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The value of pharmacological dosage in the management of chronic inflammatory bowel disease treated with anti-TNF agents

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ABSTRACT: *Introduction:* The advent of biotherapies has radically changed the management of IBD. However, the use of these drugs may in some cases result in to primary non-response or a loss of secondary response. Therapeutic Drug Monitoring (TDM) is a tool that was developed to manage biotherapy as accurately as possible in these situations.
Material and methods: This is a retrospective descriptive study spread over 8 years of 53 patients followed for IBD put on anti-TNFα, in whom assays of residual levels of anti-TNF and anti-drug antibodies were carried out.
Results: 48 suffer from Crohn's disease and 5 from ulcerative colitis. Of these patients, 41 were on infliximab and 12 on adalimumab. The TDM performed in front of a primary non-response in 18 patients, and a loss of secondary response in 34 patients. We found immunization in 28% of patients, underdosage in 56%, and 15% had a normal dosage. Therapeutic optimization was adopted in 52% of patients, a switch in 19%, a swap in 25% of patients, and the addition of an immunosuppressant in 6.5%. The evolution was marked by the achievement of a prolonged remission in 69% of these patients.
Conclusion: Pharmacological dosage of the residual rate of the anti-TNF and anti-drug antibodies currently constitutes an important element for managing the primary non-response or the loss of secondary response to anti-TNF in patients with IBD treated by biotherapy.

KEYWORDS: IBD, Crohn's disease, Ulcerative colitis, Anti-TNF, Pharmacological dosage, Therapeutic Drug Monitoring.

1 INTRODUCTION

Chronic inflammatory bowel disease (IBD) is a disease characterised by chronic or recurrent inflammation of the intestinal wall, the evolution of which is responsible for multiple complications that may lead to recourse to surgery and functional sequelae.

Until the early 2000s, the main objective of IBD treatment was symptom control to maintain clinical remission, and when medical treatment was ineffective or poorly tolerated, resection was used as one of the treatment options.

A better understanding of the natural history of IBD and the emergence of anti-TNF (tumour necrosis factor) agents in recent years have considerably altered the therapeutic objectives and management of these disorders.

The aim of current treatment is to achieve a complete absence of activity and progression of these diseases, and without surgical resection, the possibility of living a completely normal life while minimising the risks associated with treatment.

These strategies include the identification of patients at risk of developing these complications, the early treatment of these patients with drugs likely to prevent this development (immunosuppressants and anti-TNF) and discussions about stopping these treatments when the disease appears to be sufficiently controlled.

Some patients do not respond immediately to anti-TNF (primary non-responders), others will have a loss of secondary response, and some patients will be intolerant to treatment. When faced with these situations, the attitude was to engage in empirical or symptomatic therapeutic modifications, which were not always effective. This is why TDM (Therapeutic Drug

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Monitoring) was developed, a precision medicine tool that measures the serum concentration of the drug, maintains a sufficient dose to ensure the drug's efficacy and avoids drug toxicity [1].

More recently, TDM has been applied to anti-TNFs, primarily to monitor drug efficacy and guide the management of suspected treatment failures in IBD patients treated with biologics [2-3].

The aim of our work is to demonstrate: The value of pharmacological assays of residual levels of anti-TNF alpha and anti-biological antibodies in the management of IBD.

2 MATERIAL AND METHODS

2.1 PRESENTATION OF THE STUDY

This is a retrospective descriptive study spread over a period of 8 years between September 2014 and December 2022 in the hepato-gastroenterology I department, Military Hospital Mohamed V of Rabat.

The study included 53 patients with IBD (Crohn's disease/haemorrhagic rheumatoid arthritis) treated with anti-TNF alpha (Infliximab (IFX) and/or Adalimumab (ADA)) as monotherapy or in combination with immunosuppressive therapy, and who needed to have residual anti-TNF and anti-drug antibody levels measured during their follow-up.

From the patients' clinical records, we collated the following parameters:

2.2 DEMOGRAPHIC DATA

- Age
- Sex

2.3 CLINICAL DATA

- Type of IBD
- Age of onset
- Description of IBD according to the Montreal classification
- Age at introduction of anti-TNF therapy
- History of IBD surgery
- Type of anti TNF used
- Whether or not combined with an immunosuppressant (combination therapy)

2.4 INDICATION FOR PHARMACOLOGICAL DOSAGES

In our study, the indication for pharmacological dosages was either primary non-response or loss of secondary response.

