

Monitoring Anti-Tnf Drug Treatment in Inflammatory Bowel Disease. Is it Useful in Clinical Practice?

Abstract

Despite the efficacy demonstrated by anti-TNF drugs in treating inflammatory bowel disease, there is a significant percentage of patients for whom the drugs fail or the response to the drugs is lost. The limitations in managing these patients and the increase in costs necessitate an individualised strategy to optimise their clinical management. Recent studies have noted the relationship between the clinical outcome and therapeutic adjustments based on monitoring anti-TNF levels and the presence of antibodies, taking into account other factors such as the type of disease and its severity. This study reviews the available information and proposes a clinical management algorithm to achieve a more efficient result.

Background

The treatment of inflammatory bowel disease (IBD) has undergone a marked change since the introduction of biologic agents, which are effective in inducing and maintaining remission both in Crohn's disease (CD) and ulcerative colitis (UC) [1-5].

Despite their efficacy, approximately 30% of patients do not respond to these therapies, and up to 40% of those who do respond lose efficacy over time [6]. To date, when faced with the failure to respond, the approach was to act empirically by intensifying the employed anti-TNF or by changing to another anti-TNF or a drug with a different therapeutic target. However, we need to find strategies that optimise these treatments, taking into account both the pharmacokinetics and pharmacodynamics [7,8].

One of these strategies is the use of drug levels and their corresponding antibody in clinical practice, with the intent of optimising the results of our treatments [9].

Efficacy of Anti-Tnf Drugs and Mechanisms of Loss of Response

The overall rate of response to anti-TNF drugs in placebo-controlled trials is approximately 60%, while remission is somewhat more than 30%. However, up to 25-40% of patients (according to the definition used) present secondary response failure [10,11]. The risk per patient-year is 13% for infliximab (IFX) [6] and 20.3% for adalimumab (ADA) [12].

In recent years, there has been research into the causes of the treatment failure, and various mechanisms involved in the failure have been described:

- i. **Immunologic:** characterised mainly by the development of anti-TNF antibodies (aTNF-ab) [11,13,14].
- ii. **Non immunologic:** characterised by the absence of a TNF-ab. This mechanism can present low drug levels (reported in 16-39% of patients) [15-18] and is mainly attributed to pharmacokinetic factors that cause a greater clearance of the

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drug [14]. Another possibility is the presence of adequate drug levels with no efficacy, which can be explained by the activation of inflammation pathways not mediated by TNF or by the paradoxical exacerbation of the disease by anti-TNF [19-21].

Primary failure has involved the presence of antibodies, the high faecal loss of IFX and the presence of high TNF levels as potential causes. Secondary failure, however, has been related to the presence of antibodies, low trough levels of the drug or the presence of other causes of the clinical manifestations [22].

Pharmacokinetics of Anti-Tnf Drugs

The pharmacokinetics of anti-TNF drugs is determined mainly by 3 factors: the administration route (intravenous or subcutaneous), the half-life of the drug and the peak and trough concentrations achieved [10].

The intravenous route allows for the infusion of larger volumes with immediate distribution, there is less variability among individuals, and it is less immunogenic. In contrast, subcutaneous administration only allows for the administration of approximately 1 mL quantities, with variable bioavailability and slower absorption [14]. The drugs also differ in their half-lives: 7.7-9.5 days for IFX, 14 days for ADA and certolizumab (CTZ) and 12 days for golimumab [8,23].

The anti-TNF drugs used to date in IBD have shown a linear relationship between dose and peak concentration. However, there is significant interindividual variability between dose and trough levels [24]. The anti-TNF elimination pathways, which are not fully known, mainly involve proteolysis after the endocytosis of the antibody (mediated by various mechanisms: phagocytes, cells with surface antigens in its membrane or reticuloendothelial

system cells) and are not eliminated renally or hepatically due to their high molecular weight [25-27]. Some of these mechanisms are saturable, which results in the baseline inflammatory condition (and thus the antigenic burden [TNF- α]) significantly affecting the pharmacokinetics of these drugs [20].

