REVIEW ARTICLE

DOSE ESCALATION OR SWAP FOR LOSS OF RESPONSE TO BIOLOGICAL THERAPY IN IBD?

Benítez Cantero JM

DIGESTIVE SYSTEM CLINICAL MANAGEMENT UNIT. REINA SOFÍA UNIVERSITY HOSPITAL, IMIBIC, CIBEREHD. CÓRDOBA. SPAIN.

Abstract

Biological therapies have transformed the management of inflammatory bowel disease (IBD). Nevertheless, a substantial proportion of patients experience primary non-response or secondary loss of response during treatment. This phenomenon represents a major therapeutic challenge and often requires treatment optimization strategies. Among these, dose escalation increasing dosage or interval shortening, and switching to a drug with a different mechanism of action (swap) are the most frequently considered approaches. The decision between these strategies depends on several factors, including the type of therapeutic failure, drug serum concentrations, anti-drug antibodies and the patient's clinical context. Therapeutic drug monitoring has emerged as a key tool to identify mechanisms of treatment failure and guide clinical decision-making. This article reviews the magnitude of loss of response to biological therapies in IBD, especially to anti-TNF agents, describes the underlying mechanisms and summarizes the available evidence to guide the choice between dose escalation and switching therapeutic targets.

Keywords: escalation, swap, loss of response, biological therapy, anti-TNF, inflammatory bowel disease.

Introduction

Inflammatory bowel disease (IBD) encompasses a group of chronic inflammatory disorders of the gastrointestinal tract, primarily Crohn's disease (CD) and ulcerative colitis (UC). Both conditions are characterized by a fluctuating clinical course,

José Manuel Benítez Cantero
Reina Sofía University Hospital. Córdoba.
jmbeni83@hotmail.com

Benítez Cantero JM. Dose escalation or swap for loss of response to biological therapy in IBD? RAPD 2026;49(4):117-124. DOI: 10.37352/2026494.1

with periods of activity and remission, and by a significant impact on the quality of life of patients who suffer from them.

Over the past two decades, the treatment of IBD has undergone profound changes thanks to the development of biologic therapies and, more recently, small molecules targeting various inflammatory pathways. These advanced therapies have demonstrated significant efficacy in inducing and maintaining clinical remission, achieving mucosal healing, and reducing the need for surgery in patients with moderate-to-severe disease. However, despite these therapeutic advances, a significant proportion of patients do not respond to treatment from the outset or lose their response over time.

Primary nonresponse or primary failure is defined as the absence of clinical improvement after completing the induction phase of treatment, typically assessed between weeks 12 and 14. On the other hand, *secondary loss of response or secondary failure* is defined as the recurrence of inflammatory activity during the maintenance phase in patients who had initially responded to the drug during induction.

When we encounter a loss of response to treatment (primary or secondary), we must first confirm that the lack of improvement or clinical worsening is due to inflammatory activity in IBD. To do so, we must use surrogate markers of inflammation (fecal calprotectin, C-reactive protein) and/or tests that objectively assess this activity (ileocolonoscopy, intestinal ultrasound, enteric MRI, etc.) in clinical practice. It is essential to rule out other causes responsible for clinical worsening, such as inflammatory mechanisms unrelated to IBD (infection, ischemic colitis, vasculitis, diverticulitis, etc.) or non-inflammatory mechanisms (irritable bowel syndrome, fibrotic strictures, lactose intolerance, cancer, bile salt malabsorption, bacterial overgrowth, etc.).

This loss of response poses a significant challenge for the clinician, as it requires a reevaluation of the treatment regimen. Available strategies include intensifying treatment by increasing the dose or shortening the interval between doses of the same drug, switching to another drug within the same therapeutic class (switch), or swapping to an agent with a different mechanism of action (swap). Choosing among these alternatives requires understanding the mechanisms responsible for treatment failure and carefully assessing each patient's clinical context.

