Novel strategies for the treatment of inflammatory bowel disease

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Abstract
Crohn’s disease and ulcerative colitis are chronic inflammatory bowel diseases (IBD) of unknown etiology but demonstrate a rising incidence in many Western countries. The immunology of mucosal inflammation in both diseases is characterized by an overwhelming preponderance of pro-inflammatory cytokine expression with an apparent inability to adequately downregulate immune activation. With the development of defined immune interventions single steps in the immune cascade can be targeted and evaluated for therapy.

Key words: IBD, biological therapy, immunomodulatory therapy

Introduction
Crohn’s disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) of unknown etiology but demonstrate a rising incidence in many Western countries. Although little is known about inflammatory pathomechanisms which are specific to either CD or UC, a distinction between both diseases can often be made by typical clinical manifestations, endoscopic appearance or histologic characteristics. The immunology of mucosal inflammation in both diseases is characterized by an overwhelming preponderance of pro-inflammatory cytokine expression with an apparent inability to adequately downregulate immune activation. Moreover, it appears that CD does not describe a single clinical entity: the ability to develop certain disease characteristics (e.g. fistula or stenosis formation) varies between individuals and may be a constant characteristic not being altered in the natural course of disease. From clinical observations it can be therefore concluded that disease subgroups may exist which could be distinctly different in disease pathophysiology and treatment response. With the development of defined immune interventions single steps in the immune cascade can be targeted and evaluated for therapy. The aim of this article is to present a wide range of various strategies for IBD treatment according to different pathomechanisms presumably leading towards inflammation.

The management of growth failure in childhood inflammatory bowel disease
IBD present in childhood is around 1 in 4 patients with the majority at time of their pubertal growth spurt. Growth failure in IBD is characterized by delayed skeletal maturation and a delayed onset of puberty, and is best described in terms of height-for-age standard deviation score (Z score) or by variations in growth velocity over a period of 3-4 months. Growth failure is common at presentation in CD, but less common in UC. The etiology of growth failure is multifactorial. Poor nutrition and the consequences of prolonged corticosteroid use as well as the inflammatory process per se, with proinflammatory cytokines (e.g. interleukin (IL)-1beta, IL-6) contribute to the significant reduction in final adult height of almost 1 in 5 children [10]. Initially a prompt, where possible steroid-free, induction of remission is indicated. The ideal is then to sustain a relapse-free remission until growth is complete, which is often not until early adulthood. These goals can often be achieved with a combination of exclusive enteral nutrition (EEN) and early use of immunosuppressants. The advent
of potent and efficacious biological agents considerably improves the range of growth-sparing interventions available to children around puberty, although well-timed surgery remains another highly effective means of achieving remission and significant catch-up growth. Although there is clear evidence that exclusive enteral nutrition achieves mucosal healing, its effect on growth has only been assessed at 6 months. In contrast to corticosteroids, EEN has no negative effects on growth. Corticosteroids remain the key therapy responsible for medication-induced growth impairment, although the use of budesonide in selected patients may minimize the steroid effect on dividing growth plates. Immunosuppressants have become a mainstay of treatment in children with IBD, and are being used earlier in the disease course than ever before. However, there are currently no long-term data reporting better growth outcome if these agents are introduced very soon after diagnosis. In comparison, recent data from a large prospective trial of infliximab in children with moderate to severe CD suggested significant catch-up growth during the first year of regular infusions. The only other intervention that has documented clear catch-up growth has been surgical resection. Resection of localized CD, in otherwise treatment-resistant children, early in the disease process achieves clear catch-up growth within the next 6 months. There are no data available that growth hormone improves final adult height in children with CD. In conjunction with expert endocrinological support, pubertal delay, more common in boys, may be treated with parenteral testosterone if causing significant psychological problems. The optimal management of children and adolescents requires a multidisciplinary approach; Dedicated dietetic support, along with nurse-specialist, child psychologist, and with closely linked medical and surgical care will likely achieve the best possible treatment for children with chronic gut disease [3, 8, 10, 14].

