

Step Up vs. Top Down in IBD Approach

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Recently, in inflammatory bowel disease (IBD) management, other goals have been advocated, such as improving a patient's quality of life, reducing hospitalization and surgery, and mucosal healing. In the last 2–3 years, mucosal healing is the final and most important goal in IBD therapy.

The means to achieve these goals may differ depending on the clinical presentation. Similar to the heterogeneity of clinical presentation, the natural history of IBD is equally diverse and the ideal is to have tools to aid in the prediction of a severe disease course versus a more indolent type of disease, so that a more aggressive therapeutic approach can be instituted earlier instead of a more graduated approach [1,2].

Clinical parameters, largely derived from retrospective studies that predict a more aggressive disease course, include a younger age of disease onset, active smoking, extensive small bowel disease, deep colonic ulcers, perianal disease, and an initial need for corticosteroids [3,4,5].

The standard therapies for IBD available to a clinician include 5-aminosalicylates, sulfasalazine and mesalazine, corticosteroids, immunosuppressive agents, and monoclonal antibodies (MAbs), so called biologic agents.

Biologic agents have traditionally been used only after failure of, or intolerance to immunosuppressive therapy. In general, this escalating approach is referred to as “step-up therapy.” For many years it was the single approach for patients with IBD.

In last years, experts propose a more aggressive approach, the so-called top-down therapy. There is strong evidence, that a strategy of using more potent immunosuppressive therapies earlier, may be the optimal approach to therapy in properly selected patients [6].

The rationale for top-down therapy in IBD lies in the natural history of Crohn Disease (CD), particularly that of small bowel disease and those patients who require corticosteroids.

Patients progress in a stepwise fashion from inflammatory lesions (likely most amenable to therapy) toward irreversible structural disease, such as strictures and penetrating disease. This is why biologic agents, specifically TNF α antagonists, are used as the initial induction therapy, and this therapeutic paradigm has been referred to as a top-down strategy [5,7,8].

There is compelling evidence to substantiate this approach in Crohn Disease. Strong evidence comes from retrospective analyses of large randomized controlled trials of the anti-TNF agents such as the Crohn Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (the CHARM trial), which evaluated maintenance of response and remission to adalimumab, the PRECiSE 2 study evaluating maintenance of response and remission with certolizumab pegol in CD and the ACCENT-I trial evaluating induction and maintenance of response and remission with infliximab for adult CD.

Although the SONIC trial is not strictly top-down, it provides similar insight into the advantage of earlier use of an anti-TNF agent.

In Ulcerative Colitis (UC), one important long-term issue is the development of dysplasia, for which the presence of unchecked inflammation is a key risk factor. Therefore, earlier use of an agent known to exert a potent biologic effect and lead to mucosal healing could have a long-term benefit. Intervention earlier in the course of disease with effective therapy is likely to be more successful [7,8].

However, the best evidence for prevention of dysplasia currently exists for 5-aminosalicylates, and similar evidence is lacking for infliximab (ACT 1 and ACT 2) [9].

There are patients who have an accelerated disease course and would likely benefit from an earlier intervention, but the current tools do not allow reliable advance identification of these patients. Therefore, at present, there is little rationale for a top-down approach to managing UC. Further study is needed in this area of IBD management.

In the future management approach to IBD several critically important questions remain. Does top-down therapy and successful induction of mucosal healing require an ongoing biological maintenance or can it be withdrawn? Will this approach truly alter the natural history of CD in the long-term, or simply delay complications? Will this approach really heal this difficult disease? And maybe the most important question is “Will this approach be safe?”

Each answer leads to new questions, but it is clear that the management of IBD these days will continue to evolve and unprecedented progress seems imminent.

References

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