Crohn's disease therapy : step up or top down therapy

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Abstract

In most Crohn's disease scenarios a step-up approach has been used to initiate therapy according to disease severity. However, this approach has ignored the concept of inductive therapy followed by maintenance treatment to prevent relapse. It is apparent from clinical trials that the success of maintenance approaches will depend upon the inductive therapy. Furthermore, the step-up approach often results in steroid-dependent or refractory disease. The potential of aggressive initial therapy followed by step-down maintenance therapy affords the potential to modify the disease course, a possibility that has not been accomplished by current therapeutic algorithims. (Acta gastroenterol. belg., **2001**, 64, **189-190**).

Until recently, the concept of step-wise, or sequential therapy has been an empiric element of therapy for Crohn's disease. To date, most clinical scenarios in Crohn's disease have utilized a "step up" (or therapeutic pyramid) approach of adding therapies if and when patients are un-responsive to first-line, often less toxic approaches. This has been somewhat in contrast to ulcerative colitis where we have recognized the utility of sequential, acute and maintenance, therapies for several decades (1). However, in Crohn's disease the negative results from the maintenance phases of the National Cooperative Crohn's Disease Study (2) and the European Cooperative Crohn's Disease Trial (3) led to an era where maintenance therapy for Crohn's disease was, essentially, disregarded (4). Two factors have led to a reconsideration of the concept of sequential therapy for Crohn's disease. From a scientific standpoint we now have evidence-based data relating the potential for preventing or delaying relapse in Crohn's disease (maintenance therapy) (5). Secondly, the regulatory processes and authorities in North America and Europe have begun to recognize differing indications for approval and marketing of therapeutic agents for IBD based upon the status of disease activity (6).

However, the issue at hand is whether sequential therapy should follow a therapeutic pyramid similar to that proposed for rheumatoid arthritis where disease is treated according to disease severity and response to first-line agents and more potent ("disease modifying agents") are added-on for non-responders ; or, if the pyramid should be "reversed" using "disease modifying agents" first, followed by maintenance therapies to reduce clinical relapse. This consideration has increasing relevance as it is now recognized that all agents used to treat Crohn's disease are not effective in all phases of disease. In addition, steroid-sparing therapy and prevention of post-operative relapse are unique categories of maintenance treatment (4,5).

Active disease

In Crohn's disease the aminosalicylates are less efficacious than in ulcerative colitis but have been demonstrated to induce clinical remissions in patients with mild disease (9). Metronidazole and ciprofloxacin have had comparable benefits to either sulfasalazine (7) or mesalamine (8). In moderate to severe disease corticosteroids have been the standard inductive agents (5), whereas cyclosporine has also been effective either in combination with steroids or alone for fistulizing Crohn's disease (9). Most recently, the chimeric anti-TNF monoclonal antibody, infliximab, has also been demonstrated to be effective in the treatment of refractory Crohn's disease (10). After inductive (acute) therapy with any of these agents, withdrawal of therapy after acute treatment predictably leads to relapse (11,17).

Maintenance therapy

Maintenance therapy in Crohn's disease is complex due to the heterogeneity of the disease and therapies. Termination of acute therapy leads to relapse and continuation of corticosteroids do not prevent relapse despite a large proportion of patients who become steroid-dependent (5,12). Aminosalicylates have not been effective in the prevention of relapse of steroid-treated patients (13) but due delay relapse after surgical resection (14). Metronidazole has also been able to delay recurrence after resection (15) as does 6-mercaptopurine (16).

In steroid-dependent Crohn's disease azathioprine, 6-mercaptopurine (17) and methotrexate (18,19) have allowed steroid withdrawal while preventing recurrence of disease activity. It remains uncertain whether these immunomodifiers will maintain clinical remissions after inductive therapy with infliximab (11).

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Clinical-immunoinflammatory correlations

The drugs that are most consistently effective at inducing remissions in Crohn's disease (corticosteroids, cyclosporine) and, most recently, infliximab all impact upon proximal mediators of the immunoinflammatory pathways (20). These mediators include NF kappa β and the pro-inflammatory cytokines Il-1, Il-2 and TNF. In contrast, the more effective maintenance therapies (i.e. aminosalicylates) impact upon distal non-specific mediators such as prostaglandins, leukotrienes, platelet activating factor, and reactive oxygen species (21). The mechanisms of action for methotrexate and azathioprine are less understood but may be related to anti-inflammatory effects in the case of methotrexate (22) and reduction in long-lived circulating lymphocytes (NK cells) by azathioprine (23).

These observations provide speculative clues as to how future therapy can be staged in the future to alter the "natural history" of Crohn's disease. To do so requires the recognition that Crohn's disease is a chronic disease with both acute and chronic sequelae. To ameliorate or prevent the advent of chronic complications (fibrosis, stricture and possibly fistulae) it is logical that acute inflammation needs to be turned off. Long-term approaches should then be directed at prevention of amplifying events that regenerate acute inflammation. It is apparent that (in the absence of known triggering factors) targets for inductive agents are the proximal arms of immune activation including nuclear factors, cytokines or lymphocytoxicity (24). Maintenance agents are most likely agents that will prevent amplification of the early sequences of inflammation. In the future, as the immunoinflammatory sequences in Crohn's disease become elucidated, therapy may be directed at initiating events. Identification of the environmental triggers will afford another direct means of inhibition or prevention of activation. In the meantime, the ability to subgroup patients with specific disease genotypes and phenotypes is proceeding rapidly (25). Genetic markers with the potential to delineate phenotypic immune or inflammatory responses are becoming available. We can easily anticipate that sequential therapy will be defined in a pre-clinical state or at diagnosis rather than by the empiric basis by which our current approaches were derived and then tested in clinical trials.

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