Biological therapies for ulcerative colitis

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Abstract

Biological therapies are being increasingly investigated for the treatment of inflammatory bowel disease. However, a great deal more study has been devoted to studies of Crohn's disease rather than ulcerative colitis. Ulcerative colitis, like Crohn's disease, represents an area of high clinical need, particularly for those patients who have disease inadequately responsive to corticosteroids and 5-aminosalicylates. The distinct anatomic distribution of inflammation in ulcerative colitis represents an important model for study, with the entire involved mucosa entirely accessible to endoscopy. In addition, there is an opportunity for local delivery of biologic agents in left-sided disease. Distinct pathogenetic factors in ulcerative colitis raise the possibility of therapies quite different from those used in Crohn's disease. This work describes the current state of knowledge regarding biological therapy in ulcerative colitis. The role of probiotic therapy, and studies of cytokine-directed therapies, therapies targeting adhesion and recruitment, and restitution and repair are described. (Acta gastroenterol. belg., **2001**, 64, **205-209**).

Introduction

In the present state of clinical trials in IBD, far less is known about the application of biologic therapies to ulcerative colitis than to Crohn's disease. Historically, therapies that have worked for Crohn's disease, but not for ulcerative colitis, have been the exception. The two diseases share many epidemiologic risk factors as well as clinical manifestations. Subclinical markers, such as discrepancies in serum ANCA or ASCA, and in histopathologic features, suggest that at least two distinct major forms of idiopathic inflammatory bowel disease exist, if not more. Therefore, it is reasonable to anticipate that, as biologic and non-biologic therapies become increasingly specific for distinct processes and factors, treatment, too, may become more specific to either Crohn's disease or ulcerative colitis. Conversely, attempts to reason backwards from the results of clinical trials with biologic agents in IBD toward suggestions of disease pathogenesis are fraught with difficulties. Human experiments fail for a wide variety of reasons, ranging from inadequate drug delivery, to misguided hypotheses about disease pathogenesis, to logistic reasons, such as factors beyond the control of the investigator that are internal to study sponsors. This article seeks to describe the current status of biologic therapies for ulcerative colitis.

Principles of ulcerative colitis therapy

The majority of patients with ulcerative colitis have mild disease, easily controlled and maintained by simple medications such as mesalamine or sulfasalazine. This accounts for approximately 65 to 85% of patients. 5-Aminosalicylates are useful both in the treatment of mild to moderately severe flares of ulcerative colitis, and for maintenance of remission. Among this group, the average patient yet may have a flare requiring corticosteroids every year or so, but with good response. The remaining 15 to 25% of patients have a pattern best described as chronically active, with persistent symptoms requiring treatment with immune modulators such as 6-mercaptopurine or azathioprine, or in the case of more severely symptomatic disease refractory to corticosteroids, cyclosporine. This minority of patients includes, as well, those who have recurrent symptomatic flare upon taper of corticosteroids, or what has been called steroid-dependent disease. It is reasonable to conclude that biologic response modifiers, which will inevitably be much more expensive than compound-based therapeutics, will be directed toward treating the 15% or so of patients who do not do well with currently available therapies.

Ulcerative colitis therapy as it exists now offers a few contrasts to Crohn's therapy. The distinct distribution of ulcerative colitis, with disease occurring in the rectum at minimum and progressing proximally to involve more of the colon, offers the opportunity for local delivery of therapeutic agents per rectum, a means of delivery not usually feasible in Crohn's disease. Some specifics of treatment also differ. In contrast to Crohn's disease, the use of antibiotics appears to be largely adjunctive. Metronidazole, ciprofloxacin and other antibiotics may be used to good effect in cases of mild to moderately active Crohn's disease. Antibiotics have been shown to delay relapse in Crohn's disease after surgical resection. In ulcerative colitis, the role of antibiotics is far less established, although a recent report has suggested that ciprofloxacin may have a steroid-sparing effect in ulcerative colitis. Methotrexate has been shown to be effective as a steroid sparing and maintenance agent in Crohn's disease, but similar evidence is lacking in ulcerative colitis. Defined diet also appears to be less of a factor in ulcerative colitis than in Crohn's disease. In Crohn's disease, the use of strict elemental diet or restricting the patient to nothing by mouth appear to be

