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TOPIC HIGHLIGHT

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Immunosuppressive therapies for inflammatory bowel disease

Talia Zenlea, Mark A Peppercorn

Talia Zenlea, Center for Women's Gastrointestinal Medicine, The Women's Medicine Collaborative, Alpert Medical School, Brown University, Providence, RI 02912, United States
Mark A Peppercorn, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, United States
Author contributions: Zenlea T primarily wrote the manuscript; Peppercorn MA primarily reviewed and edited it.
Correspondence to: Talia Zenlea, MD, Director of Inflammatory Bowel Diseases, Center for Women's Gastrointestinal Medicine, The Women's Medicine Collaborative, Alpert Medical School, Brown University, 146 West River St, Providence, RI 02904, United States. taliazenlea@gmail.com
Telephone: +1-401-7937080 Fax: +1-401-7937801
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Abstract

Inflammatory bowel disease (IBD) is comprised of Crohn's disease and ulcerative colitis, both chronic inflammatory intestinal disorders of unknown etiology characterized by a waxing and waning clinical course. For many years, the drug therapy was limited to sulfasalazine and related aminosalicylates, corticosteroids and antibiotics. Studies suggesting that the pathophysiology of these disorders relates to a disregulated, overactive immune response to indigenous bacteria have led to the increasing importance of immunosuppressive drugs for the therapy of IBD. This review details the mechanisms of action, clinical efficacy, and adverse effects of these agents.

Key words: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease; Immunosuppressives; Tumor necrosis factor inhibitors

Core tip: This manuscript reviews the current status of immunosuppressive therapy for inflammatory bowel disease. It describes the mechanism of action, clinical efficacy and adverse effects of immunomodulators including azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine and biologics including anti-tumor necrosis factor (TNF) agents and adhesion molecule inhibitors. It emphasizes the role of azathioprine, 6-mercaptopurine, and methotrexate in the long-term maintenance of Crohn's disease, the utility of cyclosporine in severe refractory ulcerative colitis and the unique role of anti-TNF agents in the remission induction and maintenance of difficult to treat patients with Crohn's disease and ulcerative colitis.

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INTRODUCTION

Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis, both chronic inflammatory disorders of the gastrointestinal tract, characterized by a relapsing and remitting course[1]. In the United States, the incidence of Crohn's disease is estimated to be between 6-8 per 100000, with a prevalence of 100-200 per 100000. The incidence of ulcerative colitis is estimated to be between 9-12 per 100000, with a prevalence of 205-240 per 100000[2]. IBD is associated with high health care costs, and can result in a significant quality of life burden. Unlike ulcerative colitis, which is limited to the mucosa, Crohn's disease typically causes transmural inflammation, and can result in stricturing and penetrating complications. The goals of therapy are two-fold, and include in-

duction and maintenance of remission, and avoidance of complications. Remission has traditionally been defined as the achievement of clinical remission, but a more recent trend has been towards achieving mucosal healing, or deep remission[3]. These goals are achieved through lifestyle modification, medical management, and surgery when necessary. Though the underlying etiology of these diseases remains poorly understood, it is thought that Crohn's disease and ulcerative colitis are driven by an inappropriate immune inflammatory response to gut microbes, in a genetically predisposed host[4]. The role of immunity is reflected in the focus on immunosuppressive medications in inducing and maintaining remission.

Though historically reserved for patients failing "conventional" therapies (such as 5-ASAs, antibiotics, and in some cases, steroids), immunosuppressive therapies such as immunomodulators and biologics are being used earlier in an attempt to alter the natural history of IBD[5]. Though corticosteroids are among the oldest and most effective therapies in IBD[6], their side effect profile limits their appeal[5], and maintenance of a steroid-free remission has become a key tenet of the management of IBD.

The purpose of this review is to summarize the available immunosuppressive options for the medical management of IBD.

IMMUNOMODULATOR THERAPIES

Immunomodulators include thiopurines [6-mercaptopurine (6-MP) and azathioprine (AZA)], methotrexate (MTX), and cyclosporine (CSA).