Magnitude of the problem of loss of response

Loss of response to biologic therapies is a common phenomenon in clinical practice. Several studies have evaluated treatment persistence and the long-term efficacy of anti-TNF agents in patients with IBD. In a Belgian cohort of patients treated with infliximab, Schnitzler *et al.* observed that approximately one-third of patients experienced loss of response during follow-up[1]. Similar results were reported by Karmiris et al., who analyzed the course of patients treated with adalimumab and found comparable rates of loss of efficacy[2].

Long-term studies have confirmed that this phenomenon is not uncommon. In an international multicenter analysis involving more than 1,000 patients treated with infliximab, Juillerat et al. demonstrated that a significant proportion of patients required treatment intensification or a change in medication during long-term follow-up[3]. Overall, the incidence of loss of response to anti-TNF agents is estimated to range from 15% to 20% per patient-year[4].

Another interesting aspect is understanding when loss of response occurs over time. This risk of loss of response appears to be higher during the first year of treatment. Schultheiss et al. observed that the incidence of loss of response was higher during the first year (17.2% patient-years) and decreased significantly over time, to 4.8% after four years. The first year of exposure to anti-TNF was also associated with a significantly higher risk of treatment intensification or discontinuation; these events decreased as the duration of treatment increased. In fact, patients in this cohort who maintained a response for ≥2 years had a low risk of subsequent loss of response [5]. This finding suggests that mechanisms of immunogenicity and pharmacokinetic variability may play an important role in the early phases of treatment. Predictive factors associated with loss of response to anti-TNF include UC (vs. CD) and the stenotic and fistulizing phenotype of CD.

Although non-anti-TNF biologics may also experience loss of response, some registries suggest that their treatment persistence may be higher. In an Australian database that included more than 1,000 advanced treatment regimens, Ko *et al.* observed differences in persistence among different classes of biologic treatments, with significantly lower persistence for anti-TNF drugs[6]. However, the available evidence is still limited, and further comparative studies are needed.

Mechanisms of loss of response

Loss of response to biologic treatments can be explained by various pharmacological and pathophysiological mechanisms. Traditionally, three main types of treatment failure are distinguished: pharmacodynamic, pharmacokinetic, and immunogenic.

DOI: 10.37352/2026494.1

Pharmacodynamic failure occurs when the patient has adequate serum levels of the drug, but the disease remains active. In this context, blocking the specific inflammatory pathway is not sufficient to control disease activity. This phenomenon reflects the complexity of the immune networks involved in IBD, where multiple cytokines and signaling pathways contribute to the inflammatory process.

Pharmacokinetic failure is characterized by subtherapeutic serum levels of the drug in the absence of anti-drug antibodies. This phenomenon may be due to multiple factors, including increased drug clearance, an increased volume of distribution, or intestinal losses associated with severe inflammation. In these cases, optimizing treatment by increasing the dose or shortening the dosing interval can restore adequate therapeutic concentrations.

Finally, ***immunogenic failure*** occurs when the patient's immune system generates antibodies directed against the biologic drug. These antibodies can neutralize its effect or accelerate its elimination, reducing its clinical efficacy. Immunogenicity has been reported most frequently with anti-TNF therapies, especially when used as monotherapy.

Although pharmacokinetic failure was traditionally considered the most common (51%), followed by pharmacodynamic failure (30%) and immunogenic failure (19%)[7]; updated data from the Leuven group estimate pharmacodynamic failure to be the primary mechanism of loss of response (73%), followed by immunogenic failure (16%) and pharmacokinetic failure (11%)[8]. Understanding these mechanisms is essential for selecting the most appropriate therapeutic strategy. In this context, therapeutic drug monitoring has taken on a central role in the management of IBD, serving as a tool that allows for a better understanding of the causes of loss of response and improves clinical decision-making.

Therapeutic strategies for loss of response: clinical scenarios.

Once loss of response has been confirmed and other causes of clinical worsening have been ruled out, the physician must choose among different therapeutic strategies. The two main options are treatment intensification or a change in mechanism of action.

