IBD REVIEWS REVIEW ARTICLE

Efficacy of combination therapy with anti-tumor necrosis factor and immunomodulators in inflammatory bowel disease

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Abstract

It has been shown that different approaches to the classic therapeutic pyramid for inflammatory bowel disease have different effects in clinical outcome. The early top-down strategy is nowadays the subject of diverse different studies and some controversy as it has been shown that the combination of immunomodulators and anti-tumor necrosis factors appears to be more efficacious than either therapy alone, but may also confer an increased risk of infection and malignancy. When to introduce the combined treatment, which patients would benefit from this decision, and the optimal dose of each agent when used in combination is not clear yet. Nevertheless, we do have several studies that help us, to the extent possible, make the best decision for each individual case. Here, we discuss and analyze widely the up to date evidence on the efficacy of combined treatment. We consider that taking into account the studies we have so far, combination of infliximab and azathioprine is more effective than either as monotherapy, especially in early diagnosed patients, as it is proposed in the top-down approach to the therapeutic pyramid. The fear of adverse effects originating from this approach should not stop us from using combined therapy when the individual case seems suitable for it. (IBD Rev. 2017;3:3-10)

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Introduction

Inflammatory bowel disease (IBD) is a chronic disorder, characterized by remissions and relapses, that encompasses two related but distinct conditions of as yet unknown etiology: Crohn's disease (CD) and ulcerative colitis (UC)[1,2]. Following great advances in the knowledge of the pathophysiology underneath IBD, in the year 1998, a new pharmacologic treatment option, biological agents, emerged at the top of our classic therapeutic pyramid (Fig. 1), added as a step between immunomodulators (IMM) and surgery. The use of these biological agents, especially the oldest and most studied anti-tumor necrosis factor (anti-TNF) infliximab (IFX)[3], is now a common treatment for IBD patients with diverse indications, where it has shown to induce clinical and endoscopic remission in both CD and UC and to decrease exacerbations and surgery rates[4], therefore bringing us closer to the final and historical intention of inducing and maintaining clinical remission and mucosal healing[5], and to the recent shift of stopping or even preventing disease progression through resolution of gastrointestinal inflammation[6,7]. Other anti-TNF agents have been approved for the treatment of IBD, including adalimumab (ADA), which has been shown to induce clinical and endoscopic remission in both CD and UC, and certolizumab pegol (CZP), which is approved for CD[4].

On the other hand, the experience with IMM in IBD has around seven decades of evolution[8]. The most widely used are thiopurines, azathioprine (AZA) and 6-mercaptopurine (6-MP), frequently as steroid-sparing agents for the maintenance of remission of moderate-to-severe IBD[9], and less commonly, methotrexate (MTX)[10]. The combination of biological agents and IMM is nowadays often used in different inflammatory diseases, like ankylosing spondylitis, psoriasis, rheumatoid arthritis, and IBD, when such combination is demonstrated to have greater efficacy with an acceptable safety profile compared to monotherapy with either conventional or biological therapy alone[11].

Regarding IBD pharmacological therapy, it has been shown that different approaches to the classic therapeutic pyramid have different effects on the clinical outcome. Until now, there are two different strategies that have been proposed besides the conventional step-up approach (thiopurines introduced in condition of corticosteroid dependency or refractoriness), which are early top-down strategy (combination of thiopurines and anti-TNFs) and accelerated step-up therapy (thiopurines started concomitantly with the first course of corticosteroids), as depicted in figure 1[12]. Certainly, the early top-down strategy is nowadays the subject of diverse different studies and some controversy, as it has been shown that the combination of AZA and anti-TNFs appears to be more efficacious than either therapy alone, but may also confer an increased risk of infection and malignancy[13]. When to introduce the combined treatment, which patients would benefit from this decision, and the optimal dose of each agent when used in combination is not yet clear. Nevertheless, we do have several studies that help us, to the extent possible, make the best decision for each individual case. The present review will widely discuss and analyze the up to date evidence on the efficacy of combined treatment.

