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REVIEW

Management of inflammatory bowel disease in poor responders to infliximab

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Abstract: Infliximab (IFX) is an effective treatment for inducing and maintaining response in Crohn's disease and ulcerative colitis patients. Some patients present lack of response or loss of response to IFX during maintenance therapy. Empirical management with combination therapy with an immunomodulator, IFX dose escalation, or switching IFX for another antitumor necrosis factor-α drug, mainly adalimumab, is common in clinical practice. Selecting the best choice with the help of serum drug concentrations and trough IFX antibody concentrations could be a very interesting approach. In addition to surgery, a broad spectrum of new drugs has been tested and could expand treatment options in the near future.

Keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, anti-TNF, infliximab, treatment

Introduction

Inflammatory bowel disease (IBD) is a chronic disease that includes Crohn's disease (CD) and ulcerative colitis (UC). Because tumor necrosis factor-α (TNF-α) plays a key role in the development and progression of IBD, anti-TNF-α drugs are a therapeutic option for IBD patients. Currently, the anti-TNF-α agents infliximab (IFX), adalimumab, and certolizumab pegol have proven to be effective in inducing and maintaining remission in CD patients.[1] IFX, adalimumab, and golimumab are effective in the treatment of UC.[2] IFX, a chimeric immunoglobulin G1 monoclonal antibody against soluble and membrane-bound TNF-α with a murine Fv region, was the first anti-TNF-α drug available for the treatment of IBD in the late 1990s, and represented a very significant advance. Despite its undoubted benefit, anti-TNF-α therapy has some limitations, including the lack of primary response and the loss of response (LoR) to treatment in some patients. We discuss different alternatives in the management of poor IBD responders to IFX.

IFX is approved for the treatment of moderate to severe active UC in patients with refractoriness, intolerance, or medical contraindications to conventional therapy, including corticosteroids and thiopurines, and in those patients who are steroid dependent.[3,4] The Active Ulcerative Colitis Trial 1 (ACT 1) study showed a clinical response rate at week 8 of 69.4% in the group of patients with moderate to severe UC receiving 5 mg/kg of IFX versus 37.2% in the placebo group ($P<0.001$) and a remission rate of 38.8% versus 14.9% ($P<0.001$), respectively. Similar results were found in the ACT 2 trial, with a response rate of 64.5% in patients receiving 5 mg/kg of IFX versus 29.3% in the placebo group and a remission rate of 33.9% versus 5.7% ($P<0.001$)

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at week 8, respectively.[5] The meta-analysis by Gisbert et al[6] describes a mean short-term response and remission of 68% (95% confidence interval [CI]: 65%–71%) and 40% (95% CI: 36%–44%), respectively.

IFX is approved for the treatment of CD in patients with moderate to severe active disease and steroid dependency, intolerance, or refractoriness, as well as for fistulizing disease.[7] The Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF-α Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients with Moderately to Severely Active Crohn's Disease (ACCENT I) found that 58% of 573 patients treated with IFX 5 mg/kg responded after 2 weeks of induction treatment.[8]

In nearly a third of patients there is a lack of primary response to IFX treatment in clinical practice.[9] In patients who initially respond to IFX, this drug is usually maintained with a long-term scheduled regimen. However, LoR has been reported in 25%–40% of CD patients in randomized controlled trials, with an estimated annual LoR rate of about 13% per patient-year under scheduled treatment with IFX.[9]

Predictors of response

The underlying mechanisms and predispositions to respond to IFX therapy are not well known.[10] If we could predict the response to IFX, we would avoid nonbeneficial therapy in patients predisposed to an unsatisfactory response, resulting in time and cost savings. Some factors have been identified as indicative of a favorable response to IFX: young age, short duration of disease, nonsmoking, inflammatory CD phenotype, disease site limited to the colon, and concomitant immunosuppressive treatment.[10,11] An elevated baseline serum C-reactive protein (CRP) concentration with early normalization after starting IFX therapy has been associated with sustained remission.[11] In UC patients, high concentrations (>300 mg/kg) of fecal calprotectin in consecutive measurements can predict a flare-up 3 months before in IFX responders.[12] In CD patients treated with IFX, there are controversial data about the utility of calprotectin to predict a flareup.[13,14] Smoking could increase the risk of LoR in CD patients.[15]

The development of neutralizing antibodies, immune status, genetic factors, pharmacokinetic alterations, and concomitant medications have been investigated as factors that could be associated with LoR.[15] Trough anti-TNF-α concentrations have been associated with clinical and endoscopic remission.[16] CD patients with detectable IFX serum trough concentrations have better remission rates, lower CRP concentrations, and improved mucosal healing.[16]

Seow et al[17] analyzed the relationship between trough IFX concentrations and clinical outcome. They found that those UC patients with a detectable serum IFX presented higher rates of remission (69% versus [vs] 15%; $P<0.001$) and lower risk for colectomy (7% vs 55%; $P<0.001$) than patients with undetectable concentrations, irrespective of the presence of antibodies through IFX (ATI).