Primary failure

The key to reducing primary failure with anti-TNF therapy is optimizing the drug during the induction phase. The prospective study PANTS evaluated the relationship between serum levels of infliximab and adalimumab during the induction phase and long-term clinical outcomes. The authors observed that patients with higher levels after induction (measured at week 14) were more likely to maintain clinical remission throughout follow-up, at week 54[9]. Therefore, measuring post-induction levels could help identify subgroups of patients who would benefit from early drug intensification.

Based on these data, target concentrations have been proposed for different drugs. Although there are no clearly defined therapeutic thresholds, during the induction phase it is recommended to achieve levels of approximately 7–10 µg/ml for infliximab and levels above 10–12 µg/ml for adalimumab[10,11]. These concentrations have been associated with better clinical outcomes, higher long-term remission rates, and a greater likelihood of mucosal healing.

Another important aspect to consider during this initial or induction phase—and one that is closely linked to the previous point—is immunogenicity. One important concept is that anti-drug antibodies develop during anti-TNF induction therapy; these are not detected by standard drug-sensitive assays but are detected by drug-tolerant assays capable of identifying antibodies in the presence of the drug. In this context, Tournier *et al*[12] reported on a cohort of 108 patients with ulcerative colitis (UC) and Crohn's disease (CD) treated with adalimumab and infliximab, in whom anti-drug antibodies were detected by week 2. They observed that patients who developed anti-drug antibodies early (week 2) had a less favorable outcome, with higher rates of treatment discontinuation due to loss of response at 6 months compared to patients who did not develop antibodies; this was true for both those treated with infliximab and those treated with adalimumab. Therefore, the ability to monitor drugs using drug-tolerance tests would allow us to detect antibodies early and identify subgroups of patients at risk for drug loss in the following months.

The reason for discontinuing the first anti-TNF drug determines the success of the second anti-TNF drug. And among the various causes, primary failure is associated with the worst remission rates achieved with the second anti-TNF agent—around 34% compared to 41% if the reason for discontinuing the first anti-TNF agent is secondary failure, or 78% if the first agent was discontinued due to intolerance[13].

Furthermore, primary failure not only has a negative impact on the benefit of the second anti-TNF agent but also represents the situation in which we will achieve the least benefit from other non-anti-TNF biologics in second-line or subsequent treatments, as it results in a 25% lower response