Lastly, although studies performed in CD and rheumatic diseases have shown similar pharmacokinetics, there appear to be appreciable differences with UC, as observed in the study by Seow et al. (16), where up to 61% of patients have no detectable drug levels. This fact could be related to the greater drug clearance due to higher baseline TNF- α levels or to the increased faecal elimination, which would explain the frequent need for intensifying the treatment [28]. The following table lists a number of the factors that influence the pharmacokinetics of these drugs (Table 1).

Table 1: Factors modifying pharmacokinetics of anti-TNF drugs.

Presence of aTNF-ab	Reduction of anti-TNF level Increased clearance Worse clinical outcome
Concomitant administration of immunosuppressants	Reduce ab production Increase anti-TNF level Reduce clearance
High baseline TNF level	Increase anti-TNF clearance
Low baseline albumin level	Increase clearance Worse clinical outcome
High baseline CRP level	Increase clearance
Body mass index	Increase clearance
Gender	Higher clearance in males

Immunogenicity

All anti-TNF drugs have the capacity to generate an immunologic response, with the formation of antibodies that neutralise its effect or increase its clearance by forming immune complexes that are eliminated by the reticuloendothelial system [3,4,18,29], thereby shortening the half-life and reducing serum levels [8,30-32].

Although this process has been reported in all diseases treated with these drugs, the rates vary significantly, which can be explained by the different analysis methodologies and the time of implementation, as well as to the various factors related to immunogenicity (Table 2).

The drug administration schedules have a marked influence. Thus, several studies in both adult and paediatric populations [17,18,33,34] have shown that the onset of antibodies is more common with episodic treatment (37-61%) [35] than with a maintenance regimen (6-17%) [36]. The administration route can affect immunogenicity by the presence of antigen-presenting cells in the subcutaneous cell tissue, which can increase the formation of antibodies [37]. The use of concomitant therapy with immunosuppressants has been shown to reduce the rate of antibody formation, which is discussed in more detail later in this article. The degree of humanisation of the drug also affects the onset of antibodies. However, other variables such as sex,

smoking, disease location and the use of mesalazine do not seem to affect the onset of aTNF-ab [35]. These antibodies are highly specific and do not affect the bioavailability of another anti-TNF agent, although a number of studies have shown that the risk of developing aTNF-ab is greater if they were present before the first anti-TNF agent [38,39]. These data agree with the proven clinical utility after changing the anti-TNF although with a poorer response [40,41].

Table 2: Factors modifying immunogenicity.

Patient related	Polymorphism HLA-DR1 (IFX) No differences between UC/CD
Drug related	Degree of humanisation Inadequate manipulation (eg. pH, T ^a , exposure to light)
Administration related	Schedules (maintainance vs episodic) Concomitant ID Dose and drug trough level Route (sc vs iv)

Another important fact is the variation in antibody levels over time and even their disappearance in some cases (28-63%) over the course of the disease [36,38,42], as well as the increase in serum drug levels [36]. Although it is not completely clear, these are believed to be transitory antibodies of little clinical significance. In other cases, these antibodies might be related to the addition of concomitant immunosuppressants or dose intensification, which leaves 60% of cases unexplained [42].

Lastly, studies have confirmed the progressive negativisation of a TNF-ab after withdrawing IFX, although they can **persist** as positive for an extended period (>3 years), which is important information when deciding on its reintroduction [36].

Methods for Measuring Levels and Antibodies

There are various types of analysis for detecting both anti-TNF and antibody levels, which hinders the comparison.

Solid-phase ELISA is the most widely used method due to its relative simplicity, reproducibility and low cost. The assay consists of binding the study drug's antigen to the solid matrix through a monoclonal antibody. The matrix is then incubated with the patient's serum, which will contain the drug in variable quantities. This drug is detected with anti-idiotypic antisera or immunoglobulin anti-Fc, labelled with biotin or peroxidase [43].

Another technique is the reporter gene assay (RGA), which stimulates the fluorescence of the luciferase gene in the presence of TNF α , which is inhibited in turn in the presence of the anti-TNF drug. Lastly, the hamster sperm motility assay (HSMA) is a chromatography technique that uses high-performance liquid chromatography (HPLC) to differentiate proteins of greater weight. TNF α bound to anti-TNF forms immune complexes of greater weight, measurable with this technique.