A retrospective analysis of the ACCENT I trial shows that those patients with a sustained clinical response during 54 weeks of follow-up presented higher IFX trough concentrations (4.0 μg/mL vs 1.9 μg/mL; $P=0.03$) at week 14 than patients without a sustained response, but only in the subgroup of patients with immunomodulator use at baseline (4.6 μg/mL vs 1.7 μg/mL; $P=0.005$).[18] The authors suggest that a combination of IFX and an immunomodulator may be efficacious due to increased trough concentrations rather than any synergistic mechanism. An IFX trough concentration ≥3.5 μg/mL and CRP decrease ≥60% from baseline at week 14 were the best predictors of a sustained response to scheduled maintenance with IFX 5 mg/kg.

A recent meta-analysis indicates that patients on immunomodulators during maintenance with IFX therapy had a reduction in their risk for ATI development (relative risk [RR] 0.6, 95% CI: 0.4–0.9; $P=0.02$) and infusion reactions (RR 0.6, 95% CI: 0.4–0.8; $P<0.001$).[19] ATI modified the pharmacokinetics of IFX by increasing its clearance.[15] Azathioprine (AZA) appears to decrease the formation of ATI and could improve the response rate to IFX therapy.[20] Nanda et al[21] published a meta-analysis about the relationship between clinical outcomes and the presence of ATI and concentrations of IFX in IBD patients. The presence of ATI was associated with a risk of LoR to IFX of 3.2 (95% CI: 2.0–4.9; $P<0.0001$) compared with patients without ATI formation globally, though this risk in UC patients was not significant, possibly because of a lack of large studies.

It has been reported that the presence of pre-existing IFX-reactive immunoglobulin G antibodies is associated with clinical response in IBD patients. Steenholdt et al[10] found in an observational retrospective study, including 29 CD and 22 UC patients, that serum concentrations of immunoglobulin G antibodies to the Fab region of IFX measured before the initiation of IFX therapy were significantly lower among patients with CD in clinical remission at 1 year of IFX therapy than in patients who did not achieve remission (median 91 mU/L vs 639 mU/L; $P=0.0014$). Their data suggested that a cutoff value of 439 mU/L antibodies was clinically relevant and distinguished IFX responders from nonresponders (100% sensitivity and 67% specificity). They found a similar but

not statistically significant tendency in UC patients. Their detection could help physicians select patients with a lower probability of achieving remission to choose another therapy. More data are needed to define the clinical utility of measuring pre-existing IFX–Fab-reactive antibodies.

Nowadays, the management of patients with LoR is empirical. In clinical practice, measurement of trough IFX and ATI concentrations might help us decide which strategy should be followed in case of LoR, although there is no widely accepted algorithm. It has been proposed that in patients with high IFX concentrations and LoR, intensification of IFX therapy will probably not be useful, and changing to another treatment with a different mechanism of action might be the best approach.[22] In case of low or undetectable IFX concentrations, an increased dose with or without adding an immunomodulator to achieve detectable IFX concentrations appears to be an appropriate approach. In patients with high ATI concentrations, the recommendation has been to add an immunomodulator to decrease immunogenicity, switching to another anti-TNF-α or starting a treatment with a different mechanism of action in case of lack of response to this approach.[23] Recently, the presence of transient ATI has been described in some IBD patients. It has been associated with a significantly lower need to discontinue IFX treatment compared with patients with sustained high levels of ATI.[24] In this way, it can be recommended to confirm that the positivity of ATI is maintained during consecutive measurements before IFX is withdrawn. In case of disappearance of ATI and recovery of clinical response, IFX therapy may be continued. A reliable, easy, and widely available test and more data about the clinical utility of measuring IFX and ATI concentrations are needed before recommending their routine use.