Primary non-response was defined as the absence of clinical response at the end of induction treatment (S14 for Infixlimab, S12 for Adalimumab).

Loss of secondary response refers to patients who initially respond to treatment during the induction phase and then experience a return of clinical symptoms during maintenance treatment.

2.5 RESULTS AND THERAPEUTIC ADJUSTMENTS

Statistical analysis was performed using JAMOVI software. Quantitative variables were described in terms of mean and standard deviation, and qualitative variables were described in terms of numbers and percentages.

3 RESULTS

3.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

Over a total duration of 08 years, 53 of our IBD patients on anti-TNF, had pharmacological dosage.

The mean age of our patients was 37±11 years with extremes ranging from [18-61 years].The sex ratio was 1.3 with a male predominance [23F, 30H].

48 of our patients had Crohn's disease (91%) and 05 of our patients in whom the tests were performed had haemorrhagic rectocolitis (9%).

The age at diagnosis of the disease was 27±13 years, with extremes ranging from [8-59 years].

Among our patients with crohn's disease, the location was ileal in 4% of cases (n=2), colonic in 19% of cases (n=9), ileocolic in 50% of cases (n=24). The upper gastrointestinal tract isolated in 4% of cases (n=2) and associated perineal in 23% of cases (n=11) with a fistulising (B3) phenotype in 32.4% of cases (n=11), stenosing (B2) in 29.4% of cases (n=10) and inflammatory (B1) in 38.2% of cases (n=13) and both stenosing and fistulising in 16. 8%.

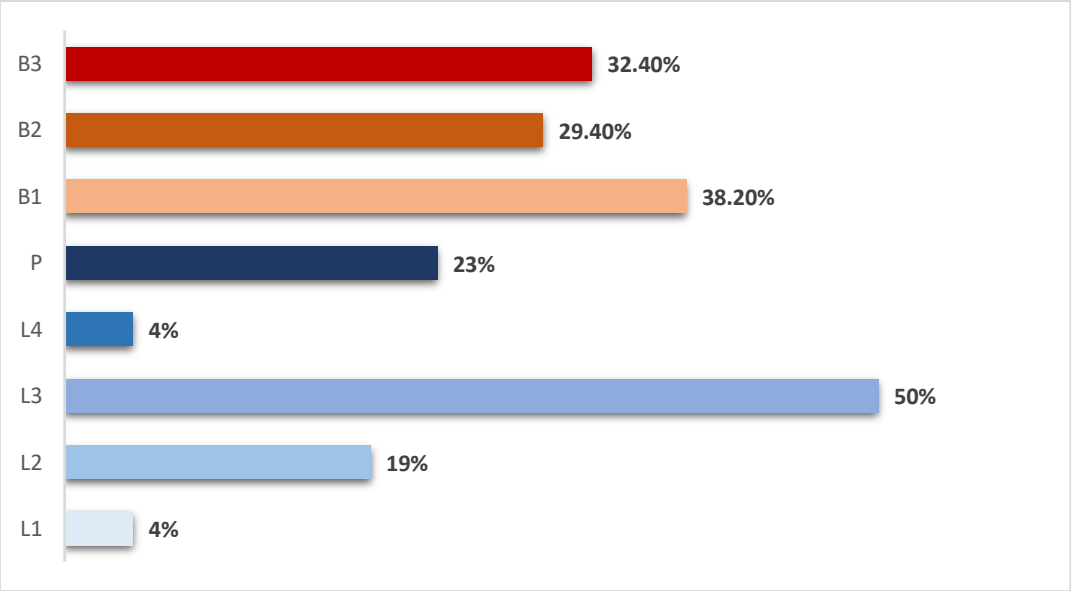


Fig. 1. Distribution according to the Montreal classification in patients with crohn's disease

For patients followed for haemorrhagic rectocolitis, 40% of cases (n=2) had a rectal location (rectitis), 20% of cases (n=1) below the left angle (left colitis) and 40% of cases (n=2) whose involvement extended beyond the left angle (pancolitis).

The age of patients at the time anti-TNF was introduced ranged from 8-57 years, with a mean of 32 years and a standard deviation of 12 years.

06 of our Crohn's patients (11.3%) had already undergone surgery for their disease.

