USE OF BIOLOGICS IN INFLAMMATORY BOWEL DISEASE - SHORT SYNOPSIS

Arvind Sangwaiya¹, Vijay Manglam², Jayantha Arnold³

INTRODUCTION

Ulcerative Colitis and Crohn’s Disease are frequently encountered disabling diseases collectively termed as inflammatory bowel disease. Ulcerative Colitis (UC) is characterized by diffuse mucosal inflammation limited to the colon. The extent of disease is often described as ‘distal’ and extensive disease. The ‘distal’ usually refers to involvement of rectum or recto sigmoid part of colon. The extensive disease usually includes ‘left sided colitis’-upto the splenic flexure, ‘extensive colitis’-upto the hepatic flexure or ‘pancolitis’ –involving the whole of the colon. Crohn’s Disease (CD) on the other hand is characterized by patchy transmural inflammation involving any part of the gastrointestinal tract. Crohn’s Disease may either be defined by its location like terminal ileal, colonic or ileocolic or by its pattern of disease like inflammatory, fistulating, strictureting. A minority of patients with Inflammatory Bowel Disease (IBD) have features consistent with both or some pattern suggestive of UC and other suggestive of CD. This is grouped as Indeterminate Colitis (IC) (1).

AETIOLOGY OF INFLAMMATORY BOWEL DISEASE

There are two broad hypotheses regarding the fundamental nature of the pathogenesis of IBD. The first hypothesis contends that the primary dysregulation of the mucosal immune system leads to the excessive immunological responses to normal microflora. The second suggests that the changes in the composition of the gut microflora and/or deranged epithelial

¹ Address for Correspondence: Dr Arvind Sangwaiya, Department Gastroenterology, Ealing Hospital NHS Trust, Uxbridge Road, Southall UB1 3HW, UK. E-mail: arvind.sangwaiya@eht.nhs.uk Tel: +44 208 967 5513 Fax: +44 208 967 5083
² Department of Gastroenterology, Ealing Hospital NHS Trust, London United Kingdom
³ Department of Gastroenterology, Ealing Hospital NHS Trust, London United Kingdom
barrier function elicit pathologic responses from the normal mucosal immune system. The recent studies done have concluded that the fundamental basis of IBD is indeed the presence of one or more genetically determined defects that result in the mucosal immune system that over reacts to the normal constituents of the mucosal microflora. It has been shown that regardless of the defect, the disease process is channelled into a final common immunopathological pathway comprising either a Th-1 type T cell mediated inflammation (Crohn’s Disease) or Th-2 type T cell mediated inflammation (Ulcerative Colitis).

This implies that, regardless of the nature of the fundamental defects, one can potentially treat IBD with therapy that addresses an essential element of the final common pathway. With this context, existing conventional treatments such as corticosteroids, 5-ASA’s and immunosuppressant’s aim broadly to block downstream inflammatory events such as the secretion of cytokines and the elaboration of immunocytes and neutrophils, regardless of the nature of the underlying T cell response that generated these events. These agents have sustained treatment of IBD for many years despite shortcomings and toxicities. Newer treatments strategies are being developed such as antibodies against TNF-α and α-integrin molecule that target the mechanisms of inflammation more narrowly by eliminating a specific major inflammatory cytokine or by disrupting accumulation of cells at areas of inflammation (2).

Therapy in IBD is rapidly evolving with many new agents being currently investigated that are bound to change the therapeutic strategy radically in the next decade. The use and scope of the conventional treatment with 5-ASA’s, corticosteroids, thiopurines (azathiopurine, 6-mercaptopurine), methotrexate and cyclosporine are beyond the scope of this article. While novel biological agents continue to be developed, most of the data till date is from the use of Infliximab (anti-TNF-α antibody). There is robust evidence for alternative anti-TNF strategies and monoclonal antibodies targeting adhesion molecules. Already anti-TNF agents have been shown to induce and maintain remission effectively in moderate to severe CD and UC. However despite the emerging data to suggest the use of biologics to modify the disease course, the data do not suggest the use of these agents as first line agents. Here we discuss novel therapies that specifically alter molecules in the inflammatory cascade. We discuss new biologic agents in the treatment of IBD (4).

