Pharmacologic therapy for inflammatory bowel disease refractory to steroids

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Abstract: Although corticosteroids are an effective treatment for induction of remission in inflammatory bowel disease (IBD), many patients are dependent on or refractory to corticosteroids. This review is based on scrutinizing current literature with emphasis on randomized controlled trials, meta-analyses, and Cochrane reviews on the management of IBD refractory to corticosteroids. Based on this evidence, we propose algorithms and optimization strategies for use of immunomodulator and biologic therapy in IBD refractory to corticosteroids.

Keywords: immunomodulators, anti-tumor necrosis factor alpha, Crohn’s disease, ulcerative colitis, drug levels, treatment optimization

Introduction

The etiology of Crohn’s disease (CD) and ulcerative colitis (UC) is not clear, and no curative therapy is therefore available. At present, the aim of treatment for inflammatory bowel disease (IBD) is to achieve mucosal healing, which is associated with fewer admissions to hospital and surgeries, and better patient quality of life.1–3 Deep remission, defined as the absence of symptoms, markers of inflammatory activity, and endoscopic lesions, is a proposed treatment objective in clinical trials.4 Conventional treatment with corticosteroids and immunomodulators (IMMs, step-up strategy) has not been able to reduce the complications of the disease or modify its course.5 The top-down approach (comprising biologic treatment from the time of diagnosis) is not without side effects, is expensive, and implies overtreatment of patients with milder IBD.6,7 At present, the accelerated step-up approach (early introduction of IMM and biologic agents in patients with more serious disease) is probably the most widely accepted management strategy.7 Studies are needed to identify universally accepted indicators of poor prognosis, with a view to individualizing therapy according to patient risk and efficacy of drugs (treat-to-target strategy). The present review addresses the concept and management of IBD refractory to corticosteroid therapy in the routine clinical practice setting.

Refractory IBD

Corticosteroids are very effective in controlling acute flare-ups of IBD, but 16% of patients fail to respond to such drugs, and 20%–30% show only a partial response.8 IBD refractory to corticosteroids includes corticosteroid-dependent patients. According to the current guides,9,10 refractory IBD is defined as active disease despite full-dose prednisolone (0.75 mg/kg/day) for 4 weeks. This period could be shortened in future,
as a threshold prior to introduction of biologic treatment. Corticosteroid-dependent IBD is defined as: inability to lower prednisolone to <10 mg/day for keeping IBD inactive for 3 months or as relapse within 3 months or less after suspending corticosteroid treatment. In severe flare-ups of UC, the response to intravenous corticosteroids is evaluated on the third day, since the seriousness of the condition requires rapid management.

Before diagnosing a patient as having IBD refractory to corticosteroids, we must confirm the activity of the disease and eliminate possible causes of false refractoriness. In the case of CD, we must rule out complications (eg, abscesses) using imaging techniques. In patients with UC, we must exclude added infections (eg, Clostridium difficile and cytomegalovirus) and rule out colorectal cancer.\textsuperscript{9,10} The rescue treatment of choice in IBD refractory to corticosteroids depends on the extent and severity of the disease, and on clinical prognosis factors.

**Immunosuppressors**

**Thiopoulos**

Azathioprine and 6-mercaptopurine are IMMs with complex metabolism involving participation of various enzymes. Thiopurine-S-methyltransferase (TPMT) plays a determining role in drug metabolism. The 6-thioguanine nucleotides are responsible for the efficacy of these drugs and also for their bone marrow toxicity. The 6-methylmercaptopurine metabolites have been related to possible inefficacy of the medication and to liver toxicity and gastrointestinal intolerance.\textsuperscript{11} At present, the usefulness of determination of TPMT activity is questionable, although it is cost-effective in clinical practice.\textsuperscript{11} Treatment can be started accordingly with the TPMT, if it is known (Figure 1). Thiopurines are slow-acting drugs, and it may take 6 months to obtain therapeutic effects.