Detecting a TNF-ab is a significant challenge due to the fact that the antigen to which the antibody is directed is in turn an immunoglobulin. In many of the techniques, the antibody is influenced by the formation of immune complexes in the presence of the drug in the blood. The methods influenced by the presence of the drug include ELISA, radioimmunoassay (RIA) and RGA.

HSMA and the pH-shift anti-idiotypic antigen-binding test (PIA), however, are not affected.

Solid-phase bridge ELISA is the most widely used method and consists of coating the solid matrix with the study drug, adding the patient's serum, and revealing with the same drug labelled with biotin. If there are antibodies against the drug, these will bind to the drug on the plate and to the biotin-labelled drug, forming a "bridge", due to the fact that IgG is a monospecific and bivalent immunoglobulin [43]. The free antidrug antibody in the patient's serum binds to both the drug in the assay plate and to the labelled drug used for the detection. This assay therefore only detects antibody levels exceeding the drug concentration. This technique is sensitive and specific but could result in false positives in the presence of a rheumatoid factor (although it has never been described) and does not detect antibodies in the presence of the drug or monovalent IgG4 isotype antibodies [20,44].

Liquid-phase RIA is more sensitive and can detect IgG1 and IgG4. The F(ab')₂ fragments of radiolabelled anti-TNF bind to antidrug antibodies immobilised in protein A-Sepharose. The assay is more complex because it uses radioisotopes but is more sensitive than ELISA [45]. RGA and HSMA may also be employed.

New assays (PIA, acid-dissociation radioimmunoassay [ARIA], temperature-shift radioimmunoassay [TRIA], etc.) are being developed that can measure antidrug antibodies (free and bound), even in the presence of the active drug. In this assay, the anti-TNF complexes and antidrug antibodies are dissociated at low pH, and the anti-TNF are blocked with antidrug Fab fragments so that the immune complex does not reform and the dissociated antidrug antibodies are subsequently detected with the standard RIA [46].

However, despite the attractiveness of measuring the total antibodies, its practical utility and the applicable conditions will have to be demonstrated, given that it can lead to unnecessary intensifications and changes in therapy. A study with adalimumab is currently suggesting the drug's involvement in an incipient loss of response [47].

Other options undergoing study employ different pharmacokinetic parameters [20,24]. A pharmacokinetic model is being developed that considers the patient's sex, weight and albumin and a TNF-ab levels as covariates when calculating drug levels over time in a stable condition. This model would allow measurements to be performed only at the start or when there are changes and would calculate the intermediate situation [48].

Comparison of Techniques

Despite the various limitations, good correlation at the clinical level has been observed when comparing the assays, classifying most of the patients similarly, despite the different sensitivities and problems of each assay [42,49]. However, the absolute values are not superimposable and should therefore be interpreted according to the methodology employed.

However, the interpretation of conflicting cases and the need to report homogeneous and comparable cut-off points requires us to define the optimal technique for the measurements, in terms of reliability, cost and technical difficulty in its implementation.

When to Perform the Technique

As we have seen, the presence of the anti-TNF drug interferes with the measurement of antibodies employing the most widely used current methods due to the formation of immune complexes [44]. For this reason, the measurements should be performed during drug trough levels, just before the next dosage. Very few studies have used other measures such as the peak level [44] or measurements halfway through the cycle [9].

The demonstrated relationship between serum anti-TNF levels and the clinical response, the reduction of which predicts the formation of aTNF-ab [16,42,50], and the fact that so far only neutralising antibodies have demonstrated clinical relevance [10] have prompted a number of authors to propose starting monitoring the serum drug levels. Only in the absence of any drug level should aTNF-ab levels be measured. However, a recent study that used HSMA reported therapeutic failure in patients with antibodies despite appropriate drug concentrations [51], an unexpected finding that needs to be confirmed.

