Clinical arguments

The monitoring of anti-TNFα treated patients is mainly based on the clinic for Chronic Inflammatory Rheumatism in IBDs and the severe forms of psoriasis. AdAβ’s presence appears to play a role in the clinical response and the appearance of side effect events.

In RA, this immunization is associated with a lower therapeutic response and is frequently associated with the appearance of clinical reactions such as immunopathologies (Bartels, Ann Rheum Dis 2007; Wolbink, Arthritis Rheum 2006).

The tolerance issues related to the development of ADAb are well documented for infliximab in IBDs (Baert, N Eng J Med 2003; Vennier, Gut 2007).

The patients having developed anti-infliximab ADAb are 2 to 3 times as much susceptible to develop reactions to the infusion.

They are essentially acute reactions among which anaphylactic reactions and delayed hypersensitivity reactions. Indeed in psoriatic patients (study EXPRESS II) (Menter, J Am Acad Dermatol 2007), 4 % of the patients to whom the treatment was reintroduced after a pause versus 1 % of those who received it without interruption presented a severe reaction to the infusion. For adalimumab, in the REVAL study with psoriatic patients, AdAβ presence in 8.8 % of the patients was not correlated to any side effect, including the reactions at the infusion point (Menter, J Am Acad Dermatol 2008). For etanercept, there seems to be no correlation between the development of ADAb and side effects. Moreover the AdAβ’s presence appear as relevant marker to reveal the patient’s aptitude to develop an immune response (Davies, Ann Rheum Dis 2011; Petitpain, Biomed Mater Eng 2009, Kobayashi, Arthritis Rheum 2011).

How to use these assays in practice?

Non responder patients showing low plasma level of biologics without ADAb:

- Fast clearance of the biologic
- Increase of the medication

Patients showing initial clinical response but in a loss response trend situation or either partial responders or non responders with low efficient biological levels in presence of ADAb:

- switch to another anti-TNFα
- Dual methotrexate therapy to prefer
- Optimization of the therapeutic strategy for the IBD

Good patient responders, without ADAb, showing efficient plasma level of biologic but in supral therapeutic level:

- reduce the medication dose in an economical concern and in order to reduce at the same time the isothymic aspect due to overdose

To measure the efficacy of Biotherapies

- Diagnostic tool allowing the individual or simultaneous dosage of:
  - the prescribed drug,
  - antidrug Antibodies (ADAb).
- Complete range of assays
- ELISA format for an easy use in routine
- Standardized protocols
- Ready to use reagents
- Flexible formats and breakable wells
- Rapid: 3 hours
- Automated (e-Robot², DsX, Triturus, etc.)
- CE marked kit

LISA TRACKER

Principle of the therapeutic monitoring

In order that a drug enables a Therapeutic Drug Management (TDM) program, it usually has to show the following characteristics (Widmer 2008, Kangi 2009):

1. Analytical characteristics

- Availability of an appropriate dosage method with acceptable cost.

2. Pharmacokinetic characteristics

- High inter-individual variability of the drug availability in the body.
- Inter-individual pharmacokinetic parameters not very reliable.
- Low intra-individual variability in the drug availability.

3. Pharmacodynamic characteristics

- Pharmacologic effect consistently linked to the blood concentration.
- Reproducible pharmacologic effect over an extended period of time.
- High therapeutic window (which is low difference between effective and toxic concentrations).
- Reversible effects in case of dosage adjustment.

4. Clinical characteristics

- Absence of markers easily measurable for the monitoring (such as INR for instance, appropriate marker for oral anticoagulation).
- Demonstration of a better monitoring based rather on TDM than on the only the clinical assessment.
- Duration of the therapy sufficient so that the patient can benefit from a TDM program.

The anti-TNFα, a major therapeutic breakthrough

The anti-TNFα are a major therapeutic breakthrough in the medical care of Chronic Inflammatory Rheumatism (CIR) (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis), of Inflammatory Bowel Diseases (IBD) (Crohn Disease, ulcerative colitis) and some forms of psoriasis.