Thiopurine analogues

Crohn's disease and ulcerative colitis: Though for many years these medications have been widely used as steroid-sparing agents for the maintenance of remission in moderate-to-severe IBD, the data overall supporting their efficacy are limited and often contradictory, particularly in ulcerative colitis[7,8]. Older data have shown that thiopurines can be particularly effective in the long-term management of peri-anal and fistulizing Crohn's disease[9]. These drugs are not suited to the induction of remission[7], given a mean response time of 2-3 mo[10]. None the less, their use is widespread, and their role on the treatment pyramid well established[1,11].

6-MP and AZA are thought to act by inhibiting lymphocyte proliferation *via* the incorporation of active drug metabolites into cellular nucleotides, which likely results in anti-inflammatory effects through suppression of T cell function and natural killer cell activity[12,13]. AZA is the active pro-drug of 6-MP, and both are similarly converted to their therapeutic end-product, 6-thioguanine (6-TG), to the inactive metabolite, 6-thiouric acid, by xanthine oxidase, and to the hepatotoxic metabolite 6-methylmercaptopurine (6-MMP) by the thiopurine methyltransferase (TPMT) enzyme[1,13]. Lower doses may be needed in patients with intermediate TPMT enzyme activity in order to avoid leukopenia caused by high levels of 6-TG, and neither drug can be used at all in the 0.3% of the population deficient in the enzyme, due to the risk of life-threatening toxic complications[10]. Xanthine oxidase inhibitors can be used to boost response in patients who preferentially shunt towards 6-MMP. Testing for TPMT and measurement of both therapeutic and toxic metabolite levels are readily available in the United States, and can be used as an adjunct to routine monitoring of blood counts and liver function tests.

Dose-independent, or hypersensitivity, reactions have been described with use of 6-MP/AZA, and include hepatitis, pneumonitis, arthritis, and fever. Perhaps the most serious dose-independent reaction is pancreatitis, which can occur in approximately 4% of treated patients[14]. The reactions usually occur early in the course of therapy, and typically resolve with discontinuation of the medication. Minor side effects such as nausea, vomiting, and flu-like illness are possible, though thiopurines are typically well tolerated in 75% of patients using them[15]. Serious opportunistic infections are possible, as with any immunosuppressant, but uncommon[7,10]. With regards to the development of cancer, and in particular lymphoma, following the use of these therapies, a recent meta-analysis[16] concluded that IBD-patients on thiopurines have a 4-fold increased risk of lymphoma, but whether this increase was due to the medication or the underlying disease could not be established. These data were comparable to those from the CESAME group[17]. Moreover, this level of risk was well below what was deemed necessary to impart significant reduction in quality-adjusted life expectancy compared to other treatment strategies[11,18]. Ongoing and past exposure to thiopurines has been shown to significantly increase the risk of non-melanomatous skin cancers[19], and as such patients on these therapies should be advised to use adequate sun protection and have routine skin examinations.

There has been particular concern with regards to the association between hepatosplenic T cell lymphoma (HSTCL) and thiopurine use. HSTCL is a rare but fatal lymphoma, which appears to occur more frequently in patients with IBD as compared to the general population, though the absolute risk remains very low[20]. The risk of HSTCL appears to be higher in patients receiving thiopurines (both for IBD or for other reasons), and especially in those with long-term exposure[20]. A 2011 review[20] of all cases of HSTCL in IBD identified 2 other factors, male gender and age 10-35, as being associated with the development of HSTCL. Though combination therapy with thiopurines and anti-tumor necrosis factors (TNFs), particularly in this cohort of young males with IBD, has been postulated to portend an even high risk for developing HSTCL, this has not actually been demonstrated and is more theoretical, particularly since there were no cases of IBD patients treated with anti-TNF monotherapy who developed HSTCL. None the less, the authors concluded that combination therapy should be used in patients with IBD only when a clear benefit was expected[20]. Combination therapy is discussed in more detail below.

