

## CLINICAL/NARRATIVE REVIEW

# Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management

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Tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) antagonists have advanced the management of inflammatory bowel diseases patients leading to an improvement of patient's quality of life with the reduction of number of surgeries and hospitalizations. Despite these advances, many patients do not respond to the induction therapy (primary non-response—PNR) or lose response during the treatment (secondary loss of response—LOR). In this paper we will provide an overview of the definition, epidemiology and risk factors for PNR and LOR, as well as discuss the therapeutic options for managing LOR.

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## INTRODUCTION

Tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) antagonists are effective for the treatment of inflammatory bowel diseases, demonstrating improvement in patients' quality of life, and reductions in surgeries and hospitalizations.<sup>1</sup> However, around 10–30% of patients do not respond to the initial treatment and 23–46% of patients lose response over time. Determining whether the reason for failure is a primary or secondary non-response is paramount to successfully treat these patients. A significant proportion of patients do not respond (primary non-response—PNR) to TNF $\alpha$  antagonists. Distinct mechanisms underlie these two forms of TNF $\alpha$  antagonist treatment failures. This paper will focus mainly on strategies to manage and prevent the development of loss of response (LOR) with a brief overview on PNR.

## PRIMARY NON-RESPONSE

**Definition.** There is no consensus in the definition of PNR. The accepted clinical definition is lack of improvement of clinical signs and symptoms with induction therapy.<sup>2</sup> Regarding the time frame, there is agreements in clinical trials that PNR to anti-TNF drugs should not be assessed prior to 14, 12, or 8 weeks following initial infusions, respectively, with infliximab, adalimumab (ADA), and certolizumab.<sup>3,4</sup>

**Epidemiology and risk factors.** The incidence of PNR varies between clinical trial and clinical practice from 10–20% to 13–30%.<sup>2,3,5</sup>

Several factors seem to negatively influence the risk to develop PNR such as disease longer than 2 years, small bowel involvement, smoking, C reactive protein, and also

genetic mutations such as FAS-L and caspase-9 in the apoptosis related genes.<sup>6</sup>

**Management.** There is evidence to suggest that optimization of the dosing regimen and combination therapy can minimize PNR. It is important to note that most evidence regarding PNR and therapeutic drug monitoring during induction results from *post hoc* analysis or retrospective data.

*No anti-TNF antibodies present with high drug level.* Several studies have demonstrated that in patients with PNR, the median trough level of infliximab (IFX) may be high and antibodies against anti-TNF may be absent.<sup>7</sup> For these patients two options are available. Switching to another anti-TNF may be useful, however large, controlled studies addressing the efficacy of a secondary anti-TNF agent in patients with PNR are lacking. The overall response rate to a second anti-TNF agent in first TNF $\alpha$  inhibitor refractory patients seems to be 50–65%.<sup>8</sup> Switch out of therapeutic class considering a drug with other working mechanism may be a worthwhile solution. Vedolizumab is a gut-selective antibody against the integrin  $\alpha 4\beta 7$ . It induces clinical remission in 26% of the patients with previous TNF antagonist failure compared with 12% in the placebo group, and has a safety profile that is similar to placebo.<sup>9</sup>

*No anti-TNF antibodies present with sub-therapeutic drug level.* One strategy for achieving response in patients with PNR is dose escalation based on the pharmacokinetic profile of the patient, in other words therapeutic drug monitoring. In the CLASSIC I trial, it was shown that remission at week 4 was achieved in more patients receiving the higher dose ADA than the lower dose.<sup>10</sup> Patients from the ULTRA-2 study who underwent dose escalation, to achieve higher trough levels seem to have an increased chance of remission at week 8.<sup>11</sup>

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*Post hoc* analyses of the ACT-1 and ACT-2 data showed that clinical outcomes such as clinical response, clinical remission, and mucosal healing are more likely to occur in patients with higher IFX concentrations than in those with lower drug concentrations. The presence of an infliximab concentration of ~41 µg/ml at week 8 was associated with a positive predictive value of 80% for clinical response.<sup>12,13</sup>

**Special populations.** Biologic dose optimization may be very relevant in patients with acute severe ulcerative colitis (UC). The inflammatory burden of UC is high and dose escalation may be required, as it has been shown that infliximab clearance in this patient population is increased, which contributes to non-response to infliximab.<sup>14</sup>

