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Impact of immunomodulatory therapy in chronic inflammatory bowel disease

Miguel Ángel Hernández-Delgado[1], Cinthya Zahidaly Castro-González[2] and Francisco Javier Bosques-Padilla[3*]

[1]Senior Medical Student, Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Mexico; [2]Gerente de Alineación de Procesos Clínicos, Hospital San José TecSalud, Monterrey, Mexico; [3]Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Dirección Médica Hospital San José, Profesor de Tiempo Completo, Facultad de Medicina, Universidad Autónoma de Nuevo León, Nuevo León, Mexico

Abstract

Patients with inflammatory bowel disease (IBD) are at high risk of side effects related to steroid use, and often enough, disease flares cannot be treated alone with them. Recent studies have tried to assess the effectiveness of immunomodulators and biological agents in maintaining or inducing remission. The fine balance between full clinical benefit and reduction of adverse events is kept only by constant medical evaluations and regular notice of complications. Thiopurines (such as azathioprine [AZA] and 6-mercaptopurine) and methotrexate (MTX) have been widely tested in the induction of remission or remission maintenance of IBD. While MTX is highly beneficial at inducing remission in CD, monotherapy in UC was proven not be effective at all. In addition to the former findings, MTX in combination therapy with biological agents has had unsatisfactory outcomes. In contrast to MTX, AZA has more substantial evidence supporting its use in moderate-to-severe IBD. AZA alone or in combination possess high efficiency in UC and CD. Despite the clear success of combination therapy with AZA or immunomodulators alone in IBD, the potential disadvantages are still vast, ranging from opportunistic infections to neoplasm proliferation. (IBD Rev. 2018;4:61-5)

Corresponding author: *Francisco Javier Bosques-Padilla, fbosques58@hotmail.com*

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Foreword

Inflammatory bowel syndrome (IBS) is composed of two different disease variants: Crohn's disease (CD) and ulcerative colitis (UC). This syndrome has an unknown etiology, but recent findings have enlightened the pathophysiological bases of IBS and many new pharmacological targets that modify the evolution of the disease. Recent therapeutic strategies include early administration of immunomodulators and the use of biological agents. This has brought many challenges in establishing adequate dosage, concerns about adverse reactions, proving the most effective combination of drugs, and the economic impact it may represent.

Corresponding author:
*Francisco Javier Bosques-Padilla
E-mail: fbosques58@hotmail.com

The combination of biological agents and immunomodulators has been beneficial in maintaining remission and reducing the deleterious use of steroids. The current problematic of this newer strategy lies in the fine balance of maximizing benefit of the more recent drugs versus reducing their side effects, the risk of neoplasia, and infectious events.

Steroids are the main drugs of treatment in IBS. It has been estimated that up to 20-50% of these patients will develop corticoid dependency or resistance. In both scenarios, immunomodulators help by regulating the immune system and inducing long-lasting remission. The term corticoid resistance refers to the incapability of steroids to manage the disease, and corticoid dependency refers to two or more upsurge of disease activity in a 6-month period that yields favorably to the administration of steroid or the incapability to withdraw steroids after two successful sequential episodes.

In this article, we will only discuss the role of thiopurines, methotrexate (MTX) alone or combined with biological agents in IBS. The utilization and usage of cyclosporine is beyond the scope of this article.

Combination therapy

It is known that the immunosuppressive therapy of IBS increases the risk of infection, either by colonization or reactivation of a latent one. In general, the absolute risk of opportunistic infections ranges from 0.5% to 30%, being virus the most common associated type of pathogen, specifically herpes virus or CMV. The most feared infection when dealing with IBS immunosuppression is related to *Clostridium difficile* infection since it is often hard to differentiate between disease reactivation and this pathology.

It is comprehended as combination therapy the use of biological agents and immunomodulators. This subject has been evaluated in clinical trials like the SONIC trial, which assessed whether combination therapy was superior to monotherapy in CD. The primary outcome was to induce a clinical remission with no steroid use at 26 weeks, defined by a CD activity index < 150 points. The combination therapy succeeded in reaching the primary outcome in 56.8% of patients, compared with monotherapy lower 30%. Besides, combination therapy showed less adverse reactions in comparison. The UC success trial addressed the same question, which, in turn, concluded similarly.