The pharmacokinetics of IFX is not well known. Some factors have been associated with a higher clearance of the drug, such as lower albumin concentrations, positive ATI, and male sex, but they explain only a small part of the pharmacokinetic variability.[25,26] The group of primary nonresponders presumably contains a subgroup of patients without TNF-α-driven disease, as indicated by observations that primary IFX response failure often occurs in the presence of high circulating drug concentrations.[27] Other patients may fail to achieve a primary response because of low bioavailability of the drug.

Identifying genes that are predictive of response to IFX would be a very interesting approach for helping manage IBD patients. Although there are various studies on this subject, further studies are needed to identify a gene panel that can be useful for predicting response to IFX in clinical practice.[28,29]

Hydrocortisone premedication

Administering hydrocortisone prior to IFX intravenous (IV) infusion has been evaluated for preventing the formation of ATI.[30] Mantzaris et al[31] prospectively compared the effectiveness of IV hydrocortisone premedication with continuous AZA therapy in preventing LoR to IFX in patients with CD. No differences were found in relation to LoR to IFX and clinical remission of disease at the end of the 2-year observation period between the two groups of patients. The cumulative probability of maintaining remission was 78% of patients with hydrocortisone premedication and 74% in the AZA group. Hydrocortisone premedication might be useful in patients on IFX monotherapy or with intolerance to immunosuppressants. Farrell et al[30] carried out a randomized controlled trial to evaluate the reduction in median ATI concentrations at week 16 in relation to IV hydrocortisone premedication. In patients with hydrocortisone premedication, 26% developed ATI, compared with 42% in the placebo group (P=0.06).

Primary nonresponse to IFX

As the structure and function of IFX and adalimumab are similar, we might think that patients who do not have a primary response to IFX will not respond to adalimumab. However, the specific characteristics of each anti-TNF-α may influence the potential usefulness of these drugs in the setting of primary failure. There are some studies that have analyzed the response to adalimumab after IFX primary nonresponse in CD patients. Crohn's Treatment with Adalimumab: Patient Response to a Safety and Efficacy Study (CARE) found in 89 IFX primary nonresponder patients a remission rate of 29% and 37% at weeks 4 and 20, respectively.[32] Ho et al[33] described a remission rate of 33% in 29 primary nonresponders at 1 year in a Scottish population. Panaccione et al[34] reported a lower remission rate (18%) in 22 patients at week 24 with a response of 68% at week 24. Although the efficacy of adalimumab is more modest than in patients who initially respond to IFX, adalimumab therapy could be a treatment option in patients with primary nonresponse to IFX.

Treatment alternatives in patients with LoR to IFX

First of all, it is important to confirm that patients' symptoms stem from inflammatory activity through clinical, analytical, endoscopic, and/or radiological testing. In patients with

LoR dose escalation, switching to another drug, adding an immunomodulator, changing to a treatment with another mechanism of action, or surgery are the most frequently used alternatives.

Combination treatment

A combination treatment with thiopurines and IFX is recommended to improve the primary response to IFX. The Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) trial showed that combination therapy with AZA and IFX in moderate to severe CD patients without previous immunosuppressant or biologic therapy obtained an increase in corticosteroid-free clinical remission at week 26 (56.8%) than those patients receiving monotherapy (44.4%; P=0.02) or AZA (30.0%; P<0.001) without an increased risk of serious infections.[35] Infliximab, azathioprine, or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis: The UC SUCCESS trial follows a similar design in UC patients.[36] The findings of the SONIC study in CD patients were confirmed with a similar strength in the SUCCESS study in UC patients. Corticosteroid-free remission at week 16 was achieved in a significantly greater percentage of patients with moderate to severe UC who were treated with combination IFX and AZA therapy (39.7%) than with AZA (23.7%; P=0.032) or IFX monotherapy (22.1%; P=0.017) patients. A greater percentage of patients on combination therapy achieved mucosal healing (62.8%) at week 16 than those on AZA monotherapy (36.8%; P=0.001) without significant differences versus IFX monotherapy patients (54.6%; P=0.295). This finding could probably be related to the delayed effect of AZA therapy. There were no differences in serious events between the three groups.