**Efficacy in CD**

The efficacy of thiopurines in the treatment of active CD is controversial, according to the results of meta-analyses.\textsuperscript{12,13} At present, thiopurines are not recommended as monotherapy for inducing remission of active CD; rather, they should be combined with corticosteroids or anti-tumor necrosis factor alpha (TNF\x3c/\x3e\textsubscript{\alpha}) agents until remission is achieved.\textsuperscript{12} Thiopurines are effective in maintaining remission of CD, are able to lessen the need for corticosteroids (number needed to treat [NNT] 3), and reduce the need for surgery by 40%.\textsuperscript{14} Azathioprine and 6-mercaptopurine are effective in achieving mucosal healing in CD, and the effect seems to be better in the colon than in the ileum (70% versus 54%).\textsuperscript{15}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of adverse events</th>
<th>Percentage of patients</th>
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<tbody>
<tr>
<td>AZA/6-MP</td>
<td>Allergic reactions: malaise, rash, fever, pancreatitis, hepatitis</td>
<td>5–10</td>
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<td></td>
<td>Bone marrow suppression: leukopenia</td>
<td>2–15</td>
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<td></td>
<td>Infections</td>
<td>0.3–7.4</td>
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<td>Liver toxicity (cholestasis, endothelial damage, portal hypertension, hepatic peliosis, venous occlusion)</td>
<td>3–10</td>
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<tr>
<td></td>
<td>Malignancies (lymphomas, non-melanoma skin cancer, leukemia, cervical cancer)</td>
<td>Lymphoma (OR 2–4.18)</td>
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<td>MTX</td>
<td>Digestive intolerance</td>
<td>13</td>
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<td></td>
<td>Pneumonitis</td>
<td>2.7</td>
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<tr>
<td></td>
<td>Bone marrow toxicity</td>
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<td></td>
<td>Liver enzyme alterations</td>
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<td></td>
<td>Liver fibrosis</td>
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<td></td>
<td>Teratogenicity</td>
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<td>CsA</td>
<td>Hypertension</td>
<td>15–30</td>
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<td></td>
<td>Nephrotoxicity</td>
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<td></td>
<td>Seizures</td>
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<td></td>
<td>Headache</td>
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<td></td>
<td>Paresthesias</td>
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<td></td>
<td>Tremor, muscle pain</td>
<td>10–15</td>
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<td></td>
<td>Infections</td>
<td>6–15</td>
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<td>Hypomagnesemia/ hypercholesterolemia</td>
<td>30–40</td>
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<td>Tacrolimus</td>
<td>Hypertension, hyperglycemia</td>
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<td></td>
<td>Paresthesias, tremor, headache</td>
<td>10–30</td>
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<td></td>
<td>Renal failure (generally reversible)</td>
<td>6–14</td>
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<td></td>
<td>Gastrointestinal intolerance</td>
<td>7–50</td>
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<td></td>
<td>Opportunistic infections</td>
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<tr>
<td>MMF</td>
<td>Diarrhea</td>
<td>30</td>
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<td></td>
<td>Histological changes similar to those of graft versus host disease</td>
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<td>Thalidomide</td>
<td>Neurological toxicity (neuropathy)</td>
<td>30–50</td>
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<td></td>
<td>Teratogenicity</td>
<td>100</td>
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**Abbreviation:** AZA, azathioprine; 6-MP, mercaptopurine; MTX, methotrexate; CsA, cyclosporine; MMF, Mycophenolate mofetil. OR, odds ratio.

**Efficacy in UC**

Thiopurines are not recommended for inducing remission of UC, probably because of the late onset of action of these drugs.\textsuperscript{16} Azathioprine is better than mesalazine for achieving remission in patients with corticosteroid-dependent UC.\textsuperscript{17} Thiopurines are effective in maintaining remission of UC. A meta-analysis found the efficacy of azathioprine/6-mercaptopurine in maintenance therapy to
be 76%, with an absolute reduction in relapse risk of 23% (NNT 5). Thiopurines have been shown to be effective in maintaining the remission induced by cyclosporine. The risk of colectomy in UC patients treated with thiopurines is 10% in the 29 months following the start of therapy. Use of thiopurines for 12 months reduced this risk by 71%.

Safety
Thiopurines give rise to adverse events in 26% of cases (Table 1), and such events require drug suspension in 17% of patients. Surveillance of possible adverse events during treatment are therefore required. Infections are among the most important problems. Herpes infections and disseminated Epstein–Barr virus infections are related to the lymphopenia (<600 per μL) induced by these drugs. An increased risk of lymphoma has been described in patients on thiopurines, attributable to the medication, severity of the disease, or both. A meta-analysis of 18 studies concluded that IBD patients treated with thiopurines have an increased risk of lymphoma (odds ratio 4.49; 95% confidence interval [CI] 2.18–7.17), in particular after 1 year of exposure and in males younger than 30 years. Lymphoma may be associated with Epstein–Barr virus infection in patients with IBD. As a result, young seronegative males are regarded as a risk group for treatment with thiopurines, and in such individuals treatment with methotrexate and/or anti-TNFα agents should be considered. There have been reports of hepatosplenic T-cell lymphoma, a fatal disease, in young males with IBD who have received thiopurines in monotherapy and associated with anti-TNFα drugs. Therefore, despite the efficacy of combination treatment (anti-TNFα and thiopurines), monotherapy must be considered after 2 years of treatment. Thiopurines increase the risk of non-melanoma skin cancer even after treatment suspension.