Influence of Combined Therapy

The concomitant use of immunosuppressives is still a controversial issue in anti-TNF treatment, with its capacity to prevent the formation of aTNF-ab as one of the justifications for its use. For infliximab, this finding has been demonstrated in studies on rheumatoid arthritis and ankylosing spondylitis with the joint use of methotrexate [52-54]. It has also been demonstrated in inflammatory bowel disease with thiopurine drugs and methotrexate [9,18,35,50,55-57], with no differences among them [50], with the frequency of aTNF-ab at 18% without Immunosuppressives and 10% with Immunosuppressives ($p=0.02$) [18,24,42].

This effect is magnified when the anti-TNF is administered episodically [18,35,50,55]. The study by Baert et al. [35] demonstrated that the combination with Immunosuppressives was a predictor of higher drug levels at 4 weeks of the infusion ($p<0.001$), a lower formation of anti-IFX antibodies (ATI) (75% vs. 43%, $p<0.01$) and a lower titration of the same.

The effect of premedication with corticosteroids with this objective is more controversial [53]. In a study of 80 patients randomised for premedicating the IFX infusion with 200 mg of hydrocortisone or placebo, there was a tendency (which did not achieve statistical significance) towards reducing the number of patients who developed aTNF-ab and lower levels of the same [56], a finding that conflicted with those of other studies [35,58,59].

The clinical relevance of the reduction in antibodies by "cotreatment" remains a subject of debate. In a study by Leuven et al. [61], cotreatment with immunosuppressives or premedication with corticosteroids non significantly reduced the formation of aTNF-ab during IFX treatment. However, its early discontinuation at 6 months did not affect the clinical response at 2 years. The patients in monotherapy, however, had lower drug levels, higher Ab titres and increased C-reactive protein (CRP) levels. Differences might therefore be found in the longer term [60].

The Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) study not only found higher drug concentrations in the patients undergoing combined treatment (1.6 vs. 3.5 µg/mL, $p < 0.001$) but also a higher remission rate free of corticosteroids [55].

A recently published retrospective study observed that the withdrawal of Immunosuppressives after at least 6 months of concomitant therapy did not reduce the infliximab levels of patients with CD. After the withdrawal, 38% of the patients required increased doses, and 18% had to discontinue the IFX (due to the lack of efficacy or because of an adverse reaction). However, the withdrawal relapse predictors are the IFX levels at the time the Immunosuppressives is discontinued, CRP levels and the prior need for intensification. None of the patients with levels > 5 µg/mL relapsed; however, all patients with undetectable drug levels did relapse [61].

Existing data for ADA are scarce; however, Reenaers et al. [64] have demonstrated the benefit of combined therapy in the first 6 months, with fewer exacerbations and failures of response [53,62].

Impact of the Serum Drug Concentration and Antibody Formation on the Clinical Response

Several studies have attempted to demonstrate the correlation among serum anti-TNF levels, the presence of aTNF-ab and the clinical response. However, when analysing the results, we must consider the retrospective nature of many of the studies, their variability in the monitoring methodology, the different study populations and the lack of a clear consensus in defining the secondary loss of response.

Since the ACCENT I (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen) study, we have known the influence of IFX levels on the clinical response [1]. There has been growing evidence that serum anti-TNF levels are correlated with the efficacy of IFX [16,17,55,60,63-65], although there have been conflicting results [66].

Baert et al. [35] measured the drug levels in 125 patients undergoing episodic treatment 4 weeks after the infusion. The patients with prior aTNF-ab had lower drug levels and a shorter clinical response. IFX concentrations > 12 µg/mL were associated with longer response, while the presence of aTNF-ab levels > 8 (µg/mL) were associated with lower response. This finding was also shown in the prospective study by Farrell et al. [56], which associated the presence of aTNF-ab with the loss of response.

More recently, Vande Castele et al. [42] retrospectively analysed 1232 samples from 90 patients with CD [64] and UC [26]. The authors observed that the presence of IFX levels < 2.2 µg/mL predicted the interruption of treatment due to loss of response or infusion reaction (82% sensitivity and 74% specificity). This article reports that the presence of aTNF-ab can be transient and might have no repercussion on the drug's efficacy. However, the patients with maintained aTNF-ab levels discontinued the treatment more than those with transient ATI (68% vs. 13%, $p = 0.0005$).