77% of our assays (n=41) were performed on patients taking Infliximab and 23% (n=12) on patients taking Adalimumab.

36 of our patients (68%) were on combotherapy (biotherapy combined with an azathioprine-based immunosuppressant).

Table 1. Demographic and clinical characteristics of patients

Demographic and clinical characteristics of patients	
Age at diagnosis	**37±11years**
Male / Female	**30 / 23**
Type of IBD	
Crohn's disease	91%
Haemorrhagic rectocolitis	9%
Age at onset of disease	**27±13years**
Location of crohn's disease	
(L1)	4%
(L2)	19%
(L3)	50%
(L4)	4%
(p)	23%
Crohn's disease phenotype	
(B1)	38,2%
(B2)	29,4%
(B3)	32,4%
(B2+B3)	16,8%
Location of haemorrhagic rectocolitis	
(E1)	40%
(E2)	20%
(E3)	40%
Age at start of IFX	**32±12years**
Previous surgery for IBD	**11,3%**
Type of anti-TNF	
IFX	77%
ADA	23%
Combo therapy	**68%**

IBD: inflammatory bowel disease; IFX: infliximab;
ADA: adalimumab; TNF: tumor necrosis factor

3.2 INDICATION FOR TDM

Serum anti-TNF assays and testing for anti-biotherapy antibodies were indicated in 35% of cases (n=18) when there was a lack of primary response and in 65% of cases (n=34) when there was a loss of secondary response.

3.3 THERAPEUTIC ADJUSTMENTS AND RESULTS

TDM results by indication:

- Among the primary non-responders, 44% of our patients had an under-dose, 6% had a normal assay and 50% had immunisation with positive anti-TNF antibodies.
- Our patients with a loss of secondary response had an underdose on TDM results in 61.7% of cases, 20% had a normal dose, while only 17.6% had immunisation with positive anti-TNF antibodies.

Therapeutic adjustments:

Overall, in 19.2% of cases (n=10), the results of these assays led to a switch of anti-TNF. 25% (n=13) of our patients were switched to Ustekinumab. In 52% of cases (n=27), we carried out an optimisation. And in 6.5% of patients (n=2) we continued the same treatment but reinforced it with an immunosuppressant.

Table 2. TDM results by indication

Indication for test	Under normal	Normal dosage	Immunisation
Primary non-responder	**44%**	**6%**	**50%**
Loss of secondary response	**61.7%**	**20.6%**	**17.6%**

Depending on the results of the CT scan, treatment adjustments were as follows:

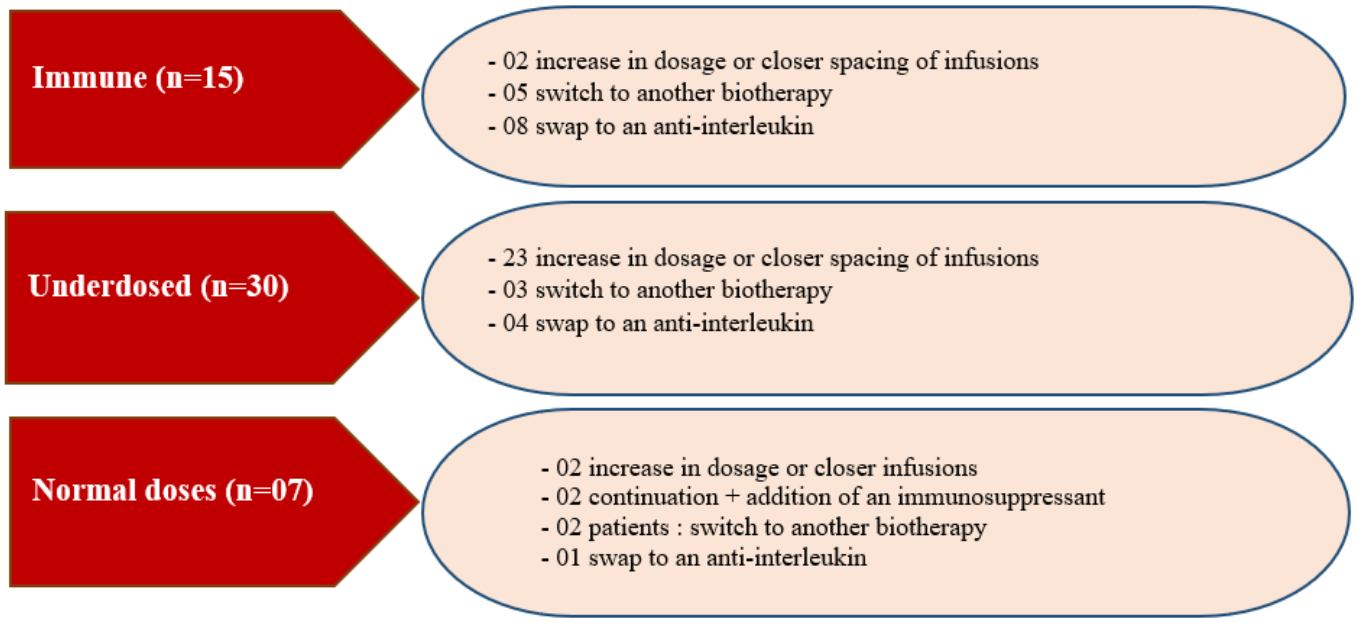


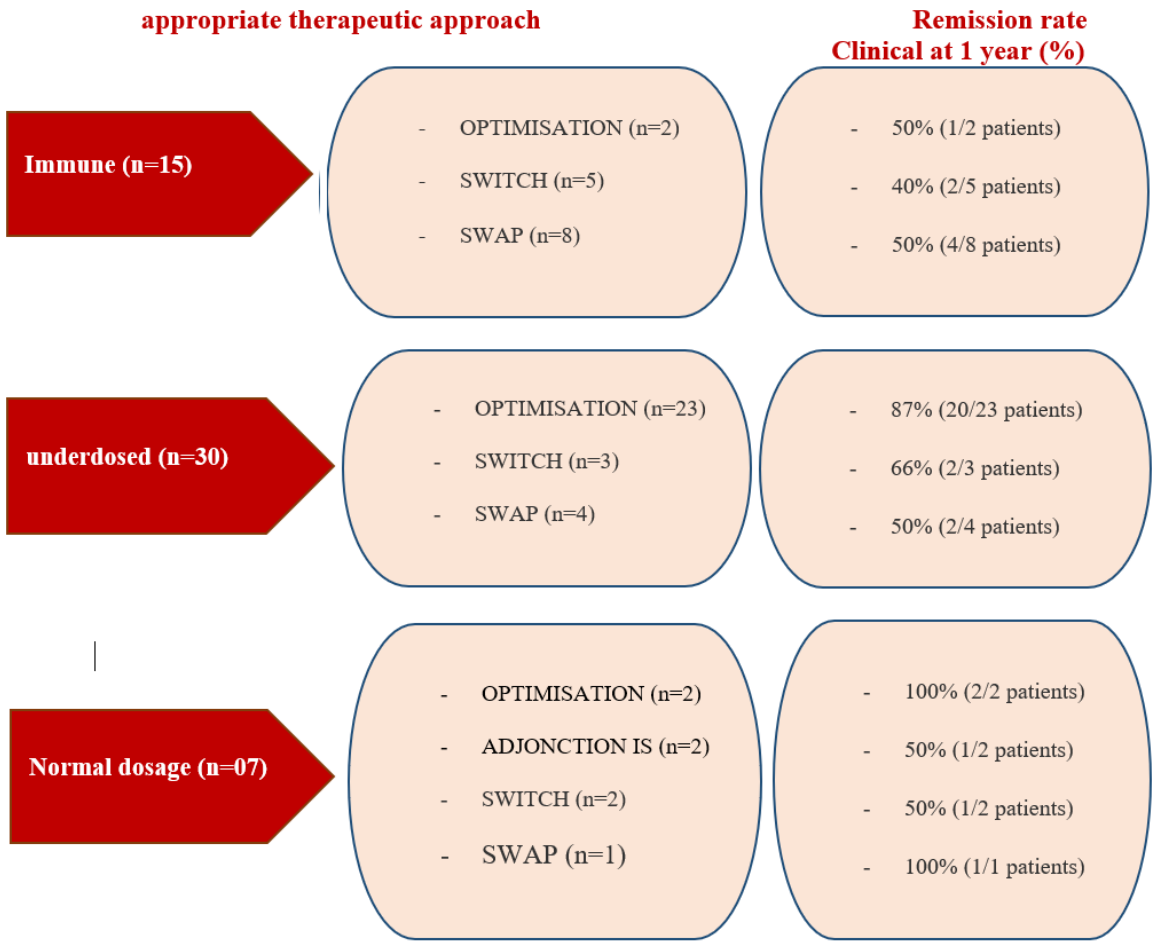
Fig. 2. Representation of the therapeutic adaptations made in the different groups