DOI: 10.37352/2026494.1

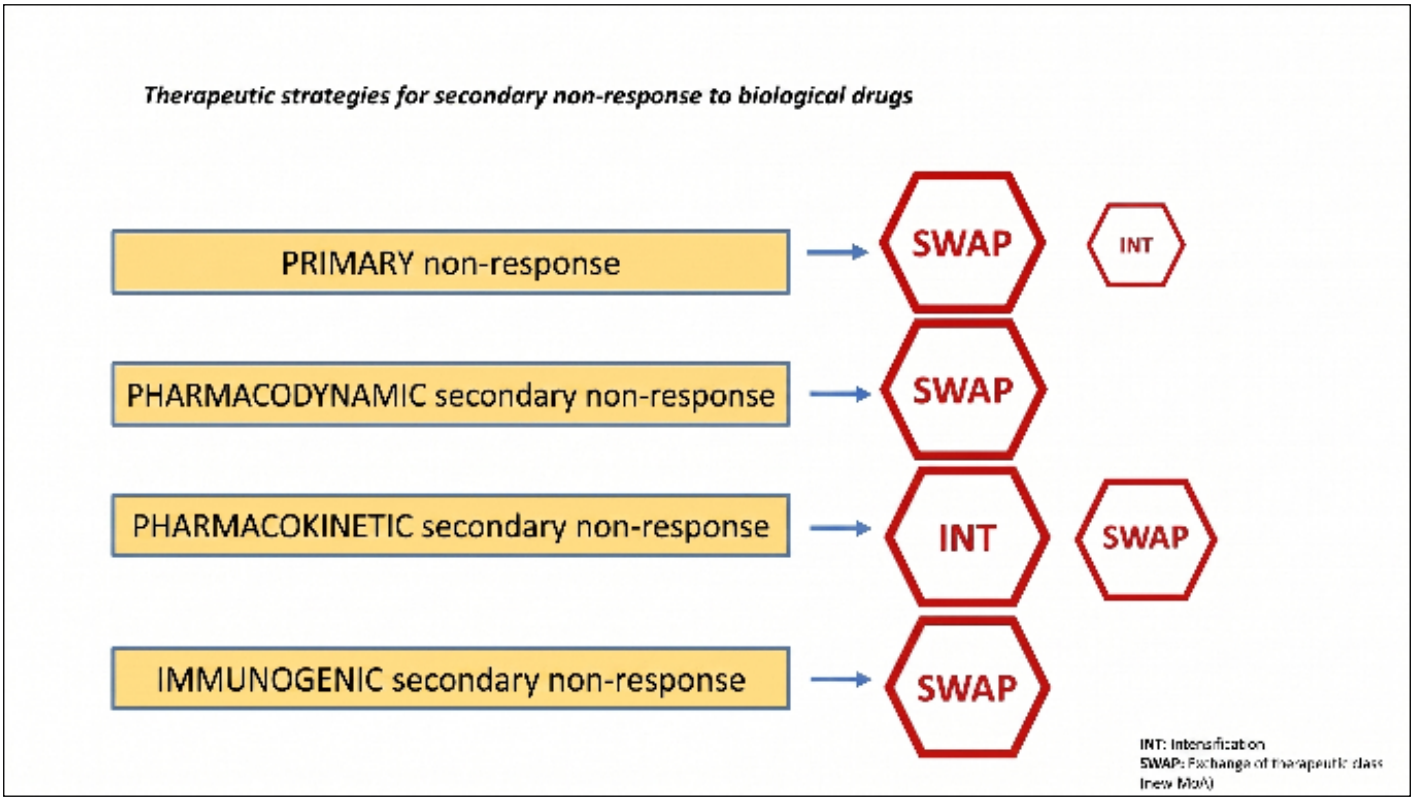

Figure 1. ***Therapeutic strategies in the event of loss of response to biologic drugs.***

rate in second-line therapy compared to secondary failure or intolerance[14]. It would seem reasonable to consider, for this second biologic indicated following primary failure of the first anti-TNF agent, higher induction doses, combination with an immunosuppressant, and early proactive optimization.

Therefore, in the event of primary failure, the swap strategy would, a priori, provide the greatest benefit, while evaluating the possibility of intensification in certain situations—especially if we have the capacity to monitor post-induction levels with the ability to detect anti-drug antibodies.

Secondary pharmacodynamic failure (therapeutic levels)

In this situation, where the patient has adequate therapeutic levels but inflammatory activity persists, intensification is usually ineffective. In such cases, switching to a drug with a different mechanism of action (swap) may yield better results. Yanai et al. demonstrated that patients with adequate therapeutic levels of anti-TNF were significantly less likely to regain response through dose escalation (30%) compared to those who switched to a drug with a different mechanism of action (68%)[15].

Roblin *et al.*[16] compared these two strategies (intensification vs. swap) in patients who had lost response to adalimumab while maintaining therapeutic levels. At 24 months, treatment discontinuation was 14.8% in the swap group compared with 59.6% in the adalimumab intensification group. Furthermore, the time to treatment discontinuation was significantly longer following the drug switch (>24 months vs. 13.3 months).

Therefore, in patients with IBD who experience a secondary loss of response of pharmacodynamic origin, switching to a biologic with a different mechanism of action is more effective than optimizing the dose of the same drug.

Secondary pharmacokinetic failure (low levels, Acs -)

Yanai *et al.* also evaluated this clinical scenario by comparing two strategies—intensification of the same anti-TNF agent versus switching to another anti-TNF agent—in a cohort of 247 patients. The percentage of patients who regained a response was significantly higher in the intensification group compared to the switch group (38% vs. 0%). Therefore, this intensification strategy is particularly effective in patients with low serum drug levels and no anti-drug antibodies, as it

DOI: 10.37352/2026494.1

can restore adequate therapeutic concentrations and regain clinical response.

