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Which patients with inflammatory bowel disease should receive combination therapy?

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Traditionally, patients with inflammatory bowel disease underwent 'step-up' therapy to induce a clinical remission. However, when step-up treatment is used, the more efficacious anti-TNF agents are reserved for patients unable to achieve remission with immune suppressants (IS). Several pivotal trials have demonstrated the superiority of early combination therapy of IS and anti-TNF to 'step-up' therapy and azathioprine or infliximab monotherapy. Concerns about treatment cost and adverse events of combination therapy have precluded widespread adoption of early combination therapy. Recent studies have demonstrated that combination treatment followed by withdrawal of IS or infliximab was not associated with an increased rate of relapse. Providers must include the benefits and risks of combination therapy in shared decision-making discussions with patients about to start treatment. Improved diagnostic and prognostic tests in the future are likely to help providers select the ideal patient for combination therapy.

The goals of medical therapy in patients with inflammatory bowel disease (IBD) are to induce clinical remission, maintain steroid-free remission, avoid short- and long-term toxicity of therapy, induce mucosal healing and prevent complications of the disease. Typically, patients with IBD undergo 'step-up' therapy. Less efficacious but potentially less toxic medications are started as a first-line treatment. If a response is not achieved, the medication is either adjusted or a new class of medication replaces or adds to existing therapy. This process is repeated until clinical remission is achieved. If a 'step-up' approach is used, the more efficacious anti-TNF α agents are reserved for patients unable to achieve clinical remission with immune suppressants (IS), such as azathioprine (AZA), 6-mercaptopurine or methotrexate (MTX).

Use of concurrent IS during anti-TNF treatment

In the early years of anti-TNF treatment for IBD, providers often continued the IS to prevent the development of anti-drug antibodies (ADA). Concurrent IS use has been shown to decrease the development of ADA; ADA are associated with infusion reactions and loss of response to treatment [1,2]. When infliximab (IFX) was the only anti-TNF agent available for treatment of Crohn's disease (CD), providers did everything possible to prolong the response to IFX. However, subgroup analyses of anti-TNF trials in CD demonstrated no improvement in clinical outcomes in patients on concurrent IS [3,4]. In addition, the major factor contributing to development of ADA was intermittent anti-TNF use [1]. Therefore, providers began to withdraw IS and continue monotherapy with an anti-TNF agent.

Several studies challenge this approach and provide compelling evidence to use the combination of an IS and biologic early in the treatment course. The first study compared two treatment approaches in patients with CD: 'step-up' or 'top-down' therapy. 'Step-up' patients received prednisone for active symptoms with a

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second course given for recurrent symptoms. IS were initiated at the time of the second steroid course. IFX was given for patients unable to taper steroids or for those intolerant of AZA. The 'top-down' group received three-dose induction therapy with IFX and AZA maintenance therapy. IFX was reinfused for recurrent symptoms; steroids were reserved for patients not responding to IFX. After 1 year of treatment, patients in the 'top-down' group were more likely to be in steroid-free remission and without surgical intervention. However, the outcomes were not different between groups after 2 years of follow-up. Importantly, in a subset of patients undergoing endoscopy at baseline and at follow-up, 'top-down' patients were more than twice as likely to achieve mucosal healing (73 vs 30%; $p = 0.003$) [5]. This study has been criticized because IFX was used only for induction without ongoing maintenance therapy, a practice uncommon in the USA. For example, a survey of members of the American Gastroenterological Association found that only 14% of gastroenterologists do not prescribe maintenance IFX therapy [6].

A prospective study compared AZA, IFX and AZA plus IFX in patients with CD that were newly diagnosed and naïve to IS or anti-TNF. AZA plus IFX was superior to either monotherapy strategy with 57% of patients achieving steroid-free remission and 44% achieving mucosal healing after 6 months. Importantly, there was no difference in adverse events between groups [7]. These findings were replicated in patients with ulcerative colitis with 40% of patients on AZA and IFX achieving steroid-free remission and 63% achieving mucosal healing [8]. A subsequent prospective trial compared the addition of MTX with IFX in patients with CD receiving steroids for induction of remission. The results conflict with the prior studies as the addition of MTX did not improve outcomes compared with IFX monotherapy. However, the latter study really compares combination therapy with steroids and IFX to triple therapy with steroids, IFX and MTX. In addition, steroid-free remission rates in this study were nearly 70% in both groups, confirming that combination therapy in some form or the other is a highly effective strategy [9].