3.4 Patient Outcome After TDM-Based Therapeutic Adjustment

Overall, 52 patients had benefited for TDM therapeutic adjustments: 69% (n=36) were in prolonged clinical remission at one year, 25% (n=13) showed a partial clinical response, while 6% (n=3) showed no improvement for which a new therapeutic attitude was taken.

According to the TDM results obtained, and depending on the therapeutic adjustments made, the remission rate at 1 year was as follows:

Table 3. Clinical remission rate at 6 months according to the adapted therapeutic approach



4 DISCUSSION

The idea of TDM is to measure the serum concentration of the drug, to maintain a dose sufficient to ensure the drug's efficacy and to avoid drug toxicity [1].

It has been used in clinical practice for many years, even before the development of biologics. In the past, TDM has been used in a variety of drugs, such as antibiotics and immunosuppressants. More recently, it has been applied to biologics, primarily to monitor drug efficacy and guide the management of suspected therapeutic failures in IBD patients treated with biologics.

In IBD, in addition to measuring anti-drug antibody, TDM also involves measuring serum drug levels, both of which are related to drug efficacy [2-3]. Despite numerous studies demonstrating its usefulness, many questions remain, such as the timing of TDM, the determination of target thresholds for serum drug levels and anti-drug antibody, and the practical application of the results. The data examining this show that there is considerable variability in target thresholds due to a number of factors, such as the different methods and tests used in TDM measurements, or the desired clinical outcome.

Finally, as the first class of biologics are anti-TNFs, the use of TDM must first be applied to patients receiving infliximab or adalimumab.

As a result, most TDM studies have focused on anti-TNFs. Over time, as new biologics for IBD have become available, further studies have investigated the use of TDM with vedolizumab or ustekinumab.

To better understand the use of TDM in IBD, it is essential to understand drug pharmacodynamic and pharmacokinetic concepts, as these are important in understanding mechanisms of treatment failure [4]. Several factors can influence a patient's

response to treatment, including low or sub-therapeutic drug levels associated with increased clearance, whether immune-mediated or not, and the underlying drug targeting pathway.

Anti-TNF agents have greatly improved the management of IBD patients. However, in spite of this, up to 30% of IBD patients do not develop any initial response after the induction period and up to 50% have a loss of secondary response after the induction period, especially during the first year [5-6].

Those with loss of secondary response initially responded, but then began to develop symptoms of disease activity, indicating treatment failure. The pharmacokinetic mechanism for both of these phenomena is thought to be due to insufficient serum drug concentrations, as evidence suggests that patients with low serum drug concentrations during induction or maintenance are less likely to achieve clinical responses [6].

Empirical methods of managing loss of response are generally considered to be suboptimal and may incur additional costs. TDM-based strategies, applying measurements of anti-TNF drug concentrations and anti-drug antibodies at the time of treatment failure, offer an alternative.

In our study, 65.4% of patients on anti-TNF therapy had a secondary loss of response. Individualised optimisation can therefore be proposed on the basis of the results reported.

In our study, 87% of patients who responded to optimised anti-TNF treatment were under-dosed.

In a retrospective study, Afiff et al [9] showed that over 80% of patients responded to IFX optimisation. For these patients, this indication is generally accepted.

In the case of immunisation with positive anti-TNF antibodies, Afif et al [9] showed that IFX optimisation resulted in a response to treatment in only 18% of cases compared with 50% of cases in our study, in contrast to switching to adalimumab where a good response was obtained in 80% of cases compared with only 40% of cases in our study.

This could be explained by the fact that most of our patients had low ATI, hence the notion of permanent and transient ATI (defined retrospectively in the studies and therefore of little use in clinical practice), which shows its importance.

In a prospective study, Paul et al [10] showed that no patient responded to IFX optimisation when ATI levels were very high (>200 ng/ml in this study).

The negative effect of high ATI levels compared with low levels was demonstrated by Yanai et al [11]: after one year, only 18% of patients were in clinical remission, compared with 50% of patients with low ATI.