TREATMENT STRATEGIES

The treatment with newer biological agents can be broadly divided into (3):

1. Inhibition of inflammatory cytokines
2. Inhibition of adhesion molecules
INHIBITION OF INFLAMMATORY CYTOKINES:

Current strategies in this group includes:

- inhibition of tumour necrosis factor (TNF)-Infliximab, Adalimumab, Certolizumab pegol
- anti-interleukin-12 p40 antibody- ABT-874, CNTO 1275
- anti-interleukin(IL)-6 receptor antibody- Tocilizumab
- anti-interferon-gamma antibody- Fontolizumab
- anti-interleukin(IL)-2 receptor (CD25) antibody –Daclizumab, Basiliximab
- antibodies to CD3- Visilizumab

INHIBITION OF TUMOUR NECROSIS FACTOR (ANTI-TNF-Α)

Infliximab (Remicade) is a chimeric anti-TNF-α monoclonal antibody with potent anti-inflammatory effects, possibly dependent on apoptosis of inflammatory cells. Treatment against TNF-α was first introduced in clinical practice in Oct 1998 in United States and since then it is one of the most widely used biologic treatments in both adults and children.

INDUCTION OF REMISSION IN CD EVIDENCE

It was first reported by van Dullemen et al that infliximab produced a rapid dramatic clinical and endoscopic improvement in 8 out of 10 patients with CD (5). The first placebo-controlled, randomized study involved 108 patients with CD, receiving single dose of infliximab (5, 10 or 20 mg per kg of body weight) or placebo (6). A clinical response was defined as a decrease in Crohn’s Disease Activity Index (CDAI) score of more than 70 points after 4 weeks. In the patients who received the 5-mg/kg dose, 81% (22 of 27 patients) responded compared with a 50% response (14 of 28) in the 10-mg/kg group, a 64% response (18 of 28) in the 20 mg/kg group, and a 17% response (4 of 24) in the placebo group. This clearly showed a significant difference between combined infliximab group compared to placebo group (p<0.001). Clinical remission (CDAI score ≤150) was achieved in 33% of patients treated with infliximab as compared to 4% in placebo. Further clinical
improvement was maintained for 12 weeks in 41% of patients ($p \leq 0.005$). Concomitant medication use (immunosuppressive agents, 5-ASA’s or corticosteroids) and disease localization did not have any influence on response to therapy, and the dose of 5 mg /kg of body weight was most effective (6).

**MAINTENANCE OF REMISSION IN CD EVIDENCE**

The use of infliximab in maintenance and remission has been studied in various randomized, double blind, multicenter, placebo-controlled, parallel-group trials. It has been concluded that a dose induction regimen at weeks 0, 2, and 6 is more effective at induction remission than a single-dose induction therapy and that the benefits of infliximab in CD could be maintained over long-term in patients treated with systemic maintenance therapy (6)(7)(8).

Infliximab treatment can cause formation of antibodies to infliximab (ATI). This in turn correlates to increased risk of transfusion reaction and during episodic therapy, with a shorter duration of response because infliximab concentrations are lower (9). The presence of higher concentrations of ATI (>8µg/mL) predicted a shorter duration of response (35 vs 71 days) and a 2.4-fold higher relative risk of infusion reactions than in patients with a lower concentration of absence of ATI (9). In ACCENT I, ATI were detected in significantly more patients treated with infliximab episodically than those treated with regularly scheduled maintenance dosing at 5 mg/kg or 10 mg/kg (30% vs 10% and 7%, respectively)(9). For this reason, along with the better efficacy results seen with maintenance therapy in the ACCENT I study, regularly scheduled maintenance therapy with infliximab every 8 weeks is the preferred treatment strategy (8).