However all the patients that are treated with these therapeutics are not all responding to the treatment and among those who are responders, the level of response is variable from one individual to another, but also for the same individual over time.

Several mechanisms can explain this variability:

- Different physiopathologies that lead among some individuals to other ways than the TNFa pathways.
- Inter- and intra-individual fluctuations of the effective serum concentration of the biopharmaceutical for a given dosage. These fluctuations can be the consequence of several elements that can be intricately linked:
  - Neutralisation of the active site of the biopharmaceutical, through anti-drug antibodies (ADAb) and the immunogenic characteristic of these molecules.
  - An acceleration of the clearance of the biopharmaceutical, independent from the presence of ADAb.
  - A high clearance of the biopharmaceutical, independent from the presence of ADAb.

The use of biological monitoring tools (serum dosage of drugs and ADAb) guides the clinicians in the adjustment of the treatment.

Theranostics is an emerging branch of in vitro diagnostics, whose objective is to provide information with which to offer greater personalization of treatment. Thus, theranostic tests are combined with a targeted biotherapy in order to predict or evaluate a patient’s response by measuring one or more biomarkers. Besides screening for disease, its purpose is to enable clinicians to establish the treatment best suited for each disease, check the results of this treatment over time, modify this treatment and even change it should it be necessary because of side effects or lack of effectiveness.

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Did you know ?

70% of today’s new drugs are biotherapies and because of that it is crucial to determine precisely and objectively the patients’ response to the treatment. Theranostics is an emerging branch of in vitro diagnostics, whose objective is to provide information with which to offer greater personalization of treatment. Thus, theranostic tests are combined with a targeted biotherapy in order to predict or evaluate a patient’s response by measuring one or more biomarkers. Besides screening for disease, its purpose is to enable clinicians to establish the treatment best suited for each disease, check the results of this treatment over time, modify this treatment and even change it should it be necessary because of side effects or lack of effectiveness.

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Immunogenicity of anti-TNFα

Therapeutic anti-TNFα antibodies were developed and used in the clinic by the end of the 90’s. Firstly produced therapeutic antibodies were 100% murine monoclonal antibodies (−mab) that were not used on humans.

Low infliximab serum concentrations during the initial phase of the treatment increase the risk to develop ADAbs in RA and spondyloarthopathies (Ducuara, Arthritis Res Ther 2011; Bendzten, Arthritis Rheum 2006). The presence of ADAbs modifies the pharmacokinetic characteristics of the anti-TNFα.

Infliximab Serum Disease and ADAbs in Crohn Disease:

- The development of ADAbs directed against infliximab was observed among 30% of the patients receiving maintenance treatment on demand, 10% of those receiving regular maintenance treatment to 5 mg/kg and 7% of those who received a dosage of 10 mg/kg (ACCENT 1 study) (Hanauer, Clin Gastroenterol Hepatol 2004).
- Patients treated by Adalimumab who received a 160 / 80 mg induction scheme have 50% less chance to need to turn later to a weekly plan of injections further to a loss of answer, than those who have received a 80 / 40 mg scheme (Loffts, J Crohns colitis 2011).

The presence of ADAbs decreases significantly the half-life of the monoclonal antibodies in the inflammatory bowel diseases (Tennor Ther Drug Monit 2008) and in the ankylosing spondylitis (Xu, J Clin Pharmacol 2008). The presence of ADAbs can modify the pharmacokinetic of the therapeutic agent by increasing its clearance and decreasing its serum concentration. Among patients treated by infliximab in the ankylosing spondylitis, the clearance of the molecule is until 75% higher in the group that developed ADAbs (Xu, J Clin Pharmacol 2008).

It is important to note that a biopharmaceutical low serum concentration does not mean a presence of ADAbs.