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effective in reducing symptoms and in inflammation. In ulcerative colitis, in contrast, these maneuvers do not appear to alter the course of a flare. Unfortunately, since each of these therapies works at multiple levels by nonspecifically suppressing inflammation or the immune response, these relatively minor therapeutic differences do not greatly illuminate the choice of therapeutic targets for biologic agents. Would a more targeted approach, such as anti-tumor necrosis antibody, prove effective in ulcerative colitis as it has in Crohn's disease ? And if it did, would this implicate TNF in the pathogenesis of ulcerative colitis ?

Pathogenesis of ulcerative colitis

In most animal models of IBD Th1 responses predominate, in a fashion very similar to human Crohn's disease. These include models as diverse as TNBS colitis, scid mouse transfer of $CD45RB^{hi}$ T cells, interleukin-2 deficient mice and interleukin-10 deficient mice. In these models, interleukin-12 drives the process, and interferon γ secretion is elevated. Transforming growth factor β (TGFβ) production is low, but induction of TGFβ greatly diminishes Th1 responses in these models. The inflammation tends to be transmural.

In contrast, relatively few models are Th2 predominant. Such models include the T cell receptor α (TCR α) deficient mouse and oxazolone-induced colitis (1). In these models, interleukin-4 and interleukin-5 production is elevated, interferon γ is low, and the process can be inhibited through inhibition of interleukin-4. TGF β production is markedly elevated, though probably insufficiently so to alleviate the acute inflammatory response. This response, as in human ulcerative colitis, tends to be confined to the mucosa. However, human ulcerative colitis is incompletely consistent with a Th2 mediated disease, since IL-4 production is not elevated (2).

The diverse nature of the immune perturbations that culminate in either a Th1 or Th2-like response in the intestine suggest that the basis of human IBD may also be diverse, with a final expression as two main disease processes recognizable as Crohn's disease or ulcerative colitis. Therefore, attempts to identify and antagonize the basic antigenic determinants of ulcerative colitis may be less successful than approaches that are directed toward the common final pathway of Th2 determinants of response or more downstream processes such as adhesion and recruitment, or repair.

Probiotic therapy

Animal models of colitis have demonstrated that the resident flora modulates intestinal inflammation. Moreover, bacterial species and subspecies may vary not only in their pathogenicity, but in their beneficial effects, as well. Kruis *et al.* reported a double-blind comparison of E. coli strain Nissle 1917 (serotype O6:K5:H1 ; Ardeypharm GmbH, Herdecke, Germany), a strain reported to have beneficial properties, against mesalazine in the maintenance of remission in ulcerative colitis (3). A total of 120 patients were randomized to receive E. coli Nissle or mesalazine 500 mg three times daily for 12 weeks. Relapse rates were not different at twelve weeks (11.3% mesalazine, 16.0% E. coli Nissle 1917), and life table analysis of time to relapse was also similar, at 103 and 106 days, respectively. This study was limited, however, by relatively small treatment groups under study for relatively short periods of time to detect relapse. In addition, the dose of mesalazine used was relatively low, suggesting superior results might have been seen with more optimal dosing.

In a separate study, E. coli Nissle 1917 was compared to mesalazine 800 mg three times daily in the treatment of 116 patients with active ulcerative colitis (4). Patients were permitted to take other medications in stable doses, and all patients received a one-week course of oral gentamicin to suppress native E. coli flora. The study was designed to detect the superiority of mesalazine if mesalazine was up to 20% better than E. coli in suppressing relapse by 1 year, using a one-sided test of significance. Failure to achieve this amount of difference was accepted as equivalency of the two treatments.

The number of patients achieving remission was similar in the two groups : 75% with mesalazine and 68% with E. coli. The mean time to remission was not different for the two groups when a two-tailed test of significance was applied. The relapse rate at one year was 73% for the mesalazine group compared to 67% for the E. coli group. The mean duration of remission in the mesalazine group was 206 days versus 221 days in the E. coli group, also not statistically significant by two-tailed tests of significance (4). The authors concluded E. coli Nissle 1917 to be as effective as mesalazine in preventing the relapse of ulcerative colitis. This study should be interpreted with caution, however, since a much higher than expected proportion of patients relapsed than would normal be expected with mesalazine.