## LOSS OF RESPONSE

**Definition.** Secondary LOR, also referred to as secondary non-response, describes patients who respond to the therapy after an induction regimen, but subsequently lose response during maintenance treatment. There is no consensus definition, but the majority of clinical trials and a recent European Crohn's and Colitis Organization workshop use clinical symptom indices (i.e., Crohn's disease (CD) activity index or the Mayo score for UC) to define response and remission.<sup>8</sup> Patients who initially experience substantial increases in these scores but later suffer from clinical relapse during maintenance therapy are considered to experience a secondary LOR.<sup>8</sup> Other definitions have been proposed for LOR, such as those requiring dose intensification or those who discontinue the drug after a period of use, but these definitions do not capture all patients who experience LOR. Since secondary LOR is defined as LOR occurring after the induction period, the timing at which this occurs is different for each TNFα antagonist.<sup>6</sup>

**Epidemiology and risks factors.** There is no consensus on the rate of LOR to TNFα antagonists. This is partly due to the various definitions of LOR. For instance, dose intensification after 12 weeks of therapy is needed in 23–46% of patients, and drug discontinuation occurs in 5–13% of patients.<sup>8,15–19</sup> Data from the ACCENT1 trial (including more than 6,000 patient-years of follow-up) estimates that ~40% of patients with CD treated with IFX will lose response eventually, and the annual risk for LOR to IFX is about 13% per patient-year of treatment.<sup>3</sup> A systematic review on LOR in adult and pediatric patients with CD reported the mean percentage of patients who lost response to ADA was 18.2% among a total of 955 primary responders, with an annual risk of 20.3% per patient-year. Dose escalation was needed by 21.4%, and the annual rate of escalation was 24.4% per patient-year.<sup>20</sup> If dose escalation is used as a surrogate for LOR in CD, its incidence is 13% for IFX and 24% for ADA across randomized trials and observational series.<sup>15,17</sup> In PRECISE 2 trial, the rate of secondary non responders to certolizumab pegol at week 26 was 38%.<sup>8</sup> A review of 16 studies for CD reported LOR to IFX at 13.1% per patient-year and LOR of 46% to ADA by 54 weeks.<sup>15</sup> In fistulizing CD, LOR at week 54 defined as recurrence of actively draining fistulas was 64%.<sup>21</sup>

ACT-1 and 2 trials evaluated LOR in UC. Clinical non remission was 66% at week 54 in ACT-1 and 74.4% at week 30 in ACT-2. Overall, there is limited data for UC.<sup>13</sup>

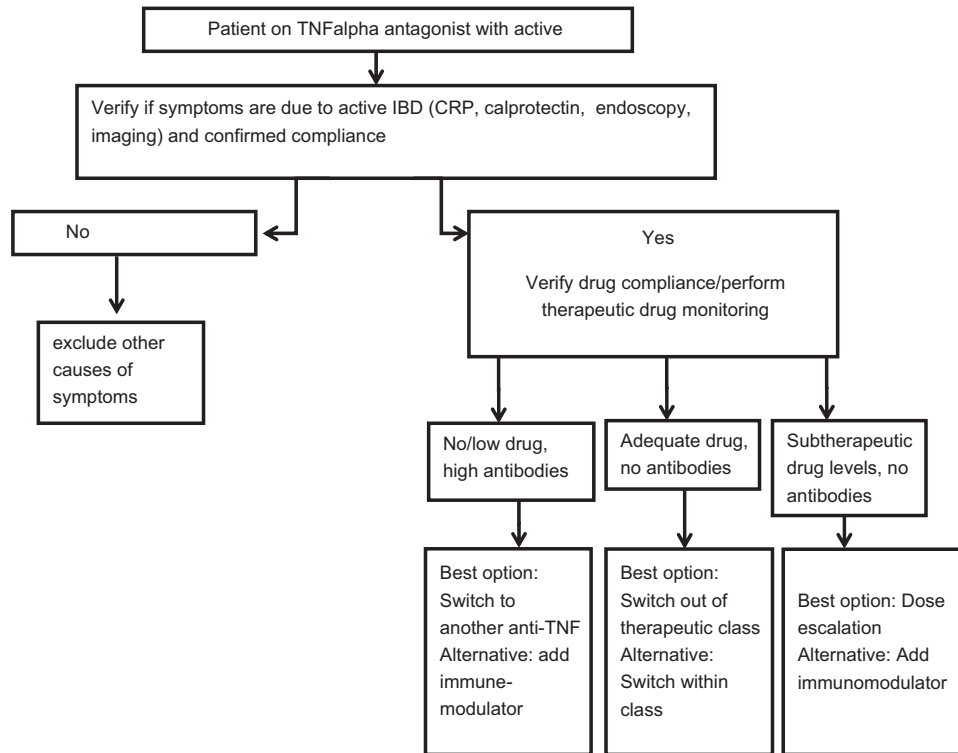
**Assessment and management.** In patients using TNFα antagonists who experience symptoms consistent with clinical relapse, the first step is to determine whether the symptoms are due to active inflammation. Symptoms from other disorders can mimic those due to inflammation, including irritable bowel syndrome, fibrostenotic strictures, cancer, dietary, amyloidosis, bacterial overgrowth, bile salt diarrhea, infections, and ischemia.<sup>8</sup> Clinical evaluation of active inflammation is unreliable and an objective assessment should be performed using endoscopy, as well as serum and stool biomarkers<sup>22</sup> (Figure 1). If "relapse" is felt to be due to active inflammation, this confirms LOR, and pharmacokinetic and immunogenic assessment with drug levels and antibodies should be performed. Treatment of secondary IFX failure using therapeutic drug monitoring has been demonstrated to reduce treatment costs compared with routine IFX dose escalation.<sup>23</sup>