Although combination therapy with AZA and IFX is a good option for the management of IBD, treatment with two immunosuppressants together could lead to a higher rate of adverse events such as serious infections and the rare hepatosplenic T-cell lymphoma, and must be considered when starting these therapies.[37] Deepak et al[38] did not find an increase in serious infections with combination therapy compared with monotherapy. Regardless, this increased rate appears to be low, with lymphoma being a very rare event, and uncontrolled IBD can lead to increased mortality because of complications and surgery.[39]

The randomized trial evaluated the efficacy of methotrexate in combination with IFX in patients with active CD who were recently treated with corticosteroids.[40] The combination of methotrexate and IFX was not more effective than IFX alone for inducing and maintaining remission (76% vs 78%; P=0.83 at week 14, and 56% vs 57%; P=0.86 at week 50), although patients treated with methotrexate were significantly less likely to develop ATI. IFX trough concentrations in the combination group were higher compared with the monotherapy group, but this difference was not statistically significant (6.35 µg/mL vs 3.75 µg/mL; P=0.08). In a Cochrane review, the combination of methotrexate with IFX therapy did not provide any additional benefit over IFX monotherapy, although more data are needed.[41]

Dosage escalation

In patients who lose their initial response to the standard IFX treatment regimen of 5 mg/kg every 8 weeks, increasing the dosage (eg, from 5 mg/kg to 10 mg/kg) or decreasing the infusion interval (eg, from every 8 weeks to every 6 weeks), or both, is an option. In the ACCENT I trial, an increase in the dosage to 10 mg/kg resulted in a 90% response in luminal CD patients.[8] In the ACCENT II study, the same strategy of increasing dosage obtained a response in 57% of patients with fistulizing CD.[42] These data are in concordance with other studies that showed that IFX dosage escalation is follow by a high rate of response, at least transiently, with fewer data about the long-term benefit.[43–45] Chaparro et al[46] found a 79% clinical response rate after the first escalated dosage in patients with CD, although the risk of loss of efficacy with the escalated treatment was 43% per patient-year of follow-up, much higher than the 13% estimated with the standard IFX dosage. This high rate of LoR after dosage escalation may be in relation to the formation of ATI.

Shortening the interval between IFX doses is a strategy often used in clinical practice in patients with LoR, especially in those patients who experience a shortened duration of response. The adjusted interval usually varies widely between 4 weeks and 7 weeks. Kopylov et al[47] analyzed the immediate clinical response and 1-year response after IFX intensification in a group with a dose every 6 weeks versus another group of patients with a dose of 10 mg/kg every 8 weeks or 5 mg/kg each 4 weeks. Immediate clinical response was achieved in two-thirds of patients in both groups without statistical differences. Approximately one-third of patients had a sustained clinical response at 12 months after IFX intensification, without differences between both groups. No clinical factor was found to be predictive of a sustained response to escalation. A further dose escalation was attempted in 28 patients without response to a first escalation. Response to this second escalation was achieved in 39% of patients.

Regueiro et al[43] found that dosage intensification was required in 31% of patients with CD treated with at least

eight doses of IFX at month 12, and 54% after 30 months of treatment. In UC patients, Seow et al[17] found that escalation of IFX therapy by shortening the interval to 6–7 weeks achieved remission in 44% of the patients and in 25% in cases of doubling the dose. Rostholder et al[48] retrospectively analyzed the need to increase IFX in ambulatory patients with moderately active UC. They found that 54% of patients required dose escalation after a mean of six maintenance infusions, with a remission rate of 19% at 12 months compared with 56% in the nonescalation group. Neither CRP concentrations nor immunomodulator combination therapy was associated with clinical remission at 12 months. The risk of colectomy was not different between the escalation and nonescalation groups.

A recent retrospective European multicenter study in patients treated with IFX describes a clinical response after the first escalated dose in 13 of 15 patients (86.7%) with a doubled dosage and in 24 of 26 patients (92.3%) with a shortened interval (P=0.96).[49] The patients who achieved rapid clinical response had significantly higher colectomy-free rates at week 52 than patients who did not (P=0.002). Half of the patients were de-escalated to a standard regimen after a mean period of 13.6 months. This de-escalation was more frequent in patients with a shortened interval (odds ratio 5.84, 95% CI: 1.41–24.17).

Steenholdt et al[50] have recently published their data from a randomized, controlled, multicenter study including patients with LoR to IFX. Sixty-nine patients were randomized to IFX dose intensification (5 mg/kg every 4 weeks) (n=36) or to follow an algorithm based on serum IFX and ATI concentrations. At week 12, the cost per patient was lower in those treated in accordance with the algorithm compared with routine IFX dose escalation (€6,038 vs €9,178; P<0.001), with similar response rates (47% vs 53%; P=0.78). Long-term data are necessary.