Methotrexate

Crohn's disease: MTX is a folic acid antagonist, and is thought to act by interrupting DNA synthesis and increasing adenosine[21], and by inhibiting interleukin (IL)-1 and suppressing T cell function. It's role in the management of IBD is much less well established than that of thiopurines. There is evidence to support the use of parenteral MTX in induction and maintenance of remission in refractory, steroid-dependent Crohn's disease[8]. There are no convincing data to support it's use in ulcerative colitis - the few studies that exist are limited both by size, quality, and the fact they used lower doses than what was shown to be effective in Crohn's disease (15 mg/wk *vs* 25 mg/wk)[8].

MTX is thought to be safe and tolerable. Nausea can occur in 15% of patients, but can typically be prevented with the co-administration of folate 1 mg/d. Leukopenia, hepatotoxicity, hypersensitivity pneumonitis, and opportunistic infections have been reported but are uncommon. MTX is teratogenic and should never be used in pregnant women or those contemplating pregnancy[8,13].

Cyclosporine

Ulcerative colitis: CSA is a calcineurin inhibitor, and is thought to act by decreasing pro-inflammatory lymphokines by inhibiting their antigen-induced secretion through the binding of calcium calmodulin-dependent protein phosphatase calcineurin[22].

The data with respect to the use of calcineurin inhibitors in IBD are very limited. CSA has proven to have promise in the induction of remission of refractory ulcerative colitis, but the data with regards to it's use in Crohn's disease are less convincing. Oral cyclosporine has not consistently been shown to be effective in the induction of remission of Crohn's disease (though one study showed a modest effect at higher doses)[23-25]. Uncontrolled data demonstrated some effectiveness in treating fistulizing Crohn's disease with parenteral CSA[26]. Studies in patients with refractory ulcerative colitis have shown that when used in the acute setting, as a bridge to thiopurine maintenance, CSA can be valuable in inducing remission and delaying or avoiding colectomy[27].

CSA is generally considered to be less safe than other IBD therapies, because of the risk of serious side effects, such as anaphylaxis, seizure, pneumocystis carinii pneumonia, and permanent nephrotoxicity[10]. Moreover, ease of use is limited by the need for close monitoring of drug levels due the narrow gap between the therapeutic and toxic ranges[27]. As such, CSA is typically reserved as a rescue agent for severe, refractory disease.

BIOLOGICS

Perhaps the most significant advance in the treatment of IBD has been the introduction of anti-TNF-alpha monoclonal antibodies, and subsequent biologic therapies, both for Crohn's disease and ulcerative colitis.

Infliximab

Infliximab (IFX) is a chimeric, monocolonal antibody (75% human, 25% mouse) that targets and binds to TNF-alpha, a potent pro-inflammatory cytokine thought to play a role in gut inflammation[28].

Crohn's disease: IFX was initially released in 1998 for the treatment of moderate-to-severe and fistulizing Crohn's disease, after it was shown to induce remission in a small, uncontrolled study of steroid-refractory patients[28]. These findings were later replicated in a larger, placebo-controlled study[29], where IFX was shown to induce remission in one third of steroid-refractory patients with luminal Crohn's. The landmark study that guides our current use of IFX as an induction and maintenance medication in luminal Crohn's disease is known as ACCENT I , which showed that the 58% of patients considered to be responders to an initial IFX infusion were more likely to have a sustained remission after 1 year when maintained on q8 week infusions after an initial loading period[30]. Subsequent research has shown a benefit of long-term therapy at 5-years[31].

IFX has also been shown to be effective in treating fistulizing Crohn's disease, resulting in both complete closure of draining abdominal and perianal fistulae at 3 mo in 55% of patients receiving IFX 5 mg/kg (compared to 13% of patients receiving placebo)[32], and in the long-term maintenance of remission of fistulizing Crohn's disease in 36% of patients (compared to 19% in the placebo group) at week 54 follow-up (ACCENT Ⅱ)[33]. A recent small-scale retrospective study has shown IFX in combination with antibiotics to be safe and effective in treating phlegmons[34].