Crohn's disease

In 2008, a two-year multicenter, open-label, randomized trial from Belgium, Holland, and Germany compared the effectiveness of the early use of combined immunosuppression with conventional management in patients with active CD who had not previously received glucocorticoids, IMM, or IFX. In this trial, 133 patients were studied and divided into two groups, early combination therapy and conventional treatment, finding that combination therapy appeared to be more effective than conventional treatment for induction of

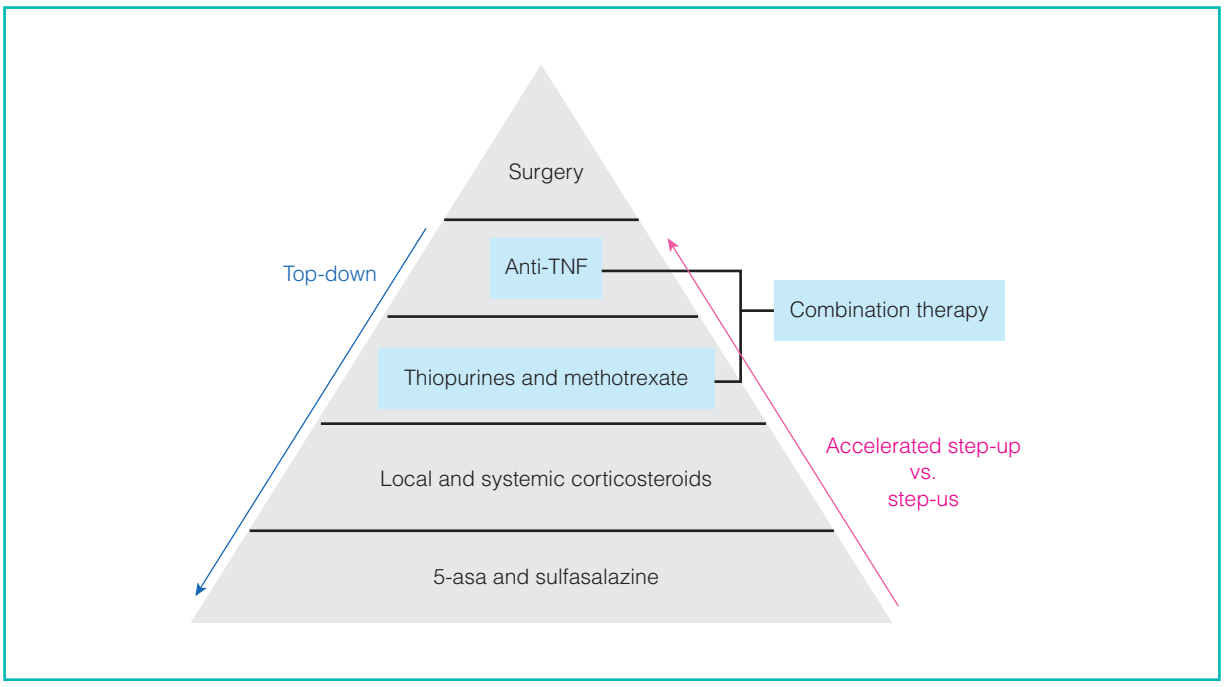

Figure 1. Classic inflammatory bowel disease therapeutic pyramid and its different possible approaches. 5-asa: 5-aminosalicylates; TNF: tumor necrosis factor.