An additional strategy for the prevention of ATI is the use of a concomitant immunomodulator. The role of concomitant immunotherapy with 6-MP, AZA, or methotrexate along with infliximab in the treatment of patients with CD is not well defined. In the ACCENT I study, 50% of the patients who received a concomitant baseline immunosuppressive maintained clinical response at week 54 compared with 41% of those not receiving such treatment, but this difference was not significant (10). Although 3 previously described studies have shown that concomitant immunotherapy reduces the risk of ATI (8)(9)(10) and 2 of the studies showed that the presence of high-titre ATI reduces the response to infliximab (9)(11). There is thus far no prospective study to compare the response and remission rates with infliximab in patients with and without concomitant immunosuppressive treatment. Although it is clear that in the treatment of patients with CD a single dose of infliximab without concomitant immunotherapy is immunogenic and is associated with a shortened duration of benefit, it is unclear if concomitant immunosuppressive therapy adds long-term benefit to regularly scheduled
dosing of infliximab (13). Likewise, it is unclear if infliximab can have a bridging effect to transition patients from corticosteroids to AZA or 6-MP, with the infliximab discontinued thereafter.

**FISTULISING CD**

There have been 2 randomized, double-blind, controlled studies that evaluated the efficacy of infliximab for treatment of patients with fistulising CD (13)(14). Present et al treated 94 patients with cutaneous fistulas, including 85 with perianal fistulas, with infliximab at weeks 0, 2, and 6 (5 mg/kg or 10 mg/kg) or placebo. Complete closure for 1 month was reported in 13% of patients receiving placebo but in 55% ($P = .002$ compared with placebo) of patients receiving infliximab 5 mg/kg and in 38% ($P = .02$ compared with placebo) of patients receiving infliximab 10 mg/kg(13). The median duration of remission was 3 months. In the second study (ACCENT II), maintenance therapy with infliximab in patients with fistulizing CD was studied. A total of 306 patients were initially treated with infliximab 5 mg/kg at weeks 0, 2, and 6, and responders subsequently were randomized to placebo or infliximab 5 mg/kg at 8-week intervals from week 14 until the end of the study at week 54. At week 14, 195 of 306 patients (69%) showed a response to the infliximab induction therapy with closure of at least 50% of the fistulas. The primary end point of this study was “time to loss of response to therapy.” The median time to loss of response was 14 weeks in the placebo group and 40 weeks on infliximab ($P < .001$). At week 54, 39% of patients receiving maintenance infliximab 5 mg/kg every 8 weeks and 19% of patients receiving placebo demonstrated complete closure of all fistulas ($P = .009$). Among the patients who had no response at the time of randomization to maintenance therapy, 16% of those patients who subsequently received placebo responded compared with a response in 21% of those patients who subsequently received infliximab ($P = .6$), suggesting that patients with fistulizing CD who have not demonstrated a response after a 3-dose induction regimen do not benefit from continued maintenance therapy. Thus, maintenance therapy should only be given to patients who respond to induction therapy. Among patients who initially responded to infliximab 5 mg/kg but subsequently lost the response, 57% responded to a higher dose of infliximab of 10 mg/kg (14). Based on the currently available data, it appears that continuous maintenance therapy with infliximab dosing every 8 weeks is necessary to maintain symptomatic remission of fistulas.
INFLIXIMAB IN ULCERATIVE COLITIS EVIDENCE

Five randomised controlled trials studying infliximab in UC have been reported (15, 16, 17, 18 19). The results of 2 larger randomized placebo-controlled trials, ACT 1 and ACT 2, were recently reported. In each of these 2 studies, 364 patients who were unresponsive to at least 1 standard therapy, including oral 5-aminosalicylates (ACT 2 only), corticosteroids, or immunosuppressants, were randomized to receive infliximab 5 mg/kg, infliximab 10 mg/kg, or placebo. Patients in ACT 1 were treated at weeks 0, 2, and 6 and then every 8 weeks through week 46, with evaluation at week 54 (20). Patients in ACT 2 were treated at weeks 0, 2, and 6 and then every 8 weeks through week 22, with the last evaluation at week 30 (18)(19)(20). In both studies, patients continued their immunomodulators and aminosalicylates throughout the trial, while corticosteroid tapering was allowed after week 8. In ACT 1, the clinical response rates at weeks 8, 30, and 54 were significantly higher for the groups treated with infliximab 5 mg/kg (69%, 52%, and 46%, respectively; \( P < .001 \) for infliximab vs placebo at all points). The \( P \) values comparing infliximab with placebo for the remission end point were all very highly statistically significant (\( P < .001 \) for all except the 30-week result for 5 mg/kg; \( P = .002 \)). Mucosal healing was seen after 8 weeks in 62% of patients receiving infliximab 5 mg/kg, 59% of patients receiving infliximab 10 mg/kg, and 34% of patients receiving placebo (\( P < .001 \) for both infliximab groups compared with placebo).