The next question regarding this optimization strategy is which intensification approach is more beneficial: increasing the dose or shortening the dosing interval. In general, combining both approaches—increasing the dose and shortening the dosing interval—is best. However, when analyzing both strategies independently, it appears that doubling the dose yields greater benefits than shortening the interval[17]. This approach of doubling the dose may seem counterintuitive at first glance, as it results in higher peak levels but lower trough levels. However, it is believed that the formation of anti-drug antibodies is suppressed when anti-TNF concentrations reach a certain threshold, at which point a state of tolerance is achieved; this threshold would be reached more easily with higher concentrations, which can be achieved by doubling the dose.

The drug levels to be achieved following dose escalation are not clearly defined and will depend on the desired treatment goals. More ambitious goals, such as mucosal healing, will require greater drug exposure and, therefore, higher concentrations than a less demanding goal such as clinical remission. Special situations, such as perianal disease, require even higher drug levels to achieve remission. In general, we could consider infliximab levels >8 µg/ml and adalimumab levels >12 µg/ml.

Another issue of great interest is determining how long to continue the intensification strategy. Although intensification is an effective strategy in this context of secondary loss of response, a subgroup of patients may not respond to intensification (tertiary nonresponse) or may not maintain a durable response with intensification (tertiary loss of response). A systematic review and meta-analysis[18] evaluates this response to anti-TNF intensification. A response to intensification (tertiary response) was more likely than a non-response within the first 6 months (RR 2.58; 95% CI 1.76–3.79). However, beyond 6 months, the probability of sustained response versus loss of response was similar (RR 1.10; 95% CI 0.75–1.61).

Non-response to intensification (tertiary non-response) occurred in up to 45% of patients within the first 6 months after intensification, while loss of response to intensification (tertiary loss of response) beyond 6 months was observed in up to 64% of patients. Given these results, it seems reasonable not to unnecessarily prolong the intensification strategy, to conduct an early evaluation of it—especially at 6 months—and to consider changing the strategy if no response is achieved.

Secondary immunogenic failure (low levels, Acs +)

The development of anti-drug antibodies represents another common scenario. The presence or formation of antibodies occurs primarily during the first 12 months, after which the curve levels off. Most non-transient antibodies are produced during this first year, and these are the ones associated with loss of response. Hence the importance of determining drug levels after induction, even during clinical remission; in this scenario, subtherapeutic levels could be associated with an increased risk of antibody formation and heightened inflammatory activity.

When these anti-drug antibodies are detected at high levels, the likelihood of regaining a response through dose escalation is low; therefore, switching to another biologic treatment (swap) is generally recommended.

Often, the pharmacokinetic profile of the first anti-TNF agent is replicated with the second anti-TNF agent, and antibodies against one anti-TNF agent predispose patients to the development of antibodies against the second anti-TNF agent. Therefore, the strategy of switching to a second anti-TNF agent following immunogenic failure with the first anti-TNF agent would not be more beneficial than switching to a drug with a different mechanism of action (swap).

When should a second anti-tnf be used after failure of the first anti-tnf?

In certain patients, the use of a second anti-TNF may be considered after failure of the first. However, in general, the benefit of switching to a second anti-TNF is less than that of switching to a drug with a different mechanism of action. Several studies have shown that the efficacy of a second anti-TNF agent depends largely on the cause of failure of the first. Gisbert et al. observed that patients with primary failure of the first anti-TNF agent had significantly lower remission rates after switching to a second anti-TNF agent[13].

Furthermore, the presence of antibodies against an anti-TNF drug may increase the risk of developing antibodies against a second drug in the same class. In this context, some authors recommend the concomitant use of immunosuppressants with this second anti-TNF drug to reduce immunogenicity and improve treatment adherence.