Optimization of therapy
Switching to 6-mercaptopurine in patients with digestive intolerance to azathioprine is effective in 69% of cases, but is less useful with other adverse events (leukopenia), and is not recommended in the presence of pancreatitis. Dose splitting reduces the levels of 6-methylmercaptopurine metabolites and thus also the liver toxicity and flu syndrome. Determination of TPMT, 6-thioguanine nucleotide, and 6-methylmercaptopurine levels may be useful for optimizing treatment (Figure 1). Patients who do not tolerate full-dose thiopurines in monotherapy, with preferential metabolization toward 6-methylmercaptopurine may benefit from the combination of allopurinol (100 mg/day). There would be a reduction of 25%–50% in the thiopurine dose however, to avoid toxicity.

Thiopurines have synergistic effects with anti-TNFα drugs and lessen their immunogenicity of biological therapy. Combination therapy is therefore recommended, since it results in greater efficacy, with less risk of loss of response due to production of antibodies against the anti-TNFα molecules. Suspension of thiopurines may be considered on an individualized basis and in selected patients who have been in deep remission for over 5 years.

Thioguanine
Evidence for the use of thioguanine in IBD is low. Liver toxicity (nodular regenerative hyperplasia) has limited the use of thioguanine.
this drug, and it is presently not recommended as a treatment for IBD. Low-dose thioguanine (10–20 mg) could be effective and safe for short periods in IBD patients who do not tolerate or are refractory to azathioprine/6-mercaptopurine.28

Methotrexate

Methotrexate is the second-line IMM option in CD in situations of failure or intolerance to thiopurines (30% of patients) and in arthropathy associated with IBD.2,9,29 The drug appears to have less bioavailability when administered via the oral route than when given intravenously.20 The latency period is 6–8 weeks, so concomitant treatment with corticosteroids is required at the start of therapy.

Efficacy in CD

A recent Cochrane review found parenteral methotrexate (25 mg/week) to be effective in inducing remission and when withdrawing corticosteroids in active CD (NNT 5).30 Recent reviews and controlled studies indicate that parenteral methotrexate (15 mg/week) is effective versus placebo in maintaining remission in quiescent CD (65% versus 39%; P=0.04; NNT 4). However, oral methotrexate (12.5–15 mg/week) is not effective versus placebo in maintaining CD remission (90% versus 67%).31 On comparing methotrexate versus azathioprine in corticosteroid-dependent CD, efficacy with regard to ability to withdraw corticosteroids was found to be similar for both drugs (methotrexate 56%, azathioprine 63%; P=0.39).32

Efficacy in UC

In a systematic review, methotrexate was not effective in inducing remission of active UC, although it may reduce steroids use in one-third of patients and may be beneficial in those who are refractory to intolerant to thiopurines.28

Safety

The incidence of adverse events with methotrexate is 20%, and in 30% of cases the drug is suspended after 5 years of follow-up33 (Table 1). Five percent of patients require suspension of methotrexate because of liver problems, particularly those with previous liver disease. Cumulative doses of 3–5 g appear to be safe in CD, and a liver biopsy is only recommended in the event of persistent changes in liver function tests.16,33

Methotrexate is teratogenic. Its use during pregnancy is contraindicated, and women who wish to have children must stop the medication 3–6 months before planning pregnancy.3,29 Methotrexate is not associated with development of tumors in IBD, and therefore might be indicated in patients with neoplasms who require IMM therapy.28

Optimization of therapy

Methotrexate is effective in cases where thiopurines have failed. Consequently, before accepting failure of IMM treatment in IBD, use should be made of methotrexate.28 Given the lower risk of lymphoma during treatment with methotrexate in IBD patients, Epstein–Barr virus-seronegative individuals, particularly young males, might benefit from methotrexate instead of thiopurines.23,28,29 The role of methotrexate in combination with biologic agents has not been well established. In the COMMIT study, a combination of infliximab + methotrexate was not found to be superior to infliximab as monotherapy.34 However, methotrexate reduces the immunogenicity of infliximab, and this might contribute to the recovery of response to the biologic agent.34