Ulcerative colitis: IFX has also been shown to have benefit in the treatment of ulcerative colitis, specifically when refractory to conventional therapies. The ACT-1 and ACT-2 trials[35] have shown that patients with moderate-to-severe active ulcerative colitis refractory to conventional treatment were more likely to have clinical response at weeks 8, 30, and 54 in the IFX group compared to placebo, and are less likely to have undergone colectomy by week 54[36]. Though some have argued for the earlier implementation of IFX therapy in less severe (*i.e.* moderate) ulcerative colitis[37], the use of IFX in ulcerative colitis has typically been reserved as third-line or rescue therapy.

Safety and tolerability: IFX is generally considered to be safe and tolerable, however a risk benefit analysis should be undertaken when considering it's use given the potential for serious complications. Using the ACCENT I trial data[30] as a fairly typical profile, 32% of patients were found to have had an infection requiring treatment by week 54, including 1 case of tuberculosis and 2 deaths from sepsis (out of 2863 treated patients). Development of a lupus-like syndrome was described though very rare, though the development of ANA and anti-ds DNA antibodies more common (up to 56% and 34% respectively). Antibodies to infliximab were detected in 14% of patients, and infusion reactions were much more common

in this group (16% *vs* 4%-6%). Infusion reactions were typically mild, and required discontinuation of drug in less than 1% of cases. Concomitant use of steroids and immunomodulators decreased the risk of infusion reaction. There was a 1% rate of development of malignancy, including lymphoma and non-melanomatous skin cancers. It is worth noting that data from the TREAT registry[38], a prospective analysis looking at the safety of IFX and other medications for Crohn's disease, taking into account confounding factors such as disease severity and use of other medications, showed that the risk of serious infection and death was no greater in patients using IFX *vs* immunomodulators, and the overall incidence comparable to that among all patients with Crohn's disease. In fact, the only independent risk factor for serious infection and death that emerged was the use of prednisone, and for serious infection alone was narcotics. Similarly though there does appear to be an increased risk of lymphoma among patients with IBD using IFX, this risk has not been quantified, and the role of confounding factors not fully understood[11].

Adalimumab

Adalimumab (ADA) is a fully humanized, recombinant monoclonal antibody against anti-TNF-alpha, and thus immunogenicity and the formation of antibodies is theoretically lower. Unlike IFX, ADA is administered subcutaneously. The safety profile of ADA is similar to that of IFX, which was discussed previously.

Crohn's disease: ADA has been shown to be effective in inducing[39] and maintaining[40] remission in IFX-naïve patients with moderate-to-severe Crohn's disease, those with loss of response to IFX[41], and in patients with fistulizing Crohn's disease[42]. Initial response rates are comparable between ADA and IFX - approximately one-third of naïve patients will achieve remission[30,39]. The effects with regards to healing fistulas were more robust for IFX[32,42]. Rates of mucosal healing in Crohn's disease were comparable with ADA and IFX[43]. Rates of antibody formation were significantly less compared to IFX[30,39].

Ulcerative colitis: ADA has also been shown to induce[44] and maintain[29] remission in patients with moderate-to-severe ulcerative colitis who have been refractory to conventional therapy with steroids, immunomodulators, or anti-TNFs, though the efficacy of ADA was lower in those who were not anti-TNF naïve.

Certolizuman pegol

Crohn's disease: Certolizuman pegol (CZP) is a humanized pegylated Fab fragment of an anti-TNF-alpha antibody. Because it does not contain an Fc portion like other monoclonal antibodies (such as IFX and ADA), CZP does not induce antibody-dependent cellular cytotoxicity. It is administered subcutaneously. It is only approved for the treatment of moderate-to-severe Crohn's disease, in patients with inadequate response to conventional therapies, and only readily available in the United States, Russia, and Switzerland. It has been shown to have a modest improvement in response and remission rates in moderate-to-severe Crohn's disease as compared to placebo[45,46], as well as with regards to fistulizing disease[47]. Rates of antibody development were comparable to those with IFX[30]. Since the lack of an Fc portion prevents the active transport of CZP across the placenta, there has been some preference for it's use in women of childbearing age, however timing of administration of ADA and IFX in the third trimester can be manipulated to reduce drug concentrations in the newborn[48]. It is generally advocated that biologic agents not be changed solely for this reason.