Taken together, the results of the ACT trials clearly establish the efficacy of infliximab in the treatment of active UC that has insufficiently responded to conventional therapies (18)(19)(20).

ADALIMUMAB IN CD.

Adalimumab (Humira) is a recombinant fully human IgG1 monoclonal antibody that binds TNF and, similar to infliximab, induces T-cell apoptosis. In the Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn’s Disease (CLASSIC) trial, patients who were anti-TNF naïve experienced significant response and remission rates when given adalimumab subcutaneously (160/80 mg) at an interval of 2 weeks (21). Clinical response (defined as a decrease in CDAI of at least 100 points) occurred in 50%, and 36% experienced clinical remission (defined as a CDAI of \( \leq 150 \) points). The CHARM (Crohn’s trial of the fully Human antibody Adalimumab for Remission Maintenance) study was a maintenance trial of adalimumab and enrolled both those who had been previously treated with anti-TNF therapy as well as anti-TNF naïve patients (22). CHARM showed that adalimumab, when given every other week to adalimumab responders, can maintain remission. At week 56, among anti-TNF naïve patients, 48%
were in remission, in contrast to 34% of patients who had been previously exposed to anti-TNF therapy. Additionally, adalimumab resulted in higher rates of corticosteroid-free remission and fistula closure at 56 weeks (22). The GAIN trial (Gauging Adalimumab effectiveness in Infliximab Non-Responders) showed that, among patients with moderately to severely active CD who were intolerant of or unresponsive to infliximab, 3 times as many patients who received adalimumab achieved clinical remission, defined as a CDAI of \( \leq 150 \) points at week 4, compared with placebo.

Adalimumab has not been studied, specifically in fistulizing CD, in children or among patients with UC. There is insufficient data to suggest use of Adalimumab in treatment of Ulcerative colitis.

CERTOLIZUMAB PEGOL IN CD

Certolizumab pegol is a pegylated Fab fragment of an anti-TNF monoclonal antibody. It does not have an IgG component and appears to function without causing T-cell apoptosis. It has been studied in two trials namely PRECiSE-1 and PRECiSE-2 in patients with CD. During the open-label induction phase, patients received certolizumab pegol 400 mg subcutaneously at weeks 0, 2, and 4. Responders, defined as those with at least a 100-point decrease in CDAI score (64.1%), were randomized in a double-blind manner at 6 weeks to receive certolizumab pegol or placebo maintenance injections every 4 weeks. Maintenance of response occurred in 62.8% at week 26 among the overall population as compared with 36.2% for placebo. Week 26 remission rates, defined as a CDAI score \( \leq 150 \), were 47.9% among the overall intention-to-treat group compared with 28.6% in the placebo group.

Certolizumab pegol has not yet been evaluated in fistulising CD, as a corticosteroid-sparing agent, in UC, or in children with IBD (23).

CONTRAINDICATIONS TO ANTI-TNF THERAPY

Contraindications to anti-TNF therapy are consistent across the class. Some of these include:

- Known hypersensitivity to agent, if severe
- Active infection
- Untreated latent tuberculosis
- Preexisting demyelinating disorder
- Moderate to severe congestive heart failure
- Current or recent malignancy, without advice from an oncologist
- Further treatment with infliximab is contraindicated when the patient presents with uncontrolled infusion reactions.
• Any anti-TNF should be discontinued when there is no response to induction therapy or when the duration of response decreases to an economically impractical time frame (less than 1 week with adalimumab, 2 weeks for certolizumab, or less than 4 weeks with infliximab).