Interestingly, in either study or their both groups, an increased rate of infections was not seen. Moreover, it can be concluded that the use of combination therapy does not increase the infection rate any more than monotherapy drugs by themselves[1].

Although infection can be one of the more obvious complications of IBS pharmacological approaches, cancer risk and its incidence are a much more serious concern among physicians. IBS alone is a risk factor of intestinal and extraintestinal neoplasms. Thus, immunosuppressive drugs may potentiate this proliferation. Evidence suggests that anti-TNF agents do not raise the peril of neoplasm. Despite its benefits, there has been reported cases of non-Hodgkin lymphoma in biological agent users.

An important point to consider when choosing the combination therapy, independently of its obvious medical indication, is the economic impact of this novel drug. CD is much more expensive annually than UC, coupled with the costly biological agent's combination strategy may be as much as a 7-fold increase in expense. Minding the expense factor and that many patients, despite being 6 months in remission with combination drugs, will fail maintenance in the first 2 years after dropping infliximab (43.9% in the 1st year and 52.2% in the 2nd year). Thus, the imperative needs for biomarker follow-up to an early detection of treatment failure and disease reactivation.

Methotrexate in CD

Methotrexate is a dihydrofolate analog that blocks the synthesis of purines and pyrimidines, leading to a net increase in extra and intracellular adenosine. This promotes the

binding of adenosine to several immune cells receptors, and thus, a net modulatory effect on the inflammatory system. For this and many other reasons, methotrexate has become an increasingly fortuitous option for treating either corticoid-dependent or corticoid-resistant CD[2].

The capability of MTX to completely induce remission was calculated at adequate 25 mg was 90, 71, and 63% after 1, 2, and 3 years of use[3].

Methotrexate has been associated with many side effects including nausea, vomiting, increased susceptibility to viral infections, headache, increase in liver enzymes, and fatigue. It is necessary to withdraw methotrexate in up to 10% of cases due to the incidence of the former. One of the most feared complications from chronic methotrexate use is due to the hepatotoxic properties and concurrent hepatic fibrosis that it generates. Although this is more prevalent in patients that also have > 100 g/week alcohol consumption, it remains in up to 20% of alcohol consumption free patients. Many of the other side effects associated with the use of methotrexate are related to the teratogenic potential of this drug, leading to the imperative need for the discontinuation of the drug for at least 3 months before conception. Furthermore, its use is absolutely contraindicated in pregnancy[2].

Since MTX has a high albumin binding, increased toxicity may be seen with concomitant use with sulfonamides or tetracyclines due to the displacement of MTX. Many factors have been associated with MTX toxicity including preexisting liver disease, low serum folate levels, low serum albumin, excessive alcohol, and impaired kidney function[3].

Despite the many inconveniences of using methotrexate, it also provides many practical perks when treating CD. The RCTs in which the drug were studied used 25 mg/week dose for treating CD and 15 mg/week for the maintaining dose. In other autoimmune diseases such as rheumatoid arthritis, the standard dose of methotrexate is usually around 7.5 mg/week. This is an important point to consider depending on the expertise of the practitioner, primarily because of the overwhelming toxicity of the drug.

It has been noted that the administration route has an important role when prescribing methotrexate. The oral route has an approximate 80% biodisponibility compared to the usual subcutaneous route. Another aspect to consider when giving an antifolate metabolite is the active replacement of folic acid, normally 10 mg/week should be enough to minimize the toxicity of the drug[3]. As of yet, it is uncertain how long should we prescribe MTX for IBS, but empiric regimens range about 3-4 years[2].

Methotrexate in UC

In contrast to the unequivocal success of methotrexate in CD, the evidence of its use in UC has been unappealing. It has been well described that the use of methotrexate can induce remission in corticoid-dependent CD but proof if its favorable impact in UC has led to the materialization of many international studies. A recent Cochrane meta-analysis showed that there is no difference between placebo and MTX groups in number of patients that maintained remission after 9 months. There is no support in recommending low-dose MTX (12.5 mg) in UC[4].

In continuation of the Cochrane results, the METEOR trial investigated the effectiveness of MTX with adequate 25 mg dose instead of earlier studies that proved no benefit from MTX but was attributed to an inadequate dosage of 12.5 mg. This study proved that MTX is not efficacious in patients with UC since the primary end point and 9 of the 10 secondary endpoints were not obtained[3,5]. MTX is not superior to placebo in inducing remission without steroids in UC when comparing with placebo groups[6].