More clearcut findings have been achieved in the prevention of pouchitis with probiotic agents. Gionchetti *et al.* randomized 40 patients who had undergone ileoanal pouch construction after total proctocolectomy to receive a probiotic mixture (VSL:3, CSL, Milan, Italy) or placebo (5). The mixture included 3 strains of bifidobacteria, 4 strains of lactobacilli, and 1 strain of Streptococcus salivarius ssp. thermophilus (6). At 12 months of treatment, only 10% of patients treated with the probiotic preparation experienced an episode of pouchitis, compared to 40% among those treated with placebo (5). To the extent that pouchitis reflects the original disease process of ulcerative colitis, these results provide perhaps the strongest experimental evidence in support of a role for probiotics in the treatment of ulcerative colitis. Open label treatment of 20 patients with ulcerative colitis in remission maintained remission in 15,

without concomitant treatment with 5-aminosalicylate (6).

Interleukin-10

Interleukin-10 is a classic counterregulatory cytokine. This anti-inflammatory and immunosuppressive cytokine has direct effects on Th1 cells, inhibiting expression of interleukin-2 and interferon-γ and on activated macrophages. Interleukin-10 deficient mice develop an enterocolitis characterized by excessive Th1 response (7). Exogenous interleukin-10 is effective in preventing the onset of colitis in the IL-10 deficient mouse, as well as in the scid CD45RB^{hi} mouse model of colitis (8). Finally, IL-10 restores tolerance to the normal intestinal flora in mouse models where tolerance has been broken by rectal administration of the hapten TNBS (9).

Initial clinical trials of interleukin-10 in Crohn's disease provided evidence of activity. A pilot study in subjects with steroid refractory Crohn's disease examined the effects of five dose levels of IL-10 (0.5, 1, 5, 10, or 25 μg/kg) or placebo given as daily infusions for seven days (10). The rate of remission was higher among subjects who received IL-10 compared to placebo-treated patients. A second study explored the efficacy of interleukin-10 dosed subcutaneously for 28 days in patients with mild to moderate Crohn's disease not being treated with other therapies (11). Using very stringent criteria of remission, the placebo remission rate was 0%, compared to 29% for the 5 μg/kg/day dose. A third study in chronic active Crohn's disease, however, failed to demonstrate clear-cut efficacy, even with adjustment of the Crohn's disease activity index for the hemodiluting effect of IL-10 (12).

A randomized controlled trial of IL-10 in ulcerative colitis was also completed. Patients were assigned to 28 days of subcutaneous dosing with IL-10 at 1, 5, 10, or 20 μg/kg/day or placebo. A higher response rate was seen with doses of 5 μg/kg and higher, but the remission rate was not significantly different from placebo (13).

The preclinical rationale for treating a Th2-like disease such as ulcerative colitis with IL-10 may have been less than that for Crohn's disease. However, as noted above, ulcerative colitis does not neatly conform to a Th2 cytokine profile. Recent investigation casts IL-10 in a broader role as a regulatory cytokine, well beyond the distinctions of the classic Th1/Th2 dichotomy. Groux *et al.* (14) demonstrated that chronic activation of CD4+ T cells in the presence of IL-10 generates T cells characterized by low proliferation, high levels of IL-10 and interferon-γ, low levels of IL-2 and no IL-4. This subset was designated as the T regulatory cell 1 (Tr1) subset, and was shown to be capable of suppressing antigen-specific immune responses potently, and to inhibit colitis in the scid CD45RB^{hi} transfer model. Therefore, the role of IL-10 as a regulatory cytokine might have broad applications in the treatment of IBD, but might depend upon a more intimate delivery of the cytokine in the intestinal milieu. Innovative approaches to delivering IL-10 to the intestinal mucosa have included gene transfer (15) and bacterial secretion of IL-10.(16). In man, liposome mediated gene transfer of interleukin-4 and interleukin-10 is being attempted as a possible treatment for rectal Crohn's disease or ulcerative colitis (17).

