** during maintenance (US guidelines)

Ongoing clinical trials - Tracker:

- Golimumab in UC patients with loss of response followed by dose optimization (GOLILOR)
- Intensive treatment to reach the target with golimumab in UC (In-TARGET)