Therefore, this strategy may be effective when discontinuation of the first drug is due to adverse effects. In any case, it will depend on the therapeutic indication and

DOI: 10.37352/2026494.1

the likelihood of response to other treatment options, as is the case with specific conditions such as perianal disease, extraintestinal manifestations, etc.

Therapeutic strategies for loss of response to non-anti-tnf biologics

The introduction of biologics with mechanisms of action different from those of anti-TNF agents has significantly expanded the therapeutic options available to patients with IBD. Notable among these are ustekinumab, vedolizumab, drugs targeting the interleukin-23 pathway (risankizumab, mirikizumab, and guselkumab), and JAK inhibitors.

Although the evidence regarding the management of loss of response to these drugs is substantially less than that available for anti-TNF agents, we do have data on treatment optimization, particularly for ustekinumab and vedolizumab. Although the utility of monitoring drug levels appears to be lower compared to anti-TNF agents, most studies reiterate the concept that higher drug exposure, higher serum concentrations of the drug, and a greater likelihood of achieving therapeutic outcomes—both clinical and endoscopic—go hand in hand.

Ustekinumab has demonstrated efficacy in both UC and CD. However, some patients also experience loss of response during treatment. This meta-analysis of 14 studies[19] evaluated loss of response to ustekinumab. In UC, the annual risk of loss of response to this drug was 21% patient-years, with approximately 25% of patients requiring a dose escalation during follow-up. Treatment intensification allowed for the restoration of clinical response in 58% of patients who had experienced a secondary loss of response. In ulcerative colitis, data are limited, although approximately 35% of patients required dose adjustment in the only available study.

Among the strategies for optimizing ustekinumab reported in the literature that allow for the restoration of response in a proportion of patients are intensification (shortening the dosing interval to every 4 or 6 weeks), intravenous maintenance every 4 weeks, and reinduction. However, two recent trials question the utility of optimizing ustekinumab in the event of loss of response. The POWER study[20] is a randomized clinical trial that evaluated intravenous (IV) reinduction of ustekinumab in patients who experienced a secondary loss of response during maintenance with the subcutaneous formulation every 8 weeks; patients were randomized to either IV reinduction or continued subcutaneous maintenance. Outcomes were assessed at 16 weeks, and no significant differences in clinical response were found between the two treatment arms. However, better endoscopic and biological outcomes were achieved with intravenous reinduction.

The REScUE study[21] is a double-blind, randomized, placebo-controlled trial that evaluated, in patients with Crohn's disease who had lost response to ustekinumab, whether intensifying treatment every 4 weeks provided additional benefit compared with continuing the drug every 8 weeks. At week 48, the rates of corticosteroid-free clinical remission, biological remission, and endoscopic response and remission showed no significant differences between the two arms.

These results call for a reevaluation of the utility of optimizing the ustekinumab dose in routine clinical practice in favor of more effective treatment strategies.

In cases of loss of response to vedolizumab, intensifying treatment by shortening the dosing interval or using weekly subcutaneous formulations may be effective. Recent results are available from the PRIVEDO study[22], a prospective study that evaluated two maintenance strategies in patients with a partial response to intravenous (IV) induction with vedolizumab: subcutaneous vedolizumab 108 mg every 2 weeks versus intensification of IV vedolizumab every 4 weeks. Steroid-free clinical remission with normalization of fecal calprotectin was significantly higher with subcutaneous maintenance at week 26 (57% vs. 25%, $p < 0.001$) and week 52 (48% vs. 25%, $p = 0.016$).

The OPTI-VEDO study[23] is a multicenter study that evaluates the intensification of subcutaneous vedolizumab to a weekly regimen following a secondary loss of response to subcutaneous vedolizumab administered every 2 weeks. With this optimization strategy, a corticosteroid-free clinical response was achieved at 3 months in 35% of patients with ulcerative colitis (UC) and 43% of those with Crohn's disease (CD), with secondary loss of response being the primary predictor of response to intensification (vs. primary nonresponse, OR 5.8).