Switching the anti-TNF-α

Switching to another anti-TNF-α drug, mainly adalimumab, is a common choice in patients with LoR to IFX, especially in patients who do not respond to dose escalation. Sandborn et al[51] reported a clinical remission rate of 12% and 29% at weeks 4 and 12 with adalimumab in 17 CD patients who had lost responsiveness or developed intolerance to IFX and with a high need for escalation of adalimumab (79% during weeks 4–6) because of partial response to the induction therapy. Papadakis et al[52] reported a complete response of 54% after 6 months of adalimumab therapy in CD patients with an attenuated response to IFX.

The placebo-controlled GAIN (Gauging Adalimumab Efficacy in Infliximab Nonresponders) trial analyzed the response to adalimumab in adult patients with moderate to severe CD who had symptoms despite treatment with IFX or who could not tolerate IFX because of adverse events.[53] At week 4, 21% (34 of 159) of patients treated with adalimumab compared with 7% (12 of 166) of patients in the placebo group achieved clinical remission (P<0.001). These data are similar to those seen in the The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) trial, which included IFX-naïve and IFX-experienced patients with a remission rate of 25% at week 4.[54]

Karmiris et al[55] analyzed the efficacy of adalimumab therapy in patients who previously discontinued IFX because of LoR or intolerance and the influence of trough serum adalimumab concentrations and antibodies to adalimumab on clinical response. They found a complete clinical response in 40.4% of patients treated with adalimumab at week 4. The probability of dose escalation was approximately 15% at 30 weeks and 80% at 120 weeks of adalimumab treatment. Patients who discontinued adalimumab by week 4 had lower adalimumab concentrations than patients with adalimumab maintenance treatment (P=0.012). Ma et al[56] reported a short-term clinical response of 41%–83% at week 4 and a clinical remission rate of 19%–68% at 12 months of adalimumab treatment following discontinuation of IFX. Taxonera et al[57] found that UC patients previously treated with IFX who achieved a clinical response to adalimumab at week 12 were colectomy free during a mean follow-up period of 48 weeks.

Kaplan et al[58] carried out a decision analysis model to compare the cost-effectiveness of IFX dose escalation with initiation of adalimumab in CD patients with LoR to IFX. Dose escalation to 10 mg/kg of IFX improved quality-adjusted life-years compared with switching to adalimumab, although the cost was considerable. The Treatment of the Human Anti-TNF Monoclonal Antibody Adalimumab in Moderate to Severe Crohn's Disease with Previous Exposure to Infliximab (CHOICE) trial evaluated the safety and effectiveness of adalimumab in patients with moderate to severe CD who had primary nonresponse or LoR or who were intolerant to IFX.[59] Complete fistula healing during adalimumab therapy was achieved in 30.8% of primary nonresponders and in 40% of the rest of the patients who previously discontinued IFX. Both patient groups experienced statistically significant improvements in the quality of life questionnaire and in-work productivity. The CARE trial showed in a large European cohort that treatment with adalimumab in CD patients previously treated with IFX,

including primary nonresponders, improves patients' quality of life and reduces the overall economic burden associated with work disability and productivity impairment at work.[60] Remission rates at week 20 were higher in IFX-naïve versus IFX-exposed patients (62% vs 42%; $P<0.001$), being similar in primary nonresponders and patients discontinuing IFX for another reason (37% vs 43%; $P=0.278$).[32]

The 26-Week open-label trial evaluating the clinical benefit and tolerability of certolizumab pegol induction and maintenance in patients suffering from Crohn's disease with prior loss of response or intolerance to infliximab (WELCOME) trial evaluated the clinical benefits and tolerability of certolizumab pegol over 26 weeks in patients with moderate to severe CD with prior LoR and/or hypersensitivity to IFX.[61] At week 6, 62% of patients achieved a 100-point decrease (64.3% in patients with prior LoR to IFX) and 69.2% achieved a 70-point or greater decrease in Crohn's Disease Activity Index scores from baseline, with a clinical remission rate (Crohn's Disease Activity Index score ≤150 points) reported in 39.3% of patients. Those patients who lost their response to certolizumab 400 mg every 4 weeks were treated successfully with dose escalation to 400 mg every 2 weeks with a response rate of more than two-thirds.

The results of these studies indicate that switching to alternative anti-TNF-α therapy with certolizumab pegol or mainly adalimumab may be an effective treatment option in patients with CD who have lost response to or experienced hypersensitivity to IFX.