Ungar et al [12] showed that loss of response was significantly greater with IFX in the presence of permanent versus transient ATI.

In a retrospective study, Vande Casteele et al [13] reported clinical response rates to IFX optimisation according to the type of previous ATI. In the absence of ATI, 94% of patients responded after IFX optimisation, 68% for transient ATI (p = NS) and 16% for permanent ATI ($p = 0.028$ between permanent and transient ATI and $p < 0.001$ between permanent and no ATI) (Figure.10).

Only one retrospective study reported conflicting results, but did not report the type of ATI or its incidence [14].

In the presence of ATI, a second possibility could be to propose the addition of immunosuppressants in patients who lose their clinical response to IFX.

Ben Holling et al [15] reported on patients who lost clinical response to IFX monotherapy with undetectable IRR and elevated ATI.

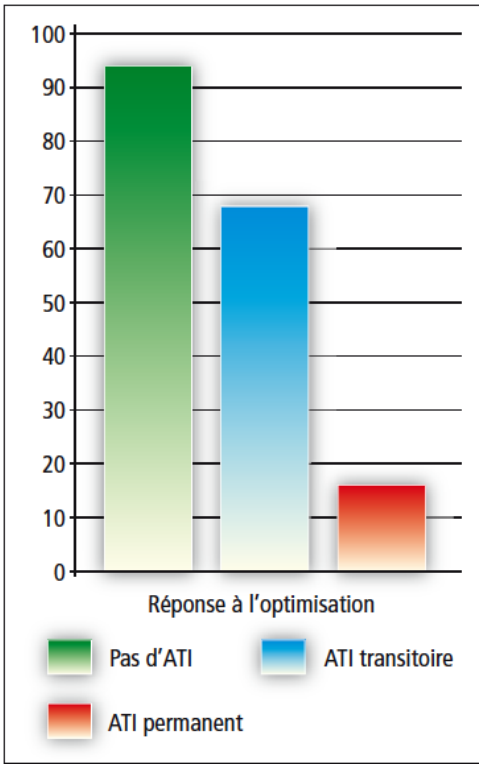


Fig. 3. Therapeutic response to IFX optimisation in patients with loss of response according to ATI before optimisation [61]

The addition of IS (thiopurine or methotrexate) normalised anti-TNF pharmacokinetics (IRR normalisation and ATI negativity) within 6 months, allowing a clinical response to be achieved. In a prospective study published at JFHOD 2013 [16], prospectively including 13 patients with CD who had failed standard-dose IFX. All patients had very high ATI levels (>200 ng/ml), but no TRI was detected. Following the addition of azathioprine, 6 of 13 patients (55%) achieved clinical remission at 6 months, with normalisation of pharmacokinetics and biomarkers.

In our study, we opted for this therapeutic approach in only 2 patients who had negative ATI and normal TRI, given that most of the patients who were on IFX had benefited from combo-therapy from the outset. Only one patient (50%) achieved clinical remission at 6 months.

In the case of normal doses, optimisation does not appear to be an appropriate solution. Afiff et al [9] reported a response rate of less than 20% after optimisation.

Yanai et al [11] showed a response rate of less than 25% at 12 months after optimisation, whereas a change of therapeutic class resulted in a lasting clinical response in more than 80% of cases ($p = 0.006$).

Paul et al showed in a prospective study [10] that if assays were normal before optimisation, the clinical response rate after optimisation was 20%.

Despite this, in our study we opted for optimisation for 2 of our patients with normal TRI assays, since we had already exhausted all other available therapeutic options. Prolonged remission at one year was obtained in both patients, results that are contradictory with other studies, and may be attributed to the assay techniques used, which overestimated IRR.

In the event of loss of response to IFX, a treatment algorithm based on the residual level and its antibody may be proposed (Table 4).

Table 4. Therapeutic algorithm in the event of loss of response to IFX based on the pharmacokinetics of the compound [64]

Perte de réponse clinique	ATI négatifs ou transitoires	ATI permanents et élevés
TRI thérapeutiques	Changement de classe	Changement de classe
TRI bas ou indétectables	Optimisation de l'IFX	Changement d'anti-TNF ou ajout d'un IS

In our study, we found that 34% had no primary response (of whom 4 were on ADA and 14 were on Infliximab), a rate comparable with most of the studies cited above.