Although clinical experience is still limited regarding optimization strategies for drugs such as risankizumab or JAK inhibitors like upadacitinib, some studies suggest that reinduction or intensification of treatment may restore the response in a considerable percentage of patients.

In the case of mirikizumab, the prescribing information includes optimization strategies such as extended induction with three additional intravenous doses starting at week 12 for patients with a partial response to induction, or reinduction with three intravenous doses for patients who lose response during maintenance therapy.

DOI: 10.37352/2026494.1

Recently, a new selective IL-23 inhibitor, guselkumab, has been approved; it has demonstrated efficacy in patients with moderate-to-severe active CD and UC. Although long-term data on loss of response and the need for dose escalation are not yet available, the prescribing information outlines a strategy for optimizing this medication with a maintenance dose of 200 mg every 4 weeks starting at week 12 for patients who, in the clinician's judgment, have not achieved an adequate therapeutic benefit following induction therapy.

Conclusions

Loss of response to biologic therapies remains one of the main challenges in the management of inflammatory bowel disease. Although therapeutic advances have considerably expanded the available options, treatment optimization remains a common strategy for maximizing clinical benefits. Therapeutic drug monitoring plays a key role, especially with anti-TNF agents, in identifying the mechanisms of treatment failure and in selecting the most appropriate strategy for each patient. In general, switching to a drug with a different mechanism of action (swap) is the most favorable strategy in most situations, particularly in cases of primary failure, secondary pharmacodynamic failure, or immunogenic failure. Treatment intensification is particularly useful in cases of pharmacokinetic failure.

As more evidence becomes available on new biologics and small molecules, it will be possible to define more precisely the optimal strategies for managing loss of response and improving long-term outcomes in patients treated with these drugs.

Bibliography

1. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease. Gut. 2009;58(4):492-500.

2. Karmiris K, Paintaud G, Noman M, Magro F, Ferrante M, D'Haens G, et al. Long-term outcome of adalimumab therapy in Crohn's disease. Gastroenterology. 2009;137(5):1628-1640.

3. Juillerat P, Wasan SK, Fowler SA, Santos MC, Coukos JA, Aumais G, et al. Efficacy and safety of infliximab in Crohn's disease: a 12-year single-center experience. Inflamm Bowel Dis. 2015;21(8):1833-1841.

4. Qiu Y, Chen BL, Mao R, Zhang SH, He Y, Zeng ZR, et al. Systematic review with meta-analysis: loss of response and requirement of anti-TNF alpha dose intensification in Crohn's disease. J Gastroenterol. 2017;52(5):535-554.

5. Schultheiss J, de Jong M, van Dop W, de Boer N, van Bodegraven A, Dijkstra G, et al. Predictors of loss of response to anti-TNF therapy in patients with inflammatory bowel disease: a systematic review and meta-analysis. Aliment Pharmacol Ther. 2021;54(5):667-677.

6. Ko Y, Lin B, Yiu TH, Vande Casteele N, Leong RW. Persistence of advanced therapies in inflammatory bowel disease: a systematic review and meta-analysis. Aliment Pharmacol Ther. 2021;54(10):1244-1256.

7. Ding NS, Hart A, De Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease – algorithm for practical management. Aliment Pharmacol Ther. 2016;43(1):30-51.

8. Alsoud D, Verstockt B, Vermeire S. Letter: immunogenicity is not the root cause for loss of response to anti-TNF agents in patients with IBD in TDM era. Aliment Pharmacol Ther. 2022;55(8):1052-1053.

9. Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, et al. Predictors of anti-TNF treatment failure in Crohn's disease (PANTS): a prospective, multicentre, observational cohort study. Lancet Gastroenterol Hepatol. 2019;4(5):341-353. (Nota: El estudio PANTS fue publicado en Lancet Gastroenterol Hepatol).

10. Cheifetz AS, Abreu MT, Afif W, Cross RK, Dubinsky MC, Loftus EV Jr, et al. A comprehensive guide to therapeutic drug monitoring in inflammatory bowel disease. Am J Gastroenterol. 2021;116(10):2014-2025.