ANTI INTERLEUKIN -20 P40 ANTIBODY
ABT-874

IL-12 plays a central role in Th1 development and is abundantly produced in the gut of patients with Crohn's disease (24). Anti-IL-12 treatment was shown to effectively ameliorate intestinal inflammation in several animal models of Th1-mediated colitis (25). Humanized immunoglobulin G1 monoclonal antibody against IL-12 p40 (ABT-874) was studied in a double-blind placebo controlled randomized study in 79 patients with active Crohn's (26). The patients were randomly assigned to receive seven weekly injections of 1 mg/kg, 3 mg/kg anti-IL-12, or placebo. The patients who received 3 mg/kg anti-IL-12 for 7 weeks showed a significantly greater clinical response than the patients treated with a placebo (75% vs. 25%). The rates of remission were also higher in the 3 mg/kg anti-IL-12 group (38%) than in the placebo group (0%) but the difference did not reach statistical significance. Anti-IL-12 therapy is therefore considered to be a safe and effective treatment for active Crohn's disease as no serious side effects requiring the discontinuation of the treatment were observed. Local reaction at the injection site was noted at a higher rate in the anti-IL-12-treated group. Anti-drug antibody was formed in some patients who received anti-IL-12 antibody.

ANTI INTERLEUKIN 6 RECEPTOR ANTIBODY (ANTI-IL-6 ANTIBODY)

Toctilizumab

IL-6 is one of the major inflammatory cytokines. Both IL-6 ligand and its receptor expression are increased in patients with active Crohn's disease. Humanized anti-IL-6 receptor monoclonal antibody was assessed in a randomized double-blind placebo controlled trial, which showed that biweekly MRA led to significant clinical remission (80% vs. 31% in the placebo) (27). Treatment was generally well tolerated without any significant side effect (3).
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ANTI –INTERFERON GAMMA ANTIBODY

Fontolizumab

IFN\(\gamma\) is a key pro-inflammatory cytokine that enhances the development of a Th1 immune response in Crohn's disease. Fontolizumab is a humanized monoclonal antibody directed against IFN\(\gamma\). A phase-2 study of fontolizumab in 133 patients with moderate to severe active Crohn's demonstrated efficacy after two doses, the second 56 days after the initial dose (28). This effect was most prominent in patients with elevated baseline concentrations of C-reactive protein. An additional study of fontolizumab in 45 patients with active Crohn's did not demonstrate efficacy at day 28 (29). Both studies showed fontolizumab to be safe with no significant side effects.

ANTI-INTERLEUKIN-2 RECEPTOR (CD-25) ANTIBODY

Daclizumab

IL-2 is a major T cell growth factor that promotes cell survival and proliferation. The IL-2 receptor \(\alpha\)-chain (CD25) is a component of high affinity IL-2 receptor and it is expressed on activated T cells. Daclizumab is a humanized monoclonal antibody to CD25, which blocks the binding of IL-2 to the IL-2 receptor. The initial open-label pilot study of daclizumab suggested that it was beneficial for patients with active ulcerative colitis (30), but a further randomized double-blind placebo-controlled trail has not shown any benefit (31).

Basiliximab

A chimeric monoclonal antibody against CD25B, basiliximab, blocks the binding of IL-2 to the IL-2 receptor. Two uncontrolled pilot studies suggested that basiliximab in combination with steroids may be effective for steroid-resistant ulcerative colitis (32,33), but further studies should be done to prove safety and efficacy.

ANTIBODIES TO CD-3

Visilizumab

Visilizumab is a humanized non-FcR-binding anti-CD3 antibody and works by inducing apoptosis if mucosal T lymphocytes in UC through activation of caspase 3 and 8 dependent pathways. It was evaluated in an open
labelled phase I study. 32 patients were enrolled who received visiliximab at a
dose of 10 or 15 microg/kg, administered intravenously on 2 consecutive
days. On day 30 84% of patients demonstrated a clinical response, 41%
achieved clinical remission and 44% achieved endoscopic remission.
Visilizumab had an acceptable safety profile at 10µg/kg dose level and may
be clinical beneficial in patients with severe intravenous refractory ulcerative
colitis (34).