Calcineurin inhibitors

Cyclosporine

Controlled studies have demonstrated the efficacy of intravenous cyclosporine (4 mg/kg/day) in the management of severe UC refractory to corticosteroids (64%–80%), with a mean time to response of 2–7 days. In clinical practice, an intravenous dose of 2 mg/kg is equally effective and causes lesser toxicity.10,35 The clinical response should be evaluated within the first 48–72 hours. The drug requires adjustment according to serum levels (150–200 mg/mL), which limits its use. Once the response has been induced via the intravenous route, azathioprine/6-mercaptopurine is introduced in patients naïve to thiopurines.18 Despite the initial benefit obtained, over 50% of responders to intravenous cyclosporine will require colectomy in the next 3–7 years.36 Rescue treatment with cyclosporine does not increase the postoperative complications.36

Cyclosporine and infliximab show similar response rates with regard to induction of remission in patients with severe flare-ups of UC refractory to corticosteroids (80%), and there are no differences between these drugs in terms of the colectomy rate after 3 or 12 months. The choice of one drug or the other depends on patient comorbidity, the experience of the center, the availability of cyclosporine level determinations, and cost.37 Sequential therapy with infliximab after failure of cyclosporine is not advised until conclusive data are obtained, in view of the risk of complications, particularly infection.35

A systematic review concluded that cyclosporine via the oral route (5 mg/kg/day) was not effective in inducing remission of CD in patients refractory to corticosteroids.38

Cyclosporine is associated with numerous adverse events, most of which are dose-related (Table 1). Low cholesterol levels (<110 mg/dL) increase the frequency of adverse events. Opportunistic infections (3.5%) are among the most serious
complications of cyclosporine treatment, particularly those caused by *Pneumocystis jiroveci*. Chemoprophylaxis with trimethoprim-sulfamethoxazole is therefore recommended in the event of triple IMM therapy.\textsuperscript{21} The drug is not adequate for use in cases of thiopurine intolerance or failure.\textsuperscript{10,33}

**Tacrolimus**

Tacrolimus is a calcineurinic IMM with functions similar to those of cyclosporine, but with a more predictable adverse event profile. Tacrolimus has been used in refractory UC.\textsuperscript{10,35} Following induction of remission with tacrolimus, maintenance therapy should be started with thiopurines in naïve patients.\textsuperscript{38} Tacrolimus has been used via the rectal route in proctitis refractory proctitis, with promising results.\textsuperscript{28} Further controlled studies are needed to confirm the efficacy and safety of tacrolimus in patients with CD.\textsuperscript{39} The main limitations to use of tacrolimus are the need to determine therapeutic levels and the adverse events (Table 1).

**Other immunosuppressors**

**Mycophenolate mofetil**

Mycophenolate is not recommended for the treatment of IBD refractory to corticosteroids, although it could constitute an alternative in patients who fail to tolerate thiopurines, possibly affording a greater effect in UC.\textsuperscript{40} Adverse events related to mycophenolate mofetil are seen in 20%–30% of patients (Table 1).

**Thalidomide**

At present, thalidomide is only recommended in active CD refractory to IMM and biologic drugs.\textsuperscript{41} There is no evidence warranting use of thalidomide in refractory UC. Side effects may limit long-term use (Table 1). The drug is teratogenic and effective contraceptive methods must be used.

**Biologic agents**

Biologic agents used in the treatment of IBD include monoclonal antibodies against key targets in the intestinal inflammatory process (Table 2).

**TNFα antibodies**

The anti-TNFα agents used in IBD are infliximab, adalimumab, certolizumab, and golimumab. Infliximab was the first anti-TNFα agent approved for the treatment of CD. ACCENT-I\textsuperscript{4} and ACCENT-II\textsuperscript{42} demonstrated the efficacy of infliximab in maintenance of remission achieved after the initial response, the safety profile of the drug, and the optimum doses and posology. ACCENT-I showed that scheduled treatment was more effective than sporadic treatment, and suggested a greater probability of mucosal healing, with fewer hospital admissions.\textsuperscript{43}

CLASSIC-I\textsuperscript{44} demonstrated that adalimumab was superior to placebo in terms of inducing remission of active CD, and the 160/80 mg dose was found to be the most effective. CLASSIC-II showed adalimumab at doses of 40 mg every 2 weeks to be effective in maintaining disease remission until week 56.\textsuperscript{45} CHARM\textsuperscript{46} and EXTEND\textsuperscript{47} demonstrated the efficacy of adalimumab in long-term maintenance therapy (with 30% of patients in remission after 4 years). GAIN is the first study to evaluate the efficacy of a second anti-TNFα drug in patients who do not tolerate or lose response to infliximab.\textsuperscript{48} In week 4, the remission was 21% in patients on adalimumab and 7% in those on placebo (*P*<0.001).