After TDM, 50% had immunisation against anti-TNF compared with 44% who were underdosed and only one patient on ADA had a normal dose.

Two major points should be borne in mind before discussing our therapeutic modification in the event of a loss of response:

1. The loss of efficacy against TNF is not limited to the appearance of Ac (immunogenic effect). There are many other possibilities to discuss. It is therefore imperative to check whether the patient's disease has actually appeared (endoscopy, imaging, biology, faecal calprotectin), because intestinal functional impairment (IFI) is very common (between 30% and 50%). Table5 summarises the different mechanisms of loss of anti-TNF response

Table 5. Mechanisms of loss of response to anti-TNF

Inflammation non contrôlée de la MICI (taux sériques bas d'anti-TNF)
Perte de réponse liée à la présence d'anticorps anti anti-TNF
Consommation de l'anti-TNF par une inflammation
Clairance non liée à un phénoméne immunogéne
Non observance thérapeutique
Inflammation non contrôlée de la MICI (taux sériques thérapeutiques d'anti-TNF)
Exarcerbation paradoxale par un anti-TNF
Autres mécanismes d'inflammation que le TNF
Inflammation non liée à une poussée de MICI (taux sériques thérapeutiques, CRP élevée)
Infection !
Autres (vascularites, ischémie)
Mécanismes non inflammatoires (taux sériques thérapeutiques, CRP normale)
Sténoses fibreuses
Cancer
TFI
Autres

2. The choice of IFX optimisation:

The results were the same with a decreasing interval (every 6 weeks) and an increasing dose (10 mg/kg) every 8 weeks [17]. No study has examined whether such an algorithm could be provided in patients who have lost clinical response to adalimumab. In one study [18] of IBD patients, patients were unresponsive to adalimumab and serum ADA and anti-ADA antibody measurements were taken prior to optimisation. All patients were optimised with ADA (40 mg/7 days). For this reason, we propose a comparable treatment algorithm for patients losing clinical response to ADA (40mg/14d SC) (Figure 4).

In terms of cost-effectiveness, Steenholdt et al [19] were able to demonstrate that an individualised approach using reactive CT was actually more effective [19]. Similar results were replicated in a study by Velayos et al. again demonstrating that dose adjustment based on a TDM-based algorithmic approach was more cost-effective than empirical dose escalation [20].

Figure 4 summarises the suggested treatment algorithm for optimal management of anti-TNF treatment failure based on TDM findings [21].