Therapies targeting tumor necrosis factor

Therapeutic agents targeting tumor necrosis factor (TNF) have proven to be highly effective in Crohn's disease for the treatment of inflammatory symptoms and fistulizing disease. Elevated TNF has been found in the stool of children with ulcerative colitis (18), and ex vivo stimulation of lamina propria lymphocytes from individuals with ulcerative colitis results in excessive production of TNF (19). Generally, however, levels of TNF have been found to be lower in ulcerative colitis than in Crohn's disease. In the cotton-top tamarin model of ulcerative colitis, treatment with CDP571, a humanized IgG4 antibody against TNF, yielded a reduction in diarrhea, weight gain, and improvement in histologic scores (20).

CDP571 has also been tried in mild to moderate ulcerative colitis. Fifteen patients were enrolled in an open label study of single intravenous infusions of CDP571 at 5 mg/kg (21). Patients were monitored for response. Eleven patients had left-sided disease, four had pancolitis, and six were steroid-unresponsive. The mean Powell-Tuck score decreased from 6.7 to 4.6 ($p = 0.023$) by week 1, but increased slightly to 5.5 by week 2 ($p = 0.218$). The half-life of the agent was approximately 7 days. Reductions in erythrocyte sedimentation rate and C-reactive protein were also observed in the first 2 weeks. Sigmoidoscopic appearance was also observed to improve over two weeks. This study raised the possibility that TNF inhibition might prove a useful therapy for ulcerative colitis.

A randomized, double-blind, placebo-controlled study was begun, but not completed, with infliximab in the treatment of severe, steroid-refractory ulcerative colitis (22). Enrollment was terminated after the eleventh of 60 planned patients. Patients were assigned to placebo or to infliximab at 5, 10, or 20 mg/kg after having failed 7 days of corticosteroid therapy, the equivalent of 40 to 60 mg/day of prednisone, with at least 5 days of intravenous corticosteroid. Patients all had moderate to severe sigmoidoscopic changes extending to involve the left colon at minimum. All patients had a modified Truelove and Witts score of greater than 10. The primary endpoint was defined as treatment failure at 2 weeks : failure to achieve a Truelove and Witts score < 10 and a 5-point reduction in severity score compared to the baseline score ; increase in corticosteroid dose to > 60 mg per day ; the addition of cyclosporine or other immunosuppressive agents ; elective or nonelective colectomy, or death.