A common mechanism implicated in the development of LOR is immunogenicity due to the formation of antibodies against the TNFα antagonists. These antibodies interfere with the binding of TNF to its receptor or hasten the clearance of drug through the reticuloendothelial system.<sup>24</sup> Formation of antibodies against TNFα antagonists correlates with lower serum drug levels and less duration of response. The percentage of positive antibodies varies widely between studies, and was reported to be between 0.04 and 35% in studies examining antibodies to ADA in CD patients.<sup>25–28</sup> Reasons for antibody formation should be explored. Use of episodic TNFα antagonists compared with regular dosing may lead to antibody formation, and subsequently cause LOR. Up to 15–29% of patients treated with ADA or IFX are not compliant with infusions or injections. LOR can also be related to individual differences in bioavailability and pharmacokinetics leading to immunogenicity or other factors that increase drug clearance.<sup>29–30</sup>

Several therapeutic drug monitoring algorithms and scenarios have been proposed for managing LOR.<sup>31–37</sup> In Figure 1, we propose an algorithm based on therapeutic drug monitoring, and here below, we provide the rationale for using TDM for LOR management.

## Potential outcomes of therapeutic drug monitoring

**Anti-TNF antibodies present.** The presence of antibodies suggests that immunogenicity against the TNFα antagonist has developed and places the patient at risk for decreased clinical response and possible infusion reactions.<sup>38</sup> In a retrospective study examining patients with LOR to IFX with detectable antibodies, change to another TNFα antagonist agent was associated with a complete or partial response in 92% of patients, whereas increasing the dose led to only a 17% response ( $P < 0.004$ ).<sup>31</sup> Patients with high titers of anti-drug antibodies (levels of antibodies against ADA > 4 µg/ml or against IFX > 9 µg/ml) do not respond well to dose escalation of the same drug, but switching within therapeutic class to another anti-TNF agent may restore clinical response ( $P < 0.03$ ).<sup>25</sup>



**Figure 1** Management of patients with LOR. CRP, C reactive protein; LOR, loss of response.

In the scenario of low level of antibodies, dose intensification is also an option. Yanai *et al.*<sup>32</sup> have shown that patients with no/low-titer ADA responded significantly better to dose intensification compared with the anti-TNF switch as dose intensification significantly increased anti-TNF drug levels in patients with no/low ADA titers.

Another approach to LOR in patients with antibodies is to add an immunomodulator. Concomitant use of immunosuppressive agents such as thiopurine or methotrexate reduce the risk of antibody formation against TNF $\alpha$  antagonist agents, and concomitant use has been associated with improved clinical outcomes.<sup>39–41</sup> When a patient loses response to TNF $\alpha$  antagonist monotherapy, consideration can be given to addition of an immunomodulator. Two small case series have demonstrated reductions in antibody levels and increases in drug trough levels that led to restored clinical response.<sup>42–43</sup> It has recently been shown that concentrations of 6-thioguanine nucleotide correlate with trough levels of infliximab in patients with inflammatory bowel disease on combination therapy. A level of 6-thioguanine of 125 pmol/8  $\times 10^8$  RBCs or greater has been described to be adequate for assuring therapeutic levels of infliximab.<sup>44</sup>