Argument against combination therapy

So, why not treat all patients with combination therapy? First, this may result in overtreatment of patients with mild IBD that are unlikely to have progression of disease. Second, patients undergoing treatment with AZA and an anti-TNF are now susceptible to side effects from two drug classes (synergy of side effects). Short-term trials comparing combination therapy with AZA and IFX monotherapy have not shown increased rates of adverse events in the combination group [7,8]. This is not surprising because uncommon to rare adverse events are often not discovered during clinical trials. However, long-term retrospective and prospective series have demonstrated that the combination of AZA and anti-TNF is associated with a higher relative risk of opportunistic infection, lymphoma and nonmelanoma skin cancer [10–12]. For example, the risk of lymphoma is 3.6 per 10,000 patients treated with AZA compared with 6.1 per 10,000 in patients treated with AZA plus IFX [11]. Of particular, concern is the development of a hepatosplenic T-cell lymphoma (HSTCL), which predominately affects men less than 35 years of age on AZA and anti-TNF. HSTCL is almost uniformly fatal [13,14]. Third, combination therapy including early IS and anti-TNF use is more costly than either agent alone. Fourth, no prospective studies have evaluated whether using an anti-TNF alone with prospective monitoring of drug levels is as efficacious as concurrent therapy with IS.

Withdrawal of IS or anti-TNF in patients on combination therapy

Because of concerns regarding risks of long-term combination therapy, why not consider an approach with early IS and anti-TNF treatment with de-escalation of treatment over time? Several studies address this concept. In the 'step-up' versus 'top-down' study, patients in the top-down group did not receive maintenance IFX. Over the course of the study, only 15% of patients required IFX after induction therapy [5]. A prospective study compared withdrawal of AZA in patients with CD being treated with AZA and IFX in remission for at least 6 months. Patients were randomized to continue combination therapy or IFX monotherapy. During 2 years of follow-up, there was no difference in outcomes between groups. Interestingly, combination therapy patients had lower C-reactive protein levels and higher trough IFX levels compared with the IFX monotherapy group [15]. Another prospective study evaluated the outcomes after IFX withdrawal in CD patients treated with AZA and IFX. Overall, 44% of patients relapsed 1 year after IFX withdrawal. Eighty-eight percent of relapsing patients responded to reinfusion with IFX without sequela. The investigators found that several clinical factors predicted relapse after IFX withdrawal including C-reactive protein >5 mg/l, hemoglobin ≤14.5 g/dl, white blood cell count >6.0, fecal calprotectin ≥300 mcg/g, male gender and no prior history of surgery. When two or fewer of these factors were present, the risk of relapse was only 15% after IFX withdrawal [16].

Recommendations

So, what should the provider do? Combination therapy for every IBD patient? Only for high-risk subgroups of patients with IBD? A shared decision-making approach should be initiated with patients. The benefits and risks of 'step-up' versus 'top-down' approaches and combination therapy compared with anti-TNF monotherapy should be initiated in most IBD patients undergoing treatment for moderate to severe symptoms. Combination therapy should be a preferred strategy in patients with risk factors for disabling disease, complications or surgery. Risk factors in CD include young age at diagnosis, current tobacco use, perianal disease, small bowel involvement and multiple extraintestinal manifestations [17–19]. Combination therapy is the preferred strategy in ulcerative colitis patients requiring hospitalization at diagnosis, younger age at diagnosis, with derangements in laboratories such as sedimentation rate, and extensive colitis [20,21]. In young men, MTX can be substituted for AZA to decrease the risk of HSTCL. If a patient chooses to start combination therapy, how long is this

continued? It is reasonable to continue combination therapy for 6–24 months before having a discussion about drug withdrawal. Shared decision making is critical. Patients must be informed of the risks and benefits of stopping therapy. It is my practice to stop the IS as opposed to the anti-TNF agent.

In the future, these decisions should become easier as we develop better diagnostic and prognostic tests to determine optimal therapy (or combinations of therapy) for patients with IBD. This era of personalized medicine will take much of the guesswork out of drug(s) selection. We also anticipate prospective studies to determine whether combination therapy is superior to anti-TNF therapy with prospective monitoring of drug levels.

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