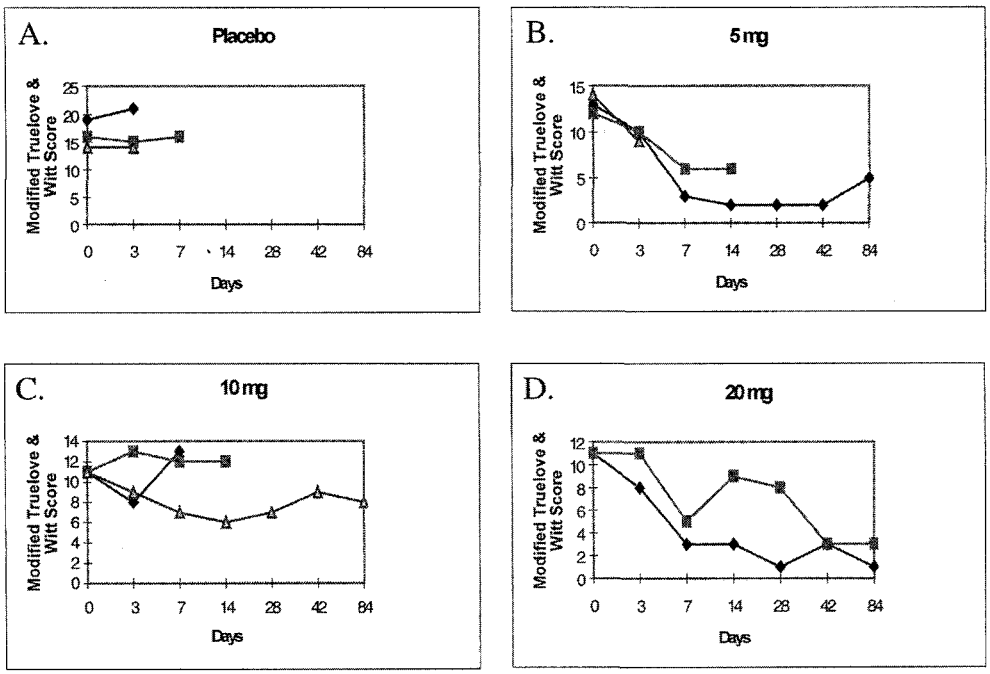

Fig. 1. — Treatment of severe, steroid-refractory ulcerative colitis with infliximab. Modified Truelove and Witts Scores over time (days), displayed by treatment assignment. A. Placebo ; B. 5 mg/kg ; C. 10 mg/kg ; D. 20 mg/kg. (Ref. 22).

Four of 8 patients who received infliximab were considered successes at 2 weeks, with no successes observed among the 3 patients assigned to placebo. (See Figure 1 for details of each patient's response). Improvement in erythrocyte sedimentation rates, serum concentrations of C-reactive protein, and interleukin-6 correlated with the clinical response among patients receiving infliximab. These results, though far from conclusive, suggested that infliximab might be beneficial in the treatment of ulcerative colitis. Definitive investigation remains warranted.

Therapies targeting adhesion

Adhesion molecules are critical to the amplification of the inflammatory response in IBD. Through a coordinated expression of adhesion molecules, the migration of large numbers of neutrophils, lymphocytes, and macrophages/monocytes is coordinated. ISIS-2302, an antisense oligonucleotide against ICAM-1 (intercellular adhesion molecule 1) has been tried in Crohn's disease (23), but a subsequent large randomized controlled trial did not demonstrate efficacy. Post hoc analysis of the results of this study have suggested that efficacy was observed in individuals in whom very high levels of oligonucleotides were observed. Therefore, strategies to deliver higher concentrations of oligonucleotide to the intestinal vascular endothelium, the presumed site of action, might yet prove effective. This raises the possibility that local delivery per rectum could prove effective in distal ulcerative colitis.

The preclinical data in support of anti-α4β7 approaches in IBD is strong, and rests upon the current understanding of the role of recruitment of activated lymphocytes and monocytes, in part through adhesion of the integrin α4β7 to MAdCAM in the mucosa. In the cotton top tamarin, the only existing primate model of ulcerative colitis, anti-α4 antibody proved effective in treating active inflammation (24). Similarly, an antibody specific for the integrin α4β7 was effective in the same model (25). Antegren is a recombinant humanized antibody against α4 integrins (26). Adults with active ulcerative colitis (defined as a Powell-Tuck score greater than 4) were given a single open label infusion of Antegren 3 mg/kg (26). Five of 10 treated patients had what was described as a good clinical response at 2 weeks, and one additional patient responded well by week 4. This study was extremely preliminary, but suggests activity in ulcerative colitis. It is possible that further dose exploration might optimize efficacy.

Restitution and repair

Given the dramatic epithelial disruption seen in ulcerative colitis, agents capable of promoting healing of the mucosa by direct effects on the epithelium could prove beneficial. Moreover, this represents an entirely novel mode of therapy. Studies in animal models have shown the beneficial effects of epidermal growth factor (27), transforming growth factor α (28), and keratinocyte growth factor (29).

Trefoil proteins are small peptides found highly expressed throughout the GI tract. Trefoil proteins interact with mucin glycoproteins to form the protective vis-

coelastic layer of the alimentary tract. In addition, trefoil proteins are highly expressed in a cell lineage that arises adjacent to ulceration (30). Mice deficient in intestinal trefoil protein have greatly increased susceptibility to injury and develop colitis (31). Trefoil proteins appear to be beneficial in treating animal models of colitis (32).

Conclusions

Although the state of knowledge of biological therapies for ulcerative colitis currently lags behind Crohn's disease, many promising therapies remain in various stages of therapy. Agents already approved for or being investigated for Crohn's disease are obvious choices for further investigation in ulcerative colitis. However, as more is learned about the etiologic differences between Crohn's disease and ulcerative colitis, biological therapies may become increasingly specific to each disease.

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