Controlled studies of certolizumab (PRECISE 1–4) involving 1,891 patients revealed the efficacy of certolizumab
at a dose of 400 mg in the induction and maintenance of moderate to severe CD. Two meta-analyses concluded that certolizumab may be an efficacious and safe treatment for CD as maintenance therapy. Certolizumab shows significant efficacy versus placebo in patients who had lost response to infliximab or who failed to tolerate this drug. All anti-TNFα drugs are more effective than placebo in achieving mucosal healing.

Comparative efficacy

All the anti-TNFα drugs neutralize the action of TNFα, although their structure, mechanism of action, pharmacokinetics, and pharmacodynamics differ, a fact that may have implications regarding their therapeutic efficacy. No significant differences have been observed between the drugs, although a greater induction response rate was seen with infliximab, while adalimumab proved superior in terms of maintenance therapy. Among the subcutaneous anti-TNFα drugs, adalimumab was superior to certolizumab in inducing remission (relative risk 2.93; 95% CI 1.21–7.75).

Efficacy in UC

The ACT-I and ACT-II trials showed the efficacy of infliximab in the treatment of UC refractory to at least one standard drug. The two studies had a similar design and both showed that infliximab is significantly superior (P<0.001) to placebo in moderate to severe UC refractory in terms of induction of clinical response and remission. Infliximab was superior to placebo in inducing clinical remission (relative risk 3.22; 95% CI 2.18–4.76) and endoscopic remission (relative risk 1.8; 95% CI 1.54–2.28) in patients with moderate to severe UC refractory to steroids.

Järnerot et al compared the efficacy of a single 5 mg/kg dose of infliximab versus placebo for severe flare-ups of UC refractory to corticosteroids. The results showed statistically significant superiority of infliximab in controlling flare-ups and in terms of the colectomy rates (29% for infliximab versus 67% for placebo) after 1 and 3 months.

ULTRA-1 and ULTRA-2 demonstrate the efficacy of adalimumab in induction of remission and maintenance of remission in moderate to severe UC exhibiting inadequate response to conventional treatments. At week 8 in ULTRA-1, patients who received the dose of 160/80/40 mg showed a significantly greater remission rate than those given placebo (18.5% versus 9.2%; P=0.031).

ULTRA-2 included 494 patients with moderate to severe UC who were unresponsive to corticosteroids and IMM. Of these individuals, 40.3% had previously received anti-TNFα therapy, which was found to be more effective than placebo in securing disease remission at both week 8 (16.5% versus 9.3%; P=0.02) and week 52 (17.3% versus 8.5%; P=0.01). Patients naïve to anti-TNFα agents showed higher remission rates in weeks 8 and 52 (21.3% and 22%, respectively).

Golimumab is the newest anti-TNFα drug approved for the treatment of moderate-severe UC. The Phase III PURSUIT-SC study concluded that treatment containing subcutaneous golimumab resulted in a clinical response rate of 51%–56% at week 6 versus 30.3% in the placebo group (P≤0.0001). The PURSUIT-M study concluded that a total of 47% and 49.7% of those treated with golimumab 50 mg and 100 mg, respectively, via the subcutaneous route every 4 weeks, maintained their clinical response in week 54, versus 31.2% in the placebo group (P=0.010 and P<0.001). In weeks 30 and 54, those who had received the 100 mg dose of golimumab showed higher clinical remission (27.8%) and mucosal healing rates (42.4%) versus placebo (15.6% and 26.6%, respectively; P=0.004 and P=0.002).

All of the anti-TNF-α drugs are more effective than placebo in achieving mucosal healing in UC, and they also reduce the number of hospital admissions. Infliximab reduced the cumulative colectomy rate in week 54 (10% versus 17% placebo; P=0.0004).

Comparative efficacy

Stidham et al found that anti-TNFα drugs were superior to placebo in induction and maintenance of remission in UC. No significant differences were recorded between infliximab, adalimumab, and golimumab, and the authors concluded that the choice of drug should be based on cost, safety, administration route, and patient preference. In this meta-analysis, the response and remission rates were greater for infliximab, although statistical significance was not reached.