remission and reduction of corticosteroid use, as at week 26, 60% of patients with combined treatment were in remission without corticosteroids compared to 35.9% of the conventional treatment group (p = 0.0062). It was also concluded that the combined treatment was more effective in inducing mucosal healing and lowering of C-reactive protein (CRP) concentration[12]. Subsequently in 2010, the Study of Biologic and IMM Naive Patients in Crohn's Disease (SONIC) trial was published, evaluating the efficacy and safety of combined therapy in 508 adults, naive to IMM and biological therapy, with moderate-to-severe CD, having as a primary outcome corticosteroid-free clinical remission. In this study, it was concluded that the combination AZA/IFX is more efficacious than IFX monotherapy with respect to mucosal healing (43.9 vs. 30.1%; p = 0.06) and corticosteroid-free clinical remission (56.8 vs. 44.4%; p = 0.02)[12,14,15]. Later in 2015, a *post hoc* subgroup analysis of this trial used 188 patients with ulcerations in baseline endoscopy, and found that at week 26, all composite remission rates for combination therapy (ranging from 52.3 to 63.6%) were significantly greater than those for AZA monotherapy (12.9 to 29.0%; p ≤ 0.013 for all comparisons), and that the composite remission measure of CRP normalization, mucosal healing, and clinical remission was achieved by a greater proportion of patients who received combination therapy (52.3%) compared to IFX monotherapy (25.6%). Those conclusions were further supported by stating that "deep remission", defined as the composite treatment target of clinical and endoscopic remission, is achievable with combination therapy in a high percentage of patients with early CD[6,16]. In addition, combination therapy in this context has also proven sustained benefit in patients with perianal CD fistula, where early clinical response associated with subsequent clinical remission and radiological healing appeared in patients treated with combination regimens, although less than half of them maintained healing after cessation of anti-TNF therapy[17]. The efficacy of combined treatment has also

been reported from the Australian experience with five active CD patients who lost response to anti-TNF therapy, in which addition of a thiopurine was an effective strategy to recapture response[18]. Additionally, the early combined immunosuppression for the management of Crohn's disease (REACT) study, appeared as a clustered randomized controlled trial from Belgium and Canada, where having as a primary outcome corticosteroid-free remission, early combined immunosuppression was surprisingly not more effective than conventional management for controlling CD symptoms, but interestingly, the early start of combination therapy favored a reduction in major adverse outcomes, such as surgery, hospital admission, or serious disease-related complications, compared to conventional management[19]. The regularly used doses in this context have been 5 mg/kg of IFX and 2.5 mg/kg of AZA.

In fact, the pediatric experience in this matter has also been reported. In a multicenter, randomized, open-label trial with 99 patients with CD, after 10 weeks of induction with combined therapy, 84 responders were further assigned to continue combined therapy or discontinue the IMM until week 26. In this study, although the vast majority of patients responded to combined treatment, after the maintenance phase the groups did not differ significantly in terms of clinical and endoscopic response, and only nine serious adverse events were documented, concluding, as almost all of the studies that have been made, that 26 weeks seems a safe duration of combined therapy[20]. These ideas have been replicated by other analyses, like the one of the American Gastroenterological Association, where it was concluded from their own analysis of some previously existing trials, that fewer patients fail to achieve remission with combination therapy than with AZA monotherapy (RR: 0.61; 95% CI: 0.52-0.73), and that the use of combination therapy reduces the number of remission failures associated with AZA therapy alone, with an overall high quality of evidence[21]. Although we have seen that most of the evidence supports the use of combination therapy in appropriately selected patients, we need to take into account other studies that have not concluded the same. For instance, a meta-analysis, where experts from different countries took into account randomized controlled trials in this context, concluded that overall, combination therapy was no more effective than monotherapy in inducing six-month remission, inducing response, maintaining that response, or inducing partial or complete fistula closure; additionally, in subgroup analyses of individual anti-TNF agents, combination therapy was not more effective than monotherapy in inducing six-month remission in those treated with IFX, ADA, or CZP[22]. These results should be interpreted with caution because, although this meta-analysis was published in 2015, it took into account trials published until 2008 and excluded those who included patients naive to anti-TNF and IMM therapy, which would support only the idea that continued use of IMM therapy after starting anti-TNF is no more effective than anti-TNF monotherapy in inducing or maintaining response or remission, which does not necessarily contradict the previously commented evidence.

Finally, the overall consideration of the studies made until now has allowed us to accept combination therapy as a good therapeutic approach in early diagnosed CD in well-selected patients. This has recently been strongly supported by Hirschmann and Neurath, taking into account the importance of identifying the correct candidates for top-down therapy, which, according to what we know until now, would be the ones who have several risk factors for a severe course of disease[23]. Combined treatment has also proved to be cost-effective compared to IFX monotherapy in the context of drug-refractory CD, and even the additional lymphoma risk of combination therapy, which will be discussed further on, has little significance on this cost-effectiveness[24].