11. Sparrow MP, Papamichael K, Ward MG, Riviere P, Laharie D, Paul S, et al. Therapeutic drug monitoring of biologics in IBD: a practical guide. J Crohns Colitis. 2020;14(8):1121-1132.

12. Tournier Q, Paul S, Williet N, Charlois AL, Berger AE, Roblin X. Early detection of anti-drug antibodies during initiation of anti-tumour necrosis factor therapy predicts treatment discontinuation in inflammatory bowel disease. Aliment Pharmacol Ther. 2021;53(11):1190-1200.

DOI: 10.37352/2026494.1

13. Gisbert JP, Chaparro M. Systematic review: the efficacy of a second anti-TNF after failure of a first anti-TNF in inflammatory bowel disease. Aliment Pharmacol Ther. 2015;41(7):613-623.

14. Singh S, George J, Boland BS, Vande Casteele N, Sandborn WJ. Primary non-response to tumor necrosis factor antagonists is associated with inferior response to second-line biologics in patients with inflammatory bowel diseases: a systematic review and meta-analysis. J Crohns Colitis. 2018;12(6):635-643.

15. Yanai H, Lichtenstein L, Assa A, Weiss B, Gryboski M, Lev-Tzion R, et al. Levels of drug and antidrug antibodies are associated with clinical response to anti-tumor necrosis factor therapy in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2015;13(3):522-530.

16. Roblin X, Duru G, Williet N, Boschetti G, Nancey S, Paul S. Swapping versus dose optimization in patients losing response to adalimumab with adequate drug levels. Inflamm Bowel Dis. 2022;28(Suppl 1):S155.

17. Dreesen E, Van Stappen T, Ballet V, Peeters M, Compernolle G, Tops S, et al. Anti-infliximab antibody concentrations can guide treatment intensification in patients with Crohn's disease who lose clinical response. Aliment Pharmacol Ther. 2018;47(3):346-355.

18. Srinivasan A, Haifer C, Thin L, Connor S, Zhang L, Leong RW, et al. Systematic review and meta-analysis: evaluating response to empiric anti-TNF dose intensification for secondary loss of response in Crohn's disease. Ther Adv Gastroenterol. 2022;15:17562848221102582.

19. Yang H, Zhou C, Wu Q, Zhang S, Hu X, Wang Z. Systematic review with meta-analysis: loss of response and requirement of ustekinumab dose escalation in inflammatory bowel diseases. Aliment Pharmacol Ther. 2022;55(7):764-777.

20. Schreiber S, Lee SD, van der Woude CJ, Marín-Jiménez I, Wolf DC, Schnoy E, et al. Ustekinumab intravenous reinduction after secondary loss of response in patients with Crohn's disease. Inflamm Bowel Dis. 2025;31(12):3286-3297.

21. Bossuyt P, Rahier JF, Baert FJ, Louis E, Macken E, Lobaton T, et al. Low remission recapture after ustekinumab dose optimization in Crohn's disease: results of the randomized placebo-controlled double-blind REScUE study [resumen]. Presentado en: Digestive Disease Week (DDW 2025); mayo 2025. Resumen 627.

22. Macaluso FS, Fries W, Viola A, Cappello M, Melatti P, Mocciaro F, et al.; Sicilian Network for Inflammatory Bowel Disease. Switching to subcutaneous administration may offer more profound remission compared to intensified intravenous therapy in patients with inflammatory bowel disease and partial response following induction with intravenous vedolizumab: the PRIVEDO study. J Crohns Colitis. 2025;19(10):jjaf175.

23. Wils P, Altwegg R, Buisson A, Vuitton L, Nancey S, Richard N, et al.;Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID). Subcutaneous vedolizumab dose intensification in inflammatory bowel disease patients: the OPTI-VEDO multicenter study from the GETAID. J Crohns Colitis. 2025 Sep 28;19(9):jjaf166..

DOI: 10.37352/2026494.1