Decrease of ADAbs’ presence

The concomitant administration of some immunosuppressive treatments such as the methotrexate, azathioprine, or a premedication by hydrocortisone were associated with a reduction of the incidence of ADAbs directed against anti-TNFα (adalimumab) used in RA (Bardele, Ann Rheum Dis 2007), spondyloarthopathies (infliximab) (Ducuara, Arthritis Res Ther 2011) and Crohn disease (infliximab) (Hanauer, Lancet 2002; Vermeiren, Gut 2007; Farrell, Gastroenterology 2003). However, these results are contradictory in the case of a premedication by hydrocortisone in Crohn disease (Montariz, Eur J Gastroenterol Hepatol 2009).

In psoriasis, a study also suggests that the adjuection of methotrexate to infliximab in patients having developed ADAbs conduct to the reduction of these neutralizing antibodies and allows the maintenance of the clinical response (Adisen, J dermatol 2010).

The benefit generated by these therapeutic associations is probably multiple:
- Limitation of the patient’s immune response against the biologics.
- Limitation of the TNFα production, allowing a higher plasmatic trough concentration of anti-TNFα available to accelerate the clearance of ADAbs.
- The amount of ADAbs can modify the pharmacokinetic action, neutralizing ADAbs also block the interaction of the therapeutic agent with its target, making it inactive (Xu, J Clin Pharmacol 2008).

Pharmacokinetics arguments

There is today dosage methods of anti-TNFα and their corresponding ADAbs (ADAbs) at a price compatible with the TDM use and with the high cost of the treatments. A simple patient blood uptake is required with these methods.

Valid methods that are reproducible and that have predictive clinical values, have to be used. The conditions of the samples and interpretation of the results have to be provided.

Pharmacokinetic arguments

Inter-individual variability of the anti-TNFα availability in the plasma.

Pharmacokinetic variability of the anti-TNFα has been highlighted specifically in Rheumatoid Arthritis (RA) (Saint Clair, Arthritis Rheum 2002). For the same dosage, the estimation of the absorption through the measurement of the trough concentration just before a new injection is very variable from one patient to another, with cases of low or high-exposure highlighted, compared to the median exposure. This variability can be explained by the heterogeneity of the patients, their disease, and the associated medication (Mani, Arthritis Rheum 1998).

The pharmacokinetic variability has also been established for adalimumab (Weisman, Clin Ther 2003) and etanercept (Keystone, Arthritis Rheum 2004) in RA.

This pharmacokinetic variability is also known among IBDs (Borghi, Aliment Pharmacol Ther 2011).

LISA TRACKER: the therapeutic decision support tool

LISA TRACKER: anticipation, optimisation & clinical guidance

Pharmacodynamics arguments

There is a correlation between the anti-TNFα concentration and the clinical response.

In the case of infliximab administration, the drug’s probability of clinical response increases with the trough concentration of the anti-TNFα (Arthritis Rheum 2002; Wolbink, Arthritis Rheum 2005). This correlation was also established for adalimumab (Bartels, Ann Rheum Dis 2007) and etanercept (Jannink, Ann Rheum Dis 2011; Lee, Clin Pharmacol Ther 2003; Dalen, J Rheumatol 2012).

In RA, according to retrospective data of patients on steady infliximab medication, the trough concentrations of the biologics in blood are above 1 mg / L (Rahman, Ann Rheum Dis 2007).

The existence of a prolonged therapeutics also contributes to the achievement of a high serum concentration of infliximab above the threshold of 1 mg / L (Rahman, Ther Drug Monit. 2010).

In a RA, a study driven in patients treated with etanercept showed a clear correlation between the trough concentration plasma of the molecule and the clinical response (Jannink, Ann Rheum Dis 2012). In this study, 40% of non responders had a low plasma concentration (≤ 2 ng/ml) (40%) however no patient of the study developed ADAbs.

It appears as well as in IBDs (Danese, Aliment Pharmacol Ther 2011; Bentzten, Aliment Pharmacol Ther 2011) and in Crohn disease, that trough concentrations of anti-TNFα is correlated to the therapeutic success for infliximab (Baeut, N Engl J Med 2003), adalimumab (Kamiris, Gastroenterology 2010), and in the ulcerative Crohn disease (Zuv, Curr Gastroenterol Rep 2010).