

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Step-Up Versus Top-Down Therapy in the Treatment of Crohn's Disease

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G&H Could you describe the standard step-up treatment algorithm for moderate to severely active Crohn's disease?

DH Historically, the step-up model of treatment for moderate to severe Crohn's disease has begun with a tapered dosing schedule of steroids, lasting 8–12 weeks. Although early introduction of immunomodulatory therapy is also recommended in these patients, clinicians do not generally follow this practice. If patients respond to the initial course of steroid therapy, they are taken off steroids and receive no further treatment until they experience a relapse. Upon relapse they receive another round of steroids. If there is a second relapse within the course of a single year, doctors may elect to introduce azathioprine or another immunomodulator (either 6-mercaptopurine or methotrexate). If the patient doesn't respond, they are prescribed the biologic anti-TNF- α agent infliximab (Remicade, Centocor). In a nutshell, step-up therapy consists of steroids, followed by the addition of immune modulation if steroids are not successful or cannot be weaned, and if still not successful, the final addition of infliximab. This treatment regimen reflects the labeled and recommended use for infliximab in the United States.

G&H What concerns, in terms of safety and efficacy, exist with the practice of step-up therapy?

DH Steroids are not 100% or even 90% effective. In moderate to severely active Crohn's disease patients, approximately 60–70% exhibit response to steroids. However, in the long run only a minority, approximately 45–50%, achieve true benefit from steroid therapy (even

with the introduction of immunomodulators) because a proportion of these patients will become resistant and others will develop steroid dependence. Still others will simply lose response. Clearly, from an efficacy standpoint, there is an unmet need for new induction therapy.

Further, the safety profile of long-term steroid use is extremely unfavorable. Patients, particularly young adults, are at risk for Cushing syndrome, the development of skin abnormalities, and early-onset osteoporosis. There are entire volumes devoted to the adverse events associated with steroids, and registry data have shown increased mortality in Crohn's disease patients treated with steroids alone. Finally, there are increasing amounts of data suggesting that steroids may induce disease resistance due to their antiapoptotic effect.

G&H How does the top-down strategy address the concerns associated with step-up therapy?

DH The top-down approach was developed for a number of reasons. First, given the limited efficacy and safety profile of steroids, the goal of developing an algorithm that did not include them at all seemed prudent. Conversely, infliximab has maintained a relatively safe profile over the years since its introduction. So far, its use has not been associated with malignancy. Moreover, if used properly, the risk of a serious infection is minimal and clinically acceptable. It therefore seems feasible to introduce infliximab earlier in the treatment algorithm. In addition, steroids are not associated with mucosal healing, whereas recent studies of infliximab have linked it to increased mucosal healing. Finally, and perhaps most importantly, there is the issue of inflammatory bowel disease (IBD) immunology. Recently, considerable insight has been achieved in the immune response specific for Crohn's disease. The lamina propria of patients contain T-lymphocytes that are resistant to apoptosis, and thus relatively insensitive to nonspecific medications like steroids. Infliximab is capable of inducing apoptosis of this subset of T-cells, and this has been associated with clinical response as well as mucosal healing.

G&H Can you describe the design of your study comparing step-up versus top-down therapy?

DH Ours was an open-label trial that could not be blinded at the time. However, it is important to note that we were not comparing different drugs; we were comparing different treatment algorithms. The algorithms in our two treatment arms were defined a priori so that in the step-up group, patients were treated with infliximab and in the top-down group, it was allowed that if patients were not responding to infliximab, they would be treated with steroids. Based on these assumptions, the trial was designed and powered with an adequate sample size and performed in a randomized fashion. The trial was executed at multiple centers in Belgium and the Netherlands.

We randomized 133 patients with a Crohn's disease activity index score greater than 220, diagnosed less than 4 years previously and never treated with glucocorticosteroids, immunomodulators, or infliximab. Patients in the top-down arm were treated with 3 infusions of infliximab at weeks 0, 2, and 6 and azathioprine 2–2.5 mg/kg daily. Step-up patients were treated with topical (budesonide 9 mg/day) or systemic (prednisone 40 mg/day) steroids. In the top-down group, relapse was treated with repeat infliximab infusions and glucocorticosteroids in the event of response failure. In the step-up group, azathioprine was added in cases of repeated need for glucocorticosteroids or steroid dependency and infliximab was only given after failure of immunosuppression. Patients were examined at weeks 0, 2, 6, 10, and 14 and every 3 months thereafter until month 24.

G&H What results and conclusions were derived from the study?

DH The primary endpoint of the study was remission, as defined by Crohn's disease activity index score less than 150, without steroid use and with no surgical resection necessary, at months 6 and 12. Secondary endpoints included overall treatment success (remission at week 14 and beyond, no resection, and no steroids or infliximab after week 14), mean Crohn's disease activity index scores, toxicity, and prolonged remission up to month 24.

Induction therapy was successful in 81% and 73% of top-down and in 60% and 67% of step-up patients at weeks 10 and 14, respectively. Remission without steroids or resection was attained in 60% of the top-down versus 41% of the step-up patients at 6 months and in 61% versus 50% at 12 months, respectively. At 6 months, 31% of patients in the step-up group were still receiving steroids (median dose 26 mg/day) compared with 0% for the top-down group; at 12 months, 17% of step-up patients remained on steroids (median dose 23 mg daily) compared with 0% for the top-down group. At 6 and 12 months 84% and 93% of top-down patients were using immunomodulators, versus 41% and 65% in the step-up group,

respectively. Overall treatment success was seen in 29% of the top-down and 5% of the step-up patients.

These results support our notion that step-up therapy is not efficient because most patients do not achieve remission in the first year. There were several significant differences between the two arms but the most striking was that 67% of patients in the step-up group were already treated with immune modulation after 6 months, meaning that they had failed the first two steps in the algorithm in order to achieve a remission. This shows that traditional step-up therapy is not effective and immediate use of immune modulation is advisable because two thirds of patients will be treated with it eventually, regardless of when it is introduced.

In regard to the top-down findings, this arm was designed as an induction regimen of infliximab at 0, 2, and 6 weeks only, because at the time, there was no awareness of the need for maintenance therapy to avoid the development of anti-infliximab antibodies. However, even with the use of the induction regimen with azathioprine cotherapy, there was a significant difference in success at the primary endpoints of 6 and 12 months. In addition, there was a trend toward decreased need for surgery in the first year in the top-down group.

Another important finding is that when these patients were followed up endoscopically at 2 years to assess the mucosa, there was a striking and dramatic difference in terms of mucosal healing and the development of ulcers, favoring top-down therapy. This supports the notion that early, effective, and specific treatment will favorably influence Crohn's disease outcomes.

G&H What other research is currently ongoing or in the planning stages to further validate the top-down approach to the treatment of moderate to severely active Crohn's disease?

DH Two major initiatives are required. First, the initial study results need to be confirmed in larger cohorts of patients before application in daily clinical practice. Second, research should be aimed at studying the effect of corticosteroids on tolerance induction. It is possible that steroids interfere with this process, thereby worsening the outcome of patients in the long run.

Suggested Reading

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