

Novel and Future Strategies in the Management of IBD

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The primary goal of therapy in inflammatory bowel disease is the long-term maintenance of patients. A meaningful clinical benefit is the induction of remission (as defined by a CDAI less than 100 points accompanied by mucosal healing) and a reduction or, preferably, discontinuation of glucocorticoids. The introduction of novel agents has not only led to impressive new therapeutic opportunities in Crohn's disease but also resulted in uncertainty regarding their optimal use and possible side effects.

Although the exact nature of etiologic factors is still unclear the pathophysiology of intestinal inflammation has been explored in great detail: It appears that expression and secretion pro-inflammatory mediators including the cytokines tumour-necrosis-factor alpha (TNF- α), interleukin-1 β (IL-1 β), interleukin-6, interleukin-8 and interleukin-16 is upregulated in the intestinal lamina propria of patients with inflammatory bowel disease. Cytokines often activate transcription factors as part of their signalling pathway.

It appears that the balance between pro-inflammatory and contra-inflammatory cytokines (i.e. IL-10) is shifted towards a perpetuated inflammatory reaction of the mucosa. Direct anti-inflammatory approaches include an inhibition of pro-inflammatory cytokines [(i.e. monoclonal antibodies directed against TNF- α (infliximab, CDP571, CDP870, D2E7) or IL-12)]. Anti-TNF therapy is a powerful and novel utility inducing remission in 30-50% of previously refractory cases with Crohn's disease. Recently a long-term maintenance could be established by repeated dosing of infliximab. Several clinical questions regarding anti-TNF therapies are still unanswered: An investigation of long-term outcome of sur-

gical procedures after anti-TNF therapy in Crohn's disease appears important. The concomitant use of other biologicals or of antibiotics during therapy with anti-TNF agents deserves formal evaluation, too. Future studies should also evaluate step-up approaches (i.e. the current therapeutic algorithm in inflammatory bowel disease) in comparison with step-down strategies (i.e. that anti TNF therapies are used as a first line treatment soon after diagnosis), whether the long-term course of the disease could be altered.

Attempts have been made to interrupt the inflammatory cascade by systemic application of the contra-inflammatory cytokine IL-10. Beta-Interferon has been also introduced as an anti-inflammatory agent in the therapy of encephalomyelitis disseminata. It appears that β -interferon has anti-inflammatory effects in vitro and in vivo which include the induction of IL-10 as well as direct inhibition of immune cell activation. Recently, large placebo controlled trials in steroid refractory Crohn's disease and in ulcerative colitis have started to confirm the initial, positive results from placebo controlled, small pilot studies.

The development of clinical and molecular predictors (i.e. genetic markers) to identify patients likely to respond to certain targeted interventions or those having a reduced benefit/risk ratio, respectively is urgently needed. The experimental use of these novel therapeutic agents in trials does not only open a new avenues towards more effective therapeutic algorithms but also allows us to increase the understanding of the main pathophysiological processes which drive the intestinal inflammation in IBD.

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