Despite the correlation with the clinical response, it is also important to assess the correlation with biologic and endoscopic parameters. Maser et al. [17] analysed the progression of drug levels in a group of 105 patients with CD undergoing maintenance therapy. The clinical remission rate at 1 year, CRP levels and endoscopic improvement were significantly better in the patients with detectable drug levels. A Japanese group confirmed this relationship by analysing 45 patients (78 endoscopies) while they were treated with maintenance therapy. Endoscopic activity was negatively correlated with serum IFX and albumin levels and positively with CRP levels, erythrocyte sedimentation rate and calprotectin. The presence of aTNF-ab was greater in patients with no mucosal healing [67]. The recently published study by Ungar et al. [68] confirmed this relationship between drug levels and mucosal healing in Crohn's disease.

A recent meta-analysis that included 1378 patients with IBD observed the relationship between the presence of aTNF-ab and the loss of response (RR 3.2, 95% CI 2-4.9, $p < 0.001$), although it did not achieve statistical significance for UC (86 cases) [13]. However, it is important to note the presence of significant biases in all of the included studies and the different methodologies, both in the measurements and in the assessment of the clinical response, which compromises their comparison.

The few studies performed with ADA have also shown the importance of monitoring [69,70], and the relationship with clinical remission and mucosal healing [71]. Bartelds et al. [38] reported the presence of aTNF-ab in 28% of a cohort of 272 patients with rheumatoid arthritis. This subset of patients had lower drug levels, a higher rate of study withdrawal due to treatment failure and lower levels of clinical remission. This relationship has also been described in CD. The dose increase also causes an increase in serum drug levels in those patients who respond but remaining undetectable in those with no response to the intensification. The prior presence of aTNF-ab does not affect the rate of response to ADA or the formation of aTNF-ab [31]. West et al. [39] partially confirmed these results, although the patients with high aTNF-a levels in their study had lower response rates to ADA.

CTZ and golimumab have been studied less but appear to maintain this relationship [72-75]. UC presents lower response rates than CD in anti-TNF therapy. In a study with 115 patients, detectable trough levels were found in only 39% of the patients. This subset had a higher remission rate (69% vs. 15%), endoscopic improvement (76% vs. 28%) and a lower rate of colectomy (7% vs. 55%), without the presence of aTNF-ab having an effect [16].

The relationship between the drug levels reached during the induction phase and the patient's response was recently studied. A prospective study of 19 patients with UC observed that there was a difference between the drug levels achieved at week 8 between the responders and the nonresponders (8.1 µg/mL and 2.9 µg/mL; $p = 0.03$), and the difference was correlated with the clinical response and endoscopy [28].

The Relationship between the Presence of Antibodies and Safety

Infusion reactions are potentially severe adverse effects

related to the IFX infusion and are associated with a high rate of treatment withdrawal and lower clinical response rate at 2 years [24].

Numerous studies have shown that the presence of aTNF-ab is directly correlated with infusion reactions both in CD [17,18,35,56] and in UC [15]. Farrel et al. [56] reported an incidence rate of 40% of infusion reactions in aTNF-ab-positive patients compared with 4.7% for the aTNF-ab-negative ones ($p=0.001$), with an increased rate of severe reactions (28% vs. 0%; $p=0.001$). The study associated concentrations $>8 \mu\text{g/mL}$ (ELISA) with a greater risk, a finding replicated in the study by Baert et al. [35].

In a number of cases, these concentrations have also been associated with late hypersensitivity [76]. There have also been reports that patients with antibodies experience more pain at the injection site and more local reactions than those who do not have the antibodies when using CTZ [77].