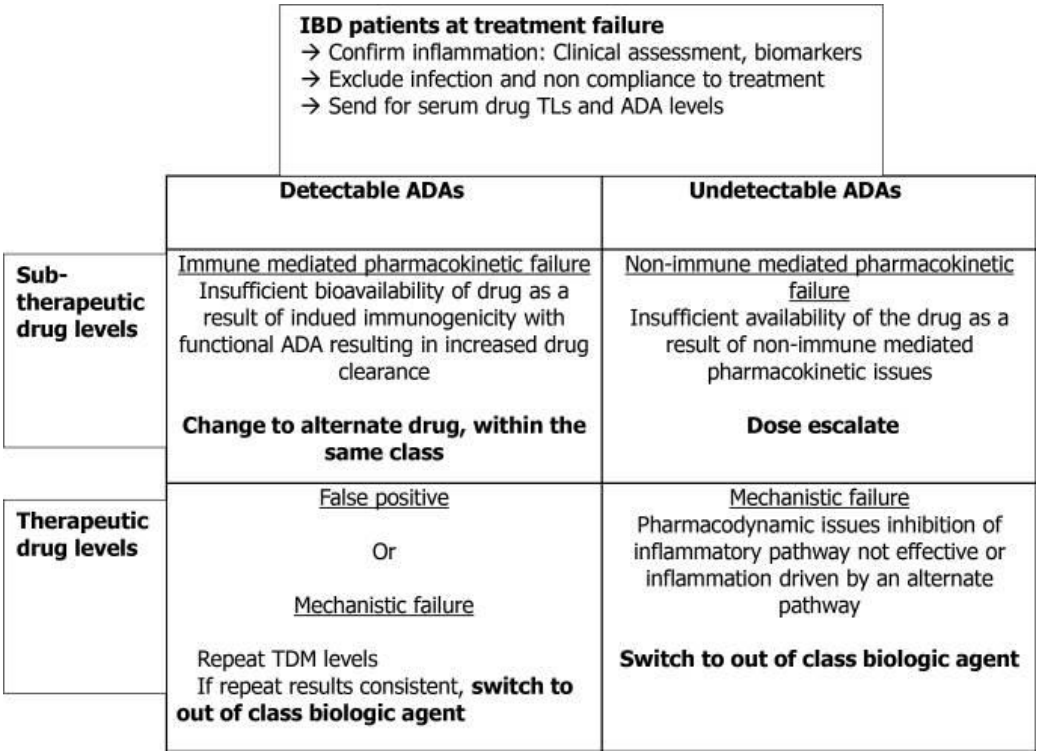


Fig. 4. Approach based on therapeutic follow-up of treatment failures [21]

Following numerous exposure-response relationships linking targeted T lymphocytes (TLs) to treatment outcomes, the idea of a proactive approach was born to target specific thresholds to avoid primary non-response or loss of secondary response.

The concept of proactive TDM relies heavily on achieving and maintaining threshold drug levels to improve long-term outcomes. However, it is often observed that patients with a lower inflammatory load respond better to treatment and also have favourable pharmacokinetics, leading to higher measured trough concentrations - in this case, the trough concentration is more of a biomarker of favourable pharmacokinetics, rather than a causal factor in improving outcomes [22].

According to one meta-analysis, routine proactive TDM, with repeated measurements of biologic drug concentrations and iterative dose adjustments to achieve target ranges in all patients, regardless of disease activity, provided no additional benefit over conventional management. In eight trials of patients during the maintenance phase of anti-TNFα therapy, most patients had at least a partial clinical response to induction therapy and a fraction were in clinical remission - these patients may have a favourable pharmacokinetic profile, although a detailed analysis of pharmacokinetics was not feasible in this study-level synthesis. This may also explain the lack of difference in the proportion of patients reaching the target threshold and the proportion of patients developing anti-drug antibodies between the proactive CT group and conventional management. It is possible that early measurement of biologic drug concentrations, to identify patients who may have accelerated clearance, and optimisation of a subset of these patients at the start of treatment may offer benefits [23].

To date, only one trial, NOR-DRUM-A, has focused on TDM in the induction phase and has shown no benefit over standard management. Ongoing trials such as OPTIMIZE (NCT04835506) and TITRATE (NCT03937609), in which infliximab was optimised during the induction phase in patients with Crohn's disease and severe acute ulcerative colitis using a pharmacokinetic dashboard, will shed further light on the subject [24].

Another proposed benefit of proactive TDM is the earlier recognition of immunogenicity to anti-TNFα and the ability to optimise treatment by increasing the dose and/or adding immunosuppressants (particularly if anti-drug antibodies are low titre). Observational studies suggest that approximately 25% of patients with loss of response during anti-TNFα maintenance therapy are due to immunogenicity-induced pharmacokinetic failure [25].

It is unclear whether this can be done by a one-off TDM scan at the start of biologic therapy, or whether routine repeated measurements of anti-drug antibodies are required. Only a small proportion of patients in the included trials underwent pre-randomisation TDM and treatment optimisation.

Long-term follow-up (>3 years) of the trial showed no difference in the risk of IBD-related hospitalisation, surgery or corticosteroid use between the two groups; however, patients in both groups continued to receive annual assessments of drug levels and anti-drug antibodies [25].

5 CONCLUSION

Pharmacological dosage of anti-TNF drugs can provide information on the mechanisms of therapeutic escape and thus help to guide the prescription of anti-TNF drugs.

Therapeutic Drug Monitoring (TDM) therefore appears to be a relevant tool in the management of IBD patients. Nevertheless, their considerable cost makes it difficult to use them systematically in routine clinical practice, hencè the need for them to be reimbursed by national health insurance organisations.

FUNDING

No funding was received.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The authors declare no conflicts of interest. This work was performed following the code of ethics under the supervision of our institution's medical and ethics committee.

COMPETING INTERESTS

The authors declare no competing interests

ABREVIATIONS

IFX: Infliximab

ADA: Adalimumab

TRI: Residual level of Infiliximab

TRA: Residual level of ADA

ATI: Antibody anti infliximab

AAA: Antibody anti-adalimumab

IS: Immunosuppresseur

TDM: Therapeutic Drug Monitoring

AC: Antibody

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