Natalizumab

Crohn's disease: Natalizumab (NZA) is a selective adhesion-molecule inhibitor. It is a humanized monoclonal IgG4 antibody against alpha-4-integrins, which are selectively involved in leukocyte transfer across the gut and brain. It has been approved for the treatment of moderate-to-severe Crohn's disease in patients who have been refractory to conventional therapies. Though initial studies looking at NZA in Crohn's disease were less promising[49], more recent, albeit smaller studies have suggested that it may be effective in induction and maintenance of remission in moderate-to-severe Crohn's disease[50], and in particular in patients who have lost response to anti-TNF therapies[51].

Use of NZA has been limited due to its association with progressive multifocal leukoencephalopathy (PML), a devastating demyelinating CNS infection caused by the reactivation of JC virus[52]. Because of this, it can only be prescribed in the United States through a restricted distribution program. JC virus antibody testing is available, but it's use controversial as a screening tool in patients at high risk of developing PML. The majority of normal individuals are seropositive for JC virus, and any immunosuppressed patients are at risk for *de novo* infection. Using JC viuria as a marker for latent infection with high risk of reactivation is promising, but more research is needed[53].

Promising therapies

Golimumab: Golimumab is a fully human anti-TNF therapy, administered subcutaneously. It was recently approved in the Unites States for treatment of patients with refractory ulcerative colitis based on phase 2 and phase 3 studies showing efficacy over placebo in induction and maintenance of remission. Further studies are needed before use of this medication becomes more widespread[54,55].

Ustekinumab: Ustekinumab is a fully human IgG1k monoclonal antibody that blocks biologic activity of IL-12 and IL-23, an inflammatory pathway thought to be linked to the pathogenesis of Crohn's disease[56]. A phase 2b clinical trial was recently published, and demonstrated improved rates of induction response to therapy among primary and secondary anti-TNF non-responders

compared to placebo, however failed to demonstrate significant improvements over placebo in actual induction of remission[56]. None the less, phase 3 data have not yet been published, and this drug remains promising.

Vedolizumab: Vedolizumab in an investigational, humanized monoclonal antibody that selectively inhibits migration of lymphocytes into the gut by exclusively targeting alpha-4-beta-7 integrin. By being more highly selective than other anti-integrin therapies, specifically NTZ, vedolizumab is not thought to carry the same risk of PML, though long-term data are extremely limited[57]. Though phase 2 data demonstrated a positive trend, vedolizumab was not shown to induce clinical response in Crohn's disease[58]. Results were much more favourable in ulcerative colitis, where vedolizumab was found to be superior to placebo in inducing and maintaining remission[59], however more studies are needed.

Combination therapy

Therapy with anti-TNF-alpha antibodies and other biologics is limited by loss of efficacy and antibody formation to the drug, underscoring the need for further research and development of novel therapies. Concomitant use of immunomodulators has been shown to decrease antibody formation and boost longevity of biologic medications. The landmark SONIC trial[60] compared efficacy and safety of IFX and ADA alone *vs* in combination for Crohn's disease. The primary end-point of corticosteroid-free remission at week 26 was achieved by approximately 56% of patients in the combination group, *vs* 44% and 30% in the IFX and AZA groups, respectively, and this significant difference persisted through week 50. There were also significantly higher rates of mucosal healing in the combination group, without any significant increase in infections.

With respect to ulcerative colitis, the UC SUCCESS trial data, available only in abstract form to date, demonstrated superiority of IFX and AZA compared to monotherapy with either agent in inducing remission, but did not show benefit of combination therapy over IFX alone in achieving mucosal healing. This cohort was only followed for 8 wk, so no conclusion can be drawn with respect to maintenance of remission[61].

CONCLUSION

Though the underlying genetic and molecular pathways responsible for the development and severity of IBD remain poorly understood, the therapeutic focus, particularly for more advanced disease, has been on immunosuppressive medications. The goal of therapy remains maintenance of a steroid-free remission, though striving for a deep remission with mucosal healing is becoming more standard. Advances in the understanding of the molecular basis of Crohn's and ulcerative colitis have led to the development of promising new biologic therapies, which will likely be studied further both as monotherapeutic agents, and for use in combination with immunomodulators.

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