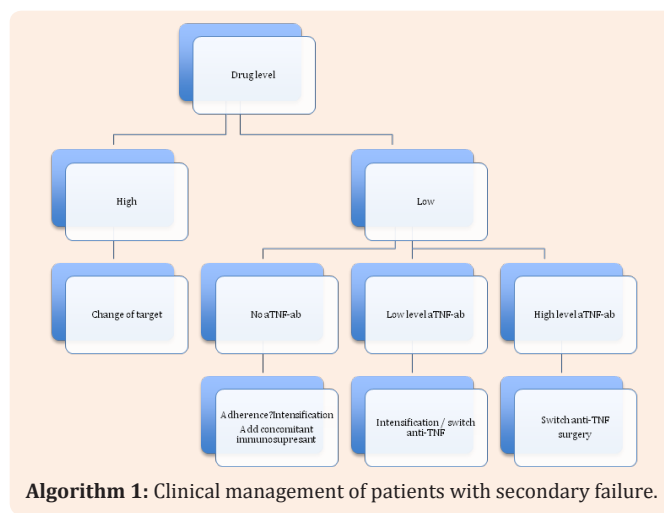
Use In Clinical Practice

There are some clinical conditions in which these measurements can be useful to us at this time:

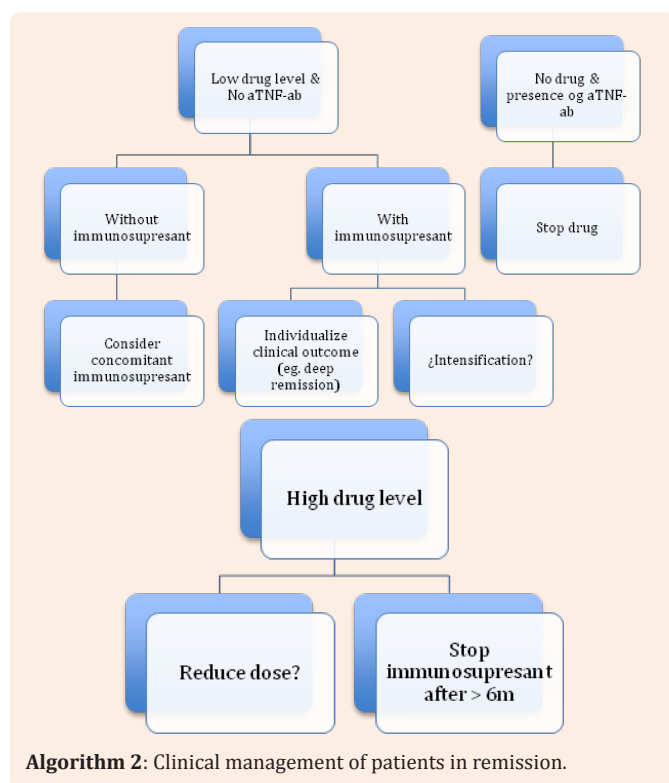
- i. During the induction phase: The measurements help us identify early on the patients at greatest risk of response failure and help guide early intensification, which is especially important in conditions such as severe UC [28].
- ii. When considering reintroducing the drug after a discontinuation period, the measurement of previous antibodies can identify patients at risk of an infusion reaction, for whom restarting the drug is not recommended.
- iii. When facing with a secondary failure. Thus, the algorithm 1, shows the strategy to follow incorporating these measurements in our standard practice. As we have seen, the loss of response during anti-TNF treatment is common. The current empiric strategy of intensification has several problems: In the presence of aTNF-ab, intensification is not typically useful, has high costs and can entail adverse effects. Intensification is also not effective in patients whose treatment failure is due to different mechanisms. Therefore, in this clinical situation, the first step is to verify the presence of active inflammation, rule out disease complications or other causes of the symptoms (stenosis, abscesses, infection, amyloidosis, bile acid malabsorption and irritable bowel) [20,47,78]. In the studies performed to date, up to 40% of patients with symptoms suggestive of exacerbation do not present active inflammation. We should examine the patient's treatment adherence, estimating that up to 17.4% of patients do not comply with the prescribed biologic treatment [79]. Once these 2 clinical conditions have been ruled out, measuring the levels can more effectively guide our treatment. A retrospective study by the Mayo Clinic, which included 155 patients with CD and UC, observed that the use of anti-TNF levels and the presence of antibodies led to changes in the therapeutic approach in 73% of the