Another meta-analysis of the efficacy of biologic drugs (infliximab, adalimumab, golimumab, and vedolizumab) in UC concluded that all of them are superior to placebo in terms of induction of remission, maintenance, and mucosal healing. The meta-analysis provided indirect evidence of the superiority of infliximab versus adalimumab in terms of induction of remission and clinical response. Specifically, the response/remission rate vs. placebo was 4.13 odds ratio, 4.13 (95% CI 2.39–7.16)/odds ratio, 5.33 (95% CI 2.28–13.63) with infliximab and odds ratio, 1.76 (95% CI 1.19–2.56)/odds ratio, 1.91 (95% CI 0.98–3.72) with adalimumab.
Combination therapy in CD and UC
The SONIC trial indicates that the combination of azathioprine and infliximab is more effective than either drug in monotherapy for achieving corticosteroid-free remission in moderate to severe CD. The mucosal healing rate was higher in the combination therapy group. The infliximab trough levels were higher in the combined treatment group. The problem with combination therapy is the increase of adverse events.

The combination of infliximab and methotrexate did not appear to be superior to infliximab in monotherapy, although anti-TNFα drug levels were higher. In UC, the SUCCESS study demonstrated that combination therapy was more effective (response rate 39.7%) than monotherapy with infliximab (22.1%) or azathioprine (23.7%). The mucosal healing rate in week 16 was higher in the combination therapy group.

Biosimilar drugs
Upon expiry of the patent covering infliximab in 2013, the European Medicines Agency authorized a drug biosimilar to infliximab, ie, CTP-13, an IgG1 type chimeric monoclonal antibody (murine-human), which has not been approved by the US Food and Drug Administration. However, two drugs biosimilar to infliximab are found on the market, ie, Remsima (Celltrion Inc., Incheon, Korea) and Inflectra (Hospira, Lake Forest, CA, USA). Biosimilar drugs are required to have the same pharmacologic presentation, dosage, and administration route as the reference biologic drug.

The European Medicines Agency approved CTP-13 for the treatment of IBD in children and adults, following extrapolation of the efficacy, safety, and pharmacokinetic results for CTP-13 in ankylosing spondylitis and rheumatoid arthritis. The European Crohn's and Colitis Organization has published a position document on the use of biosimilar drugs in IBD. The main advantage of such drugs is the cost savings they offer for health care systems, while their main inconvenience for clinicians is the lack of knowledge regarding their immunogenicity, exchangeability, and automatic substitution.

Loss of response and optimization of treatment with anti-TNFα drugs
The efficacy of anti-TNFα drugs in the treatment of IBD is far from optimum. In the clinical trials, patients with the highest response rates had higher drug levels. All biologic drugs are able to induce production of antibodies targeted against them (anti-drug antibodies). Patients with anti-drug antibodies have lower plasma drug concentrations, increased drug clearance, and more adverse reactions. In this sense, monitoring of biologic drug levels (therapeutic drug monitoring) in blood is an effective tool in management of loss of response to biologic agents. Two situations are found in clinical practice, ie, primary non-responders and patients who lose their response over time (secondary loss of response). In the clinical trials, the primary non-response rate is 10%–40%, and clinical remission is not achieved in 50%–80% of patients. The results are better, at 10%–20%, in the clinical series. A higher proportion of primary non-responders is seen in patients with moderate-severe UC flare-ups than in those with CD.

The definition of primary non-response depends on the context in which it is evaluated. Trials establish a primary remission objective (variable, depending on the design), and primary non-responders are regarded as those patients who fail to reach this objective. In clinical series, primary non-responders are patients who fail to respond to two drug infusions on average. However, other authors consider that we cannot speak of primary non-response until the patients have completed full drug induction. Recently, aiming to unify criteria, another definition of primary non-response has been proposed, ie, lack of improvement in signs of active inflammation (objectively assessed at the start of the study) following the induction phase, despite the presence of adequate drug concentrations and the absence of antibodies against the drug. Although primary non-response to anti-TNFα drugs has been attributed to inflammation being caused through another pathway in such patients, Papamichael et al have suggested a more complex mechanism (factors dependent on the drug, the patient, the disease, and/or the treatment strategy used). Traditionally, it has been suggested that switching primary non-responders to a second or third anti-TNFα drug is effective in clinical practice. Knowing the plasma drug concentration and the anti-drug antibody profile in primary non-responders might offer clues to the origin of the lack of response.