INHIBITION OF ADHESION MOLECULES

The integrins are a family of cell-surface glycoproteins involved in the
adhesion, migration and activation of immune cells. They are up-regulated in
both Crohn's disease and ulcerative colitis. The α4 integrins are expressed on
lymphocytes usually exist in combination with a β-subunit and interact with
adressins expressed on endothelium. α4β1-integrin binds to vascular cellular
adhesion molecule 1 and α4β7-integrin binds to mucosal addressing cell
adhesion molecule 1. The interaction between α4β7-integrin and MAdCAM-1
is important in mediating lymphocytes homing to the gut mucosa.

The current strategies in this group are:

- Anti –α4-integrin antibodies: Anti-α4β1 antibodies
  (Natalizumab), Anti-α4β7 integrin antibodies (MLN-02)

ANTI-A4B1 INTERGRIN ANTIBODY (NATALIZUMAB)

Natalizumab, a humanized IgG4 anti-α4-integrin monoclonal antibody,
inhibits both α4β7-integrin/MAdCAM-1 interaction and α4β1/VCAM-1
binding. It was shown to effectively induce remission in a large placebo-
controlled randomized trial including 248 patients with moderate to severe
Crohn's disease (35). A large phase 3 study of natalizumab for induction and
maintenance treatment, ENACT-I (Efficacy of Natalizumab as Active
Crohn’s Therapy) was commenced (36). A higher proportion of patients in the
natalizumab group achieved a clinical response compared with those in the
placebo group throughout the study, although the differences were not
statistically significant (of note, the lack of significance may relate to the high
placebo response, which approached 50% throughout much of study). A
subsequent study, ENCORE (Efficacy of Natalizumab in CrOhn’s Disease
Response and rEmission), showed that among patients with elevated CRP
levels, natalizumab was superior to placebo in induction of response and
remission at all time points (37).

The ENACT-2 study showed that natalizumab effectively maintains
remission. Patients who received active drug experienced significantly better
remission rates at 6 months than those receiving placebo (44% vs 26%) (36); furthermore, natalizumab induced response in 54% of patients previously treated with anti-TNF therapy compared with 15% of placebo treated patients. Steroid-sparing benefits were also shown. Among those patients who attained sustained remission with natalizumab therapy, 42% were withdrawn from oral corticosteroid therapy at 60 weeks compared with 15% in the placebo-treated group (36).

The study and marketing of natalizumab were voluntarily suspended in February 2005 due to 3 reports of JC polyoma virus–related PML among natalizumab-treated patients, 2 with multiple sclerosis (36)(37). Given this development, patients must be informed of the possibility of PML. Furthermore, proposed restrictive labeling will limit the use of natalizumab to patients who are refractory to or intolerant of an adequate trial of immunomodulator therapy and anti-TNF therapy and for whom surgery is not an acceptable option. In addition, because of the risk of PML, natalizumab should not be used concomitantly with other noncorticosteroid immunomodulators or biologic immunosuppressive agents.

ANTI-Α4Β7 INTEGRIN ANTIBODIES

MLN02

A humanized anti-α4β7-integrin (MLN-02) blocks specifically the α4β7-integrin/MAdCAM-1 interaction. In a randomized placebo controlled trial in 185 patients with mild to moderately active Crohn's disease treated with placebo, MLN-02 led to remission significantly more than placebo (38). Furthermore, MLN-02 was shown to be efficacious in ulcerative colitis as well. In both studies, apart from one patient with infusion reaction and angioedema, no significant adverse events were noted. MLN-02 appears to be an effective therapy especially for active ulcerative colitis, but further trials are warranted to confirm the efficacy of MLN-02 therapy for IBD.

IMMUNOMODULATION

This group comprises of:

- Purine analogues: Azathioprine, 6-mercaptopurine
- Inhibition of lymphocyte proliferation: mycophenolate mofetil
- Calcineurin inhibitor: tacrolimus