Restarting IFX after a previous failed IFX treatment

The reintroduction of IFX in selected patients after previous treatment could be an option in some cases. Baert et al[62] analyzed the response rate of restarting IFX in patients with LoR or serious infusion reactions. Of the 28 patients analyzed (25 of them with previous LoR), 17 (62%) had a short-term response to restarting IFX therapy after at least 6 months without IFX (during this interval these patients were treated with a variety of other agents, including investigational drugs and surgery), and 13 patients (45%) had a clinical response after 1 year of IFX. Although these rates were significantly higher in patients in whom the reason for discontinuation of first course of IFX was remission, these data show that the reintroduction of IFX in selected patients after a previous LoR could obtain an appreciable response rate. The response rate was not influenced by the duration of the drug holiday or the use of a week 0–2–6 induction regimen. Regardless, seven of the 23 patients (30.4%) with previous LoR developed serious infusion reactions after IFX restart, so more data are needed. Short-term and long-term responses were correlated significantly with higher trough IFX concentrations as well as the absence of ATI. An IFX trough concentration above 2 μg/mL and undetectable ATI early after restart were predictive of response. Combination therapy was superior, with regard to long-term efficacy and safety, only in patients with trough IFX concentrations in the lowest quartile soon after restarting, in line with previous data, suggesting that patients with high IFX concentrations could be managed with IFX monotherapy. Although more data are needed, selected patients without other appropriate treatment options could be retreated with IFX with acceptable efficacy.

Other therapies

Surgery is an option in patients with LoR to IFX, especially in UC and CD localized to a short segment of the bowel and perianal disease.[4]

A broad spectrum of new therapies for IBD patients with different targets is being developed. Golimumab is a fully human anti-TNF-α drug recently approved for the treatment of moderate to severe adult UC patients who had an inadequate response to or failed to tolerate conventional oral therapies, with a rate of adverse events similar to placebo.[63]

Natalizumab, a humanized anti-α4-integrin monoclonal antibody, is effective in the treatment of moderately to severely active CD patients, but it is not approved in Europe because it has been associated with an increased risk of multifocal leukoencephalopathy (one case/10,000 patients).[64,65] Vedolizumab is a humanized immunoglobulin G1 mAb against α4β7 integrin that has been shown to be superior to placebo in inducing and maintaining clinical and endoscopic remission in UC patients.[66] Although the results of short-term response are better in UC, long-term sustained response rates at 52 weeks are similar in UC and CD patients, around 40%.[67,68] It has an effect that is limited to the gastrointestinal tract, thereby most likely avoiding a risk of multifocal leukoencephalopathy. Ustekinumab is a humanized immunoglobulin G1 monoclonal antibody against the p40 subunit of interleukin 12 and 23. The Crohn's Evaluation of Response to Ustekinumab anti-Interleukin-12/23 for Induction (CERTIFI) trial found that ustekinumab is superior to placebo in inducing short-term response in CD patients who have previously failed anti-TNF-α therapy.[69]

Extracorporeal photopheresis and autologous hematopoietic stem cell transplantation could be alternatives in patients with CD refractory to immunosuppressants and/or anti-TNF-α, although more data are needed.[70,71]

Conclusion

IFX treatment is effective in inducing and maintaining response in IBD patients. Lack of response and LoR to IFX are common. Close monitoring during IFX therapy is recommended. Analytical data such as CRP and calprotectin together with clinical status can help us predict LoR to IFX. Once it is confirmed that the symptoms are related to inflammatory activity, escalation of IFX treatment (increasing the dosage and/or shorting the interval) or switching to another anti-TNF-α drug is useful. Serum trough IFX concentrations and ATI concentrations could guide us in this choice, though a more available test and a widely accepted algorithm are necessary before their routine use. Combination treatment with thiopurines and IFX is recommended to improve the response to IFX, but it must take into account the possible serious complications with combination treatment, such as infections and tumors. Adalimumab is effective in achieving response in patients without response to IFX in UC and CD. Certolizumab, ustekinumab, and natalizumab in CD patients, and golimumab and vedolizumab in UC patients, have shown to be effective alternatives to IFX. Surgery is a recommended alternative in selected patients with LoR to IFX. The optimal strategy in the future may comprise early detection of LoR by assessing clinical symptoms and finding evidence of activity of the disease on analytical, endoscopic, or radiological examinations when necessary, as well as better management of anti-TNF-α treatment by measuring the serum concentration of the drug and antibodies against the drug.

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