Secondary loss of response has been defined as reappearance of clinical symptoms in patients found to be asymptomatic following induction, due to the inflammatory activity of IBD. Among responders to infliximab, 37% lose their response over the years, the annual loss of response rate being 10%. In the review by Ben-Horin et al, if loss of response is measured as need to intensify the anti-TNFα drug dose, the figures are in the order of 23%–46% for infliximab and adalimumab, respectively; in contrast, if the criterion used is suspension of anti-TNFα treatment, these range drops to 7%–25%. In this
situation, we must confirm that the gastrointestinal symptoms are effectively attributable to IBD, with the exclusion of other processes.\textsuperscript{67,68} Further, when using subcutaneous treatment, we must confirm patient adherence to therapy.

Production of anti-drug antibodies is influenced by the structure of the biologic drug, the immune status of the patient, the concomitant medication used, and the administration route and dose. Therapeutic drug monitoring and measurement of antibody levels are advised in order to establish a firm diagnosis of loss of response and optimize biologic treatment. This strategy has not been implemented in the guidelines. A strategy for optimizing response in secondary non-responders is shown in Figure 2.

Safety of anti-TNF\(\alpha\) drugs

Anti-TNF\(\alpha\) drugs can give rise to a range of adverse events, which require treatment suspension in 10% of cases.\textsuperscript{28} There have been reports of infusion reactions associated with infliximab (incidence 3%–17%), although such reactions proved to be serious in only 1% of cases.\textsuperscript{33}

Opportunistic infections are among the most important adverse events (3%). The TREAT and ENCORE registries\textsuperscript{70,71} found infliximab to be associated with a risk of such infections (odds ratio 1.43; 95% CI 1.1–1.84; \(P=0.006\), although neither infliximab nor IMM therapy increased patient mortality. In addition to use of infliximab, factors associated with the risk of severe opportunistic infections were reported to be severity of disease and use of prednisone and narcotics.\textsuperscript{72}

Melanoma is more frequent in CD patients treated with anti-TNF\(\alpha\) agents (odds ratio 1.3; 95% CI 1–0.1.6).\textsuperscript{33} Anti-TNF\(\alpha\) monotherapy has been associated with a discrete increase in the risk of lymphoma; this risk increases when such drugs are combined with thiopurines.\textsuperscript{24,33} Monotherapy is therefore advised whenever possible.

Anti-TNF\(\alpha\) drugs have been shown to increase perioperative complications, especially in CD.\textsuperscript{33} The large registries indicate that anti-TNF\(\alpha\) drugs are not associated with an increased mortality risk, although there have been recent reports of increased mortality in the elderly.\textsuperscript{28,70} These drugs are safe during pregnancy.\textsuperscript{9,10}

Ustekinumab

Ustekinumab is a fully humanized IgG\(\kappa\) monoclonal antibody targeted to the p40 subunit of interleukin-12 and interleukin-23, thereby blocking their biologic activity.\textsuperscript{73} CERTIFI was a randomized, double-blind, placebo-controlled Phase IIb study that analyzed the efficacy of ustekinumab.\textsuperscript{74} The results were statistically significant at an intravenous dose of 6 mg/kg versus placebo (39.7% versus 23.5%; \(P=0.005\)). For maintenance therapy responders were randomized to 90 mg subcutaneously every 8 weeks or placebo. The clinical response and remission rates were assessed in week 22. In total, 41.7% of patients treated with ustekinumab showed clinical remission versus 27.4% of those given placebo (\(P=0.03\)), while the clinical response rates were 69.5% and 42.5%, respectively (\(P<0.001\)). In those who responded to induction, ustekinumab was significantly superior to placebo in terms of both remission and response. The safety profile was found to be similar to that of other biologic agents. At present, a Phase III trial is in progress.\textsuperscript{75}

Integrin antagonists

Natalizumab

Natalizumab is a humanized IgG4 monoclonal antibody targeted to the leukocyte integrins \(\alpha 4\beta 1\) and \(\alpha 4\beta 7\). ENACT-1 and ENACT-2 evaluated the efficacy of the drug in induction of remission and maintenance in patients with active CD.\textsuperscript{76} It was found to be superior to placebo in terms of response and remission, although statistical significance was not reached. ENCORE\textsuperscript{77} has demonstrated its efficacy in controlling active CD, particularly in patients with high C-reactive protein levels. Because of its association with progressive multifocal leukoencephalopathy,\textsuperscript{78} natalizumab has been used as a second-line molecule in CD refractory to therapy, including anti-TNF\(\alpha\) drugs, although it has not been approved by the European Medicines Agency.