Methotrexate in combination therapy

Other options have been evaluated for combination therapy, but results continue to support ADA, IFX, and AZA as the best pharmacologic agents to use in combination for induction and maintenance of remission of CD. When other IMM have been evaluated for use in combination, no better results have been found compared to AZA, as has been the case with the use of MTX[25]. Nevertheless, there are some cases in which MTX needs to be considered as an option as second-line therapy when thiopurines fail or AZA cannot be used for any reason; for instance, intolerance or lack of response[10]. The Combination Of Maintenance Methotrexate-Infliximab Trial (COMMIT) studied the effect of MTX on IFX when used in combination, but contrary to what has been described for combination with AZA, the study did not reveal a difference in clinical outcomes between combination MTX/IFX and IFX monotherapy[26,27]. The optimal dose that has been proposed for MTX when used in combination is > 12.5 mg/week as it is more effective than lower doses at maintaining clinical remission[28].

Adalimumab in combination therapy

Some studies have been done regarding other options for combination therapy; for instance, the use of ADA instead of IFX. Although ADA has been shown to be an effective therapy for CD, based on the idea that it often represents a challenging treatment as many patients need dose escalation and eventually discontinue treatment for loss of response, attempts have been made to use ADA in combination as a rescue therapy for preventing ADA discontinuation[29]. In this context, results have not been as supportive for combined therapy as they have been for IFX. In 2014, a meta-analysis concluded that IMM/ADA was mildly superior to ADA monotherapy for induction of remission in CD, where the rate of remission at one year and the need for dose escalation were similar to monotherapy[30]. As time has passed, results have not changed much as it has been shown by a recently published *post hoc* analysis of six randomized controlled trials that there are no efficacy benefits obtained with IMM/ADA combination therapy compared with ADA monotherapy in patients with inadequate disease control on conventional therapy[31]. A recent study evaluated precisely ADA and IFX as monotherapy or part of combination therapy, concluding that they have similar efficacy as initial combination therapy with an IMM; they both improve response rates, drug survival, disease activity, hospitalizations, and abdominal surgery. However, during subsequent therapeutic exposures there was a clear superiority for the use of IFX in combined therapy compared to other therapeutic modalities[32].

Ulcerative colitis

Regarding UC, less has been studied regarding combination therapy. It was not until 2014 that the SUCCESS trial studied 239 adult patients with moderate-to-severe UC, evaluating the efficacy and safety of combined treatment. It was concluded that the combined treatment was superior to IFX monotherapy in inducing clinical remission (39.7 vs. 22.1%; p = 0.017) and complete mucosal healing (29.5 vs. 11.7%; p = 0.006), taking as the primary end-point corticosteroid-free clinical remission at week 16 (instead of 26 weeks, as we saw used in CD trials). Subsequently, a *post hoc* analysis of SUCCESS was conducted to determine the proportion of patients who achieved a Mayo endoscopy subscore of 0 at week 16, and results were encouraging too as a greater proportion of patients treated with combination therapy achieved it compared to IFX monotherapy (29.5 vs. 11.7% p = 0.006)[33]. These results support the use of combination therapy in UC, consistent with what SONIC concludes, but also have some limitations, like the relatively small sample size and the limited time in which patients were followed-up. Hence, the use of combination therapy in the context of

UC should still be taken with caution because, besides SUCCESS, we have few other studies that evaluate the efficacy and safety of this type of therapy in this context, and we still need new trials that overcome the previously mentioned limitations. Nevertheless, the French experience with combined therapy sustained for at least six months in patients with UC and clinical remission was published recently. This was a multicenter retrospective study where 82 patients where included. Results support combination therapy as fewer clinical relapses were observed with combination therapy, and although no difference was observed for colectomy, when combination therapy lasted more than nine months, this was inversely associated with clinical relapse[34]. Efficacy of combination therapy was also evaluated in Italy where combination therapy with IFX/AZA was associated with a higher rate of steroid-free sustained clinical response in patients with steroid-dependent UC, and also revealed a favorable statistical trend of more benefit from the combination therapy for patients naive to thiopurines compared with exposed ones[35].