**Pharmacological therapy**

Medical management of IBD includes two treatment strategies: induction and maintenance of remission. Conventional corticosteroids, although a mainstay of the acute treatment of IBD for many years, have many drawbacks, including a variety of side effects – particularly with chronic use. Budesonide appears to be relatively safe and at least moderately effective in inducing remission in active distal UC and CD. It may be used as an enema in active distal UC or as delayed release tablets in CD. However, budesonide is not completely free from steroid side effects, and may share in some of the toxicity of older corticosteroids, particularly when high dose budesonide is administered [16, 17]. Aminosalicylates, both oral and topical, have proven useful in managing mild-to-moderate active UC and mild active Crohn's disease, as well as in maintaining remission. Data from recent trials suggest that higher doses of mesalamine are generally more efficacious than lower doses. In addition, a combination of oral and rectal formulations may succeed when one route, alone, is not successful [16, 17]. The immunomodulatory agents azathioprine, 6-mercaptopurine, and methotrexate have been shown to be effective in the treatment of chronic bowel disease. Therefore, thiopurines (azathioprine and 6-mercaptopurine) are the most efficient and used immunomodulators in IBD; steroid refractoriness, steroid dependency, and long-term maintenance of remission for both UC and CD are their main indications. Methotrexate may be used in the same clinical settings as thiopurines in CD, but not in UC; however, this drug is a second-line treatment because of safety profile and economic costs [5, 16]. Cyclosporine, although effective as the main, rapid-acting, alternative in steroid-refractory UC and CD, is associated with many toxicities, and patients must be monitored closely in centers experienced with this agent. That is why, the drug is recommend to be used only as a ‘rescue’ medication in some severe IBD cases [6, 7]. Antibiotics have been used empirically for many years in the treatment of IBD. Larger clinical trials are warranted to explore the potential efficacy of antibiotic therapy. This has been accomplished with metronidazole in CD, and other antibiotic trials are underway at this time. The investigational agents, such as aloe vera derivative acemannan, several formulations of heparin, and both transdermal and intra-rectal nicotine acemannan have also shown variable degrees of promise as possible therapies for IBD [16, 17].

**Biological therapy**

The etiology of IBD has not yet been clarified but evidence indicates that a dysregulation of mucosal immunity in the gut of IBD causes an overproduction of inflammatory cytokines and trafficking of effector leukocytes into the bowel, thus leading to an uncontrolled intestinal inflammation. Such recent advances in the understanding of the pathogenesis of IBD have led to development of potential therapeutic approach to specifically inhibit the molecules involved in the inflammatory cascade. Major targets for such treatment are inflammatory cytokines and their receptors, and adhesion molecules [2, 14]. Therefore, biotechnology agents targeted against TNF, leukocyte adhesion, Th1 polarization, T cell activation or nuclear factor-kappaB (NF-kappaB) are being evaluated as potential therapies for the treatment of inflammatory bowel disease. In this context, the therapies already used include:

- TNF-alpha inhibitors: infliximab, CDP 571, etanercept, oncept, CNI- 1493 and thalidomide;
- inhibitors of lymphocyte trafficking: natalizumab, LPD-02 and ICAM-1;
- inhibitors of Th1 polarization: monoclonal antibodies for IL-12, interferon (IFN)-gamma and anti-IFN-gamma;
- immunoregulatory cytokines: IL-10 and IL-11;
- inhibitors of nuclear factor kappaB;
- growth factors: epidermal growth factor (EGF) and keratinocyte growth factor (KGF) [11, 13].

**TNF-alpha inhibitors**

Infliximab, an IgG1 mouse/human chimeric anti-TNF-alpha monoclonal antibody has become a standard therapy for CD and it is also likely to be beneficial for UC. The medicine is proved to lead to induction and maintenance of active and fistulizing CD but with the limit of the immunogenicity. Whereas
adalimumab, a humanized anti-TNF-alpha monoclonal antibody may be useful for the treatment of patients who lost responsiveness or developed intolerance to infliximab. Both of the medicines are currently the only biologic agents approved in Europe for the treatment of inflammatory CD, but other anti-TNF biologic agents have emerged, including CDP571, certolizumab pegol, etanercept or oncept. However, CDP-571 (a humanized anti-TNF-alpha antibody) and CDP-870 (a PEGylated anti-TNF-alpha antibody) are less immunogenic, showed some efficacy in induction therapy in CD but a rapid loss of response in maintenance therapy. Etaetanercept and oncept (soluble human recombinant TNF-alpha receptors fusion proteins) seem not to be efficacious in CD demonstrating no class-effect for anti-TNF-alpha compounds. Unfortunately, the administration of anti-TNF drugs has also been associated with serious side-effects, which have raised concerns on the application of these drugs in clinical practice [2, 4, 13, 19].

Inhibitors of lymphocyte trafficking

Lymphocyte-endothelial interactions mediated by adhesion molecules are important in leukocyte migration and recruitment to sites of inflammation. Therefore selective blockade of these adhesion molecules is a novel and promising strategy to treat CD. Therapeutic agents that inhibit leukocyte trafficking include natalizumab, MLN-02 and alicaforsen (ISIS 2302) has shown promising therapeutic results. Unfortunately, natalizumab, the most effective drug of this class, approved for use in CD in USA has recently been suspected to favor serious neurological complications. The selective blocking of migration of leukocytes into intestine also seems to be a nice approach. Interesting therapeutic trials are expected against adhesion molecules (ICAM-1). Antibodies against alpha4 integrin and alpha4beta7 integrin showed benefit for IBD. Antisense oligonucleotide of intercellular adhesion molecule 1 (ICAM-1) may be efficacious for IBD. Clinical trials of such compounds have been either recently reported or are currently underway [2, 13, 19].