Vedolizumab

Approved in 2014 by the US Food and Drug Administration and European Medicines Agency for the treatment of IBD, vedolizumab is a fully humanized monoclonal antibody targeted to leukocyte integrin \(\alpha 4\beta 7\). It selectively inhibits the binding of \(\alpha 4\) and \(\beta 7\) to MAdCAM-1. Since the drug does

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**Figure 2** Optimization strategy for non-responders to anti-TNF\(\alpha\).

**Abbreviations:** ADAs, anti-drug antibodies; TNF\(\alpha\), tumor necrosis factor alpha.
not interact with VCAM1, its action is exclusively confined to the bowel.79

Efficacy in UC

GEMINI-1\textsuperscript{80} has shown vedolizumab to be more effective than placebo in inducing and maintaining clinical remission in patients with active UC. In the induction phase (vedolizumab 300 mg intravenously at weeks 0 and 2), the clinical response rate was 47.1% versus 25.5% for placebo in week 6 ($P<0.001$). In maintenance therapy, the remission rate in week 52 was 41.8% in patients administered vedolizumab every 8 weeks versus 44.8% in the group administered vedolizumab every 4 weeks. In turn, 40.9% of patients receiving vedolizumab showed mucosal healing versus 24.8% of those given placebo ($P=0.001$).

Efficacy in CD

GEMINI-2 evaluated the efficacy of vedolizumab (at the same dose and schedule as in GEMINI-1) for induction and maintenance in patients with active CD.\textsuperscript{81} The results show superiority of vedolizumab versus placebo in terms of clinical remission in week 6 (14.5% in the vedolizumab group versus 6.8% in the placebo group: $P=0.02$); in week 52, of those who responded to induction, 39% and

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Figure 3 Therapeutic algorithm in Crohn’s Disease.

Note: *indicates low drug level without ADA.

Abbreviations: ADA, anti-drug antibodies; CDAI, Crohn’s Disease Activity Index; IMM, immunomodulator; TDM, therapeutic drug monitoring; TNF$\alpha$, tumor necrosis factor alpha.

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Figure 4 Therapeutic algorithm in ulcerative colitis.

Abbreviations: IV, intravenous; TNF$\alpha$, tumor necrosis factor alpha; UC, ulcerative colitis; TPs, thiopurines.
36.4% maintained remission (maintenance every 8 and 4 weeks, respectively) versus 21.6% of those on placebo (P < 0.001 and P = 0.004). GEMINI-3 study found that use of vedolizumab was not more effective than placebo in terms of induction of remission at week 6 in CD patients unresponsive to infliximab. In sum, the GEMINI trials suggest that vedolizumab is an alternative treatment for patients with CD or UC.

The safety profile was found to be acceptable, with no cases of progressive multifocal leukoencephalopathy, although longer-term studies are needed in this respect. The therapeutic algorithms for corticosteroid-refractory IBD are shown in Figures 3–5.

Stem cell therapy

There are two types of stem cell therapy that can be used in IBD, ie, autologous or allogenic hematopoietic stem cell transplantation (HSCT) and mesenchymal stem cells. Allogenic HSCT would correct the genetic defects of the immune system, but is not accepted for IBD due to adverse events.

Autologous HSCT has been used in severe CD for non-responders to medical treatment in whom surgery is unable to solve the problem due to localization and extent of lesions. The results have now been published for the randomized, controlled, Phase III ASTIC trial, which included patients with severe CD treated using autologous HSCT. The results indicate that HSCT appears to be effective in CD, achieving mucosal healing in 22.7% of patients, which was maintained on the following year. This treatment is not free of adverse events, so must be provided at specialized centers.

Mesenchymal stem cells have been used in IBD due to their reparatory and immune-modulating properties. A conditioning cytotoxic regimen prior to transplant is not necessary with mesenchymal stem cells. Evidence in UC is less consistent than in CD. It is difficult to draw conclusions because studies are not homogeneous with regard to cell type or the doses administered. Mesenchymal stem cells are a safe therapy with no toxic effects or generation of ectopic tissue.

Disclosures

Martínez-Montiel, Casis-Herce, Gómez-Gómez, Masedo-González, Yela-San Bernardino, Piedracoba, and Castellano-Tortajada have no relevant affiliations or financial involvement with any organization or entity which has financial interest in this work. Martínez-Montiel, Casis-Herce, Gómez-Gómez, and Yela-San Bernardino have acted as advisors to Abbvie, MSD, Shire, and Ferring. The authors alone are responsible for the content and writing of the paper. The authors report no other conflicts of interest in this work.

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