Regarding ADA as another option for combination therapy in the context of UC, results are, as in CD, not supportive for combination therapy as there has not been any demonstrated efficacy benefit of combining IMM/ADA compared with ADA monotherapy in UC patients with inadequate disease control on conventional therapy[31].

The effect of immunomodulators on the immunogenicity of anti-tumor necrosis factor

The effect of concomitant use of IMM on the pharmacokinetics and immunogenicity of anti-TNF biological therapies has been evaluated in patients with CD, finding that IMM have a small effect in CZP clearance, but in the case of IFX, concurrent IMM is associated with a 14% decrease[11]. In this context, there are some studies that assess the effect of combined IMM therapy on the presence of antibodies against TNF antagonists or anti-drug antibodies, which fortunately, according to a recent meta-analysis, are at decreased risk of developing when combined treatment is used with IFX/AZA[36]. This has also been studied, although to a lesser extent, in the case of combined therapy with ADA, in which case it has been proposed that in almost half of IBD patients developing anti-drug antibodies and, thus, loss of response to ADA, established immunogenicity can be gradually reversed by the addition of IMM therapy with restoration of a clinical and biological response[37]. The resulting outcome of IMM withdrawal has also been evaluated for CD/IFX combined therapy, concluding that this does not reduce trough levels of infliximab for at least six months[38]. In this context, it appears that MTX is equally effective as AZA in suppressing antibody formation and preserving higher IFX trough levels[27,39]. The latest information in this context confirms that in 77% of IBD patients with loss of response to anti-TNFs due to immunogenicity, addition of IMM results in undetectable anti-drug antibody levels, increased serum drug concentrations, and regained clinical response, and it has been recommended that this strategy should be considered in this patient population before switching to other agents[40].

In summary, although no definitive recommendation can be established yet, taking into account the evidence we have so far, combination of IFX and AZA therapy appears to be more effective than either monotherapy alone, especially in early diagnosed patients, practicing the top-down approach to the therapeutic pyramid. The benefit of this combination is probably due to both an improvement in anti-TNF pharmacokinetics (reduced immunogenicity and improvement in drug levels) and an independent effect of the IMM on disease activity, which are most important during the first 12 months of therapy, but may persist beyond that[13]. There should be great benefits of following this type of therapeutic approach in due

time in early diagnosed and well-selected patients to achieve corticosteroid-free remission, as we already know that corticosteroid treatment is a major source of morbidity that is independently associated with an increased risk of mortality[14,41]. The adequate selection of patients who would benefit from this type of approach continues to be difficult to define, but we know we should consider the patients' age-related risks[42], safety, and cost issues when considering long-term therapy[43], and according to the idea of selecting high-risk patients or moderate-to-severe clinical pictures in early diagnosed patients to identify some of the factors that have been described to predict high-risk of complications, like young age and extensive disease involvement in both UC and CD, deep ulcerations, ileal or ileocolonic involvement, perianal and/or severe rectal disease or penetrating/stenosing behavior in the case of CD, and frequent flare-ups needing steroids or hospitalization in the case of UC[44]. In agreement with Hirschmann and Neurath[23], we believe that the rapid evolution in the development and study of biological treatment agents and further studies needed in this respect[4] will surely modify in the future the top-down strategy as we know it today.

In conclusion, combination therapy, specifically AZA/IFX, is more effective than either monotherapy alone, specifically AZA/IFX, in well-selected patients who present potential risk factors for moderate-to-severe IBD. However, monotherapy with ADA seems to be as effective as the combined therapy with thiopurines.

More studies are needed in order to fulfill the still existing gaps regarding the adequate doses and best moments to initiate and discontinue this type of therapeutic strategy.

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