Inhibitors of Th1 polarization

An imbalance of T helper cell type 1 (Th1) versus type 2 (Th2) polarization in favor of Th1 cell subsets appears to be a key pathogenic mechanism in chronic IBD, in particular in CD. The IFN gamma-inducing factor interleukin (IL)-18 acts in strong synergism with the Th1 polarizing cytokine IL-12. That is why the antibodies against IL-12 p40 and IL-6 receptor could be alternative new anti-cytokine therapies for IBD. Anti-interferon-gamma and anti-CD25 therapies were developed, but the benefit of these agents has not yet been established. Moreover, recent studies proves that IL-18 expression is increased in inflamed lesions of CD patients and neutralization of IL-18 in different models of experimental colitis resulted in a dramatic amelioration of disease severity. IL-18 and IL-1beta are cleaved and thereby activated by the IL-1beta converting enzyme (ICE). Activation of ICE also occurs during different types of infectious colitis, and ICE expression and subsequent release of IL-1beta and IL-18 significantly contribute to intestinal inflammation. Thus, inhibition of ICE represents an intriguing new target that requires further investigation in animal models [13, 20].

Immunoregulatory cytokines

It appears that the parenteral administration of IL-10, a contra-inflammatory cytokine, which downregulates immune activation in most immune and non-immune cells induces improvement in a high percentage of steroid dependent, chronic active patients with CD, similarly to infliximab. At present it is still unclear, how IL-10 needs to be administered. Studies using intravenous application of IL-10 lead to very promising results, whereas the subcutaneous administration induced a considerable less impressive therapeutic effect [20].

Inhibitors of nuclear factor kappa B

Recent studies provide evidence that IBD is associated with activation of nuclear factor kappa B (NF-kappaB) involved in regulating the expression of inducible nitric oxide synthase (iNOS) and proinflammatory cytokine genes. As theaflavin-3,3’-digallate (TFDG), the most potent anti-oxidant polyphenol of black tea, down-regulates NF-kappaB activation it was investigated if TFDG is beneficial in colonic inflammation by suppressing iNOS and proinflammatory cytokines. The results suggested that the TFDG, indeed exerts protective effects in experimental colitis and inhibits production of inflammatory mediators through a mechanism that, at least in part, involves inhibition of NF-kappaB activation (either by a direct inhibition of IkappaB kinase activity or on upstream events in the signal transduction pathway) [15, 21]. Furthermore, the ongoing studies report that not only TFDG but also other tested polyphenols such as geraniin or 5GG block phosphorylation of IKB from the cytosolic fraction, inhibit NFkappaB activity, and inhibit increases in inducible nitric oxide synthase levels in activated macrophages, which provide their anti-inflammatory and cancer chemopreventive effects [12, 15].

Experimental immunomodulatory IBD therapy

The present studies finally support the role of oxidative/nitrosative stresses and TNF-alpha in the pathogenesis of IBD. Therefore, the effect of a total extract from Ziziphora clinopoides (Kahlhotti), an Iranian folk herbal medicine, was examined in the prevention and control of experimental mouse IBD. The beneficial effect of Z. clinopoides (300 mg/kg) was comparable to that of prednisolone. It is concluded that Z. clinopoides inhibits acetic acid toxic reactions in the mouse bowel through inhibition of cellular oxidative stress. Proper clinical investigation should be carried out to confirm the same activity in human [1, 7].

Drug and surgical treatments rarely offer cure and often carry a high side effect burden. Dietary therapy is highly effective in CD. For these reasons, there is much interest in developing novel dietary treatments in IBD. Curcumin, a component of the spice turmeric, and an anti-inflammatory and anti-cancer agent, shows preclinical and clinical potential in IBD. Its mechanisms of action are unknown, but it is most likely correlated with the inhibition of the activation
of NF-kappaB and effects a reduction in the activity of p38 MAPK. The investigations show reduced p38 MAPK activation in curcumin-treated mucosal biopsies, enhanced IL-10 and reduced IL-1beta, which demonstrate dose-dependent suppression of MMP-3 in CMF with curcumin. Furthermore, they present that the agent is able to attenuate colitis in the dinitrobenzene sulfonic acid (DNB)-induced murine model of colitis. When given before the induction of colitis it reduced macroscopic damage scores and NF-kappaB activation, which was accompanied by a reduction in myeloperoxidase activity. In recent years, a large number of research papers have reported various pharmacologic effects associated with curcumin. These include inhibitory effects on cyclooxygenases 1, 2 (COX-1, COX-2), lipoxygenase (LOX), TNF-alpha, IFN-gamma, iNOS, and the transcriptional NF-kappaB, in addition to a strong anti-oxidant effect.

References


Conclusions

IBD is a chronic relapsing-remitting condition that affects millions of people throughout the world and impairs their daily functions and quality of life. While the etiology of IBD is not understood well, it appears to be driven by inflammatory cytokines such as TNF-alpha. Hence, there is a strong interest in agents that can block the generation or actions of inflammatory cytokines and seem to be highly promising as a novel treatment of IBD.

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