patients. The patients with positive aTNF-ab had a greater clinical response to the change in anti-TNF drug (92% vs. 17%, $p<0.004$), while those with subtherapeutic IFX concentrations responded better after intensification (86% vs. 33%, $p<0.016$) [9]. In fact, it has been recently reported that high anti-TNF levels ($4.5 \mu\text{g/mL}$ for adalimumab and $3.8 \mu\text{g/mL}$ for infliximab) identify patients with inadequate response to dose increases (90% specificity), which also occurs with high antibody levels ($>4 \mu\text{g/mL}$ for adalimumab and $>9 \mu\text{g/mL}$ for infliximab) [80], thereby avoiding the ineffective use of high doses of the drug. This strategy has also demonstrated its efficacy in controlling costs. The first prospective randomised study that compared the intensification strategy (in a regimen of 5 mg/kg of IFX every 4 weeks) with the use of an algorithm based on the use of the serum IFX and ATI levels has recently been published. The intent-to-treat cost was significantly lower (34%) in the algorithm group than in the intensification group (€6038 vs. €9178, $p<0.001$), with no difference in clinical response (58% vs. 53%, respectively; $p=0.81$) [81].

- iv. The fourth clinical situation in which these measurements can be useful is during patient remission (Algorithm 2).
- v. **Immunosuppressives withdrawal:** Low anti-TNF levels and the presence of biological activity are predictors of relapse if Immunosuppressives is withdrawn. In these situations, we should therefore propose maintaining Immunosuppressives even after the sixth month.
- vi. Withdrawal of anti-TNF in those cases in which a sustained response is observed, the drug is at a low level or is undetectable, and/or antibodies are present and the efficacy is not attributable to anti-TNF, and it can therefore be discontinued [36].
- vii. Dose reduction in those patients who have very high drug levels. There are however more studies in the area of rheumatology, and the optimal range for the blood drug level needs to be determined.



Better defining the optimal range of anti-TNF levels is next step of clinical research to improve patient by patient clinical decision making, including earlier detection of clinical deterioration and avoiding an excess use of the drug. The recently published Trough Level Adapted Infliximab Treatment (TAXIT) study [82], which included 263 patients with stable response to maintenance infliximab therapy, compared a patient group managed according to their symptoms with another group managed according to their blood drug concentrations. Although no differences were achieved in the primary objective (percentage of patients in remission at 1 year), there were fewer exacerbations (7% vs. 17% $p=0.018$) in those patients managed by level, and there was also an efficient use of the drug. In the case of CD, the dose increase to remain in the interval improved control of the disease (higher proportion in remission with lower CRP levels). However, one of the reasons that could justify the inability to achieve the primary objective is that, prior to the randomisation, all of the patients were optimised for a drug concentration of 3-7 $\mu\text{g/mL}$. Another important conclusion is that there were no changes in the patients' situation for those who reduced the standard dose due to being above the levels considered optimal. We should also take into account that in this study only 43.7% of the patients were in the "therapeutic range". Some 48.6% of the patients were within "supratherapeutic levels", which allowed the dose to be reduced by 93%, with a 28% reduction in costs.



Conclusion

Despite the considerable change represented by the use of biological therapies in IBD, we need strategies that help us optimise our treatments in order to improve the efficiency of these drugs.

Studies have demonstrated the relationship between blood anti-TNF levels and the clinical, biological and endoscopic response, as well as the presence of antibodies with the loss of response and the onset of infusion reactions.

Concomitant treatment reduces the frequency and levels of aTNF-ab. The clinical benefit of this finding is greater with episodic treatment, and its use is justified, but it is more debatable for maintenance therapy after six months. Other factors should be considered such as the risk of relapse (baseline levels, CRP and previous progress) and the risks resulting from the long-term use of immunosuppressants.

In conclusion, the use of drug levels, the presence of antibodies and clinical and biological activity parameters can help us tailor our therapeutic decisions in clinical practice, thereby avoiding the use of an ineffective drug, guiding early intensification strategies and even anticipating clinical exacerbations with better long-term patient monitoring. However, we need to be able to standardise the detection methodology, correctly interpret its results and validate an algorithm that combines it with the clinical and biological parameters used to date.

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