*No anti-TNF antibodies present with adequate drug level.* Patients with adequate trough levels at the time of LOR are unlikely to respond to dose intensification or change to another TNF $\alpha$  antagonist, and may benefit more from a switch to an agent out of therapeutic class.<sup>33</sup> This is, however, complicated by a lack of prospective evidence to support the trough levels to target for the individual patient. Observational studies have demonstrated that IFX levels >3 mcg/ml and ADA levels >4.5 mcg/ml are

associated with an increased likelihood of maintaining response.<sup>32,45</sup>

*No anti-TNF antibodies present with sub-therapeutic drug level.* Patients with LOR and sub-therapeutic IFX concentrations without antibodies often benefit from dose escalation. In one study, increasing the IFX dose in patients with low levels was associated with a clinical response in 86%.<sup>31,33</sup> Either an increase in dose or dosing frequency are reasonable strategies for dose escalation, but increasing the dose may lead to less costs and less patient inconvenience.<sup>23</sup> Consideration can be given to the addition of an immunomodulators for a patient with sub-therapeutic drug levels also.

**Prevention.** Between 20–40% of patients included in clinical trials for all TNF $\alpha$  antagonists do not show clinical response to therapy.<sup>3,13,20,39</sup> Reasons for non-response include symptoms other than active inflammation, non-TNF $\alpha$ -mediated inflammation, or early immunogenicity. Use of concomitant immunomodulators with TNF $\alpha$  antagonists can improve treatment outcomes. Several studies demonstrated that the use of concomitant immunosuppressive therapy along with IFX results in higher trough levels and reduced anti-drug antibody formation, contributing to clinical efficacy.<sup>46,47</sup> It is unclear if this is the case with all TNF $\alpha$  antagonists, however, nor is it clear if patients with prior thiopurine exposure attain the same benefit. A meta-analysis in CD patients treated with ADA who had prior thiopurine exposure did not find a higher rate of clinical remission at 6 months in those receiving concomitant immunomodulator therapy compared with monotherapy with ADA.<sup>48</sup>

Use of therapeutic drug monitoring may be another way to optimize treatment and prevent LOR.<sup>49</sup> The TAXIT study found that early dose optimizing of IFX to target trough levels between 4 and 7 mcg/ml was associated with superior disease control without an increase in costs.<sup>50</sup> Incorporation of therapeutic drug monitoring early in the management may help lower the risk of antibody development.

Another strategy to reduce formation of antibodies is corticosteroid pre-treatment before receiving TNF $\alpha$  antagonists. One study demonstrated hydrocortisone pre-treatment before the administration of IFX led to significantly less patients who developed antibodies (26%) compared with those who did not receive corticosteroid pre-treatment (42%).<sup>51</sup>

Finally, regularly scheduled TNF $\alpha$  antagonist administration is superior to episodic use to prevent LOR. The incidence of antibodies has been shown to be as high as 37–61% in patients receiving episodic infliximab. Scheduled treatment is associated with less immunogenicity, with an incidence of 6–16%, and consequently results in decreased risk of LOR.<sup>3,41,52–56</sup>

## CONCLUSION

Managing PNR and LOR is a frequent challenge for clinicians who manage patients with inflammatory bowel diseases. Immunogenicity is the most common cause of LOR, as formation of antibodies can neutralize the drug or hasten its clearance. The current literature supports assessment of drug levels and antibodies, i.e., therapeutic drug monitoring, to guide management decisions, such as dose intensification, addition of immunomodulator, or switching out of class. More than two-thirds of patients can be effectively managed this way. Determining whether dose intensification, addition of immunomodulators, or switching therapies is most appropriate should be based on results of therapeutic drug monitoring. Measures can be taken to prevent LOR including use of concomitant immunomodulators, corticosteroid pre-treatment, early dose optimization, and regularly scheduled use of the TNF $\alpha$  antagonist. Prospective clinical trials are needed to determine whether all of these interventions together can substantially lead to a decrease in LOR and make development of anti-drug antibodies a relic of the past.

## CONFLICT OF INTEREST

**Guarantor of the article:** Jean-Frederic Colombel, MD.

**Specific author contributions:** Giulia Roda and Bindia Jharap have been involved in planning, conducting the study, collecting and interpreting data, and drafting the manuscript. Neeraj Narula has been involved in interpreting the data and revised the manuscript. Jean-Frederic Colombel designed the study and has been involved in supervising the review.

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## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Immunogenicity is the most common cause of loss of response (LOR).
- ✓ Assessment of drug levels and antibodies should be used to guide management decisions (dose intensification, addition of immunomodulator, or switch out of class).

### WHAT IS NEW HERE

- ✓ Prevention of LOR can be achieved using concomitant immunomodulators, corticosteroid pre-treatment, early dose optimization, and regularly scheduled use of the tumor necrosis factor- $\alpha$  antagonist.

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