Methotrexate in combination with anti-tnf agents

Adding an immunomodulator to biological agents prevents antibody formation and inactivation of its salutary revenue. Adding either azathioprine (AZA)/6-mercaptopurine (6-MP) or MTX rightly reduces this concern in a compa-

rable manner. This was proven by the COMMIT trial which demonstrated that the addition of MTX to infliximab decreased antibody formation[3]. The primary outcome was time to treatment failure and lack of steroid-free remission at week 14 or fails to maintenance of remission in week 50. The trial proved that combination therapy with MTX and infliximab was not more efficient than infliximab alone comparing the combination accumulative percentage of failure with 30.6 versus 29.8% infliximab monotherapy (leading to a p = 0.63)[7].

Thiopurines in CD

Thiopurines, AZA, and 6-mercaptopurine (6-MP) have had a history of over 40 years in the setting of IBS. It has been widely accepted as a key part IBS treatment for its efficacy in maintaining remission, lower cost, and oral route of administration. However, thiopurine use has been linked to increase in non-melanoma skin neoplasms, non-Hodgkin lymphoma and T cell hepatosplenic lymphoma[1].

The usual indications for receiving AZA are corticoid-dependent, refractory CD, fistulizing disease, and remission maintenance. A recent meta-analysis found that TPs have a disease-modifying role, at the expense of a slow onset of action, thus being unable to induce remission by themselves. However, they have been proven to be effective in maintaining remission in corticosteroid-dependent CD. Despite this fact, a recent meta-analysis found that AZA is superior than placebo therapy for inducing remission, 56% in the control group versus 21% in the placebo, 67 versus 56% at the 1 year mark of remission maintenance, and 56 versus 21% of the placebo group in the control of fistulizing/perianal disease[8].

Thiopurines in UC

Although TPs are no the first-line therapy in UC, AZA has shown better rates for steroid-free remission in corticoid-dependent UC than placebo, and superiority over placebo for maintenance of remission. Unfortunately, the limitations of AZA in severe UC relate to the prolonged latency period in which the drug is therapeutically effective, it may be up to 9 months. IV administration of AZA does not reduce the response time versus oral administration. The maximum pharmacological effect is produced in the first 3-6 months of use[1]. Five control studies with placebo and control groups have searched for the efficacy of AZA in UC. These results not always demonstrating AZA superiority in comparison to placebo. Conclusively, the widest retrospective series of UC patients that underwent AZA treatment showed remission maintenance up to 65% (total) or 24% (partial) of success, adding to a total of 84% of response rate[9]. The unresolved issues of AZA use in IBS are related to the unestablished time of administrations and dosage. At present, doses of 1.5 mg/kg/day for 6-MP and 2.5 mg/kg/day for AZA are being used, at the expense that some patients may not respond favorably, and the dosage has to be increased, which is related to the intrinsic metabolic variability of the individual patient. This renders the determination of the metabolizing enzyme; as thiopurine methyltransferase, can be used as avery important index for defining the appropriate drug dosage. The administration time of AZA ranges between 1 and 4 years, and it is likely that this timeline can be extended indefinitely. The non-evolving concern about thiopurines myelotoxicity and hepatotoxicity leads to a periodic 2-4-month checkup, and also close monitoring of skin neoplasia, at least yearly by one dermatologist.

Thiopurines in combination with anti-TNF

The combination of immunomodulators and biologics such as anti-TNF antibodies has proven to improve clinical outcomes and induce a long-lasting steroid-free remission[10]. The anti-TNF antibodies delay the disease flares by modulating the inflammatory response[11]. Randomized control trials have demonstrated that

giving anti-TNF monotherapy is effective at inducing and maintaining remission in UC and CD. However has been noticed in the setting of CD, patients treated with infliximab and AZA in combination, the drugs were more effective than each other aparts[12]. In UC, the only prospective trial of combination therapy showed that this regimen was more successful than either drug apart or a swift inductor of steroid-free remission[13]. Thus, the general consensus is to give dual therapy that includes a biologic agent plus AZA or methotrexate. Furthermore, in this modality of treatment with infliximab, there is a reduction on the probability of antibody formation and/or infusion-related complications, at the expense of higher risk of lymphoma, especially in the young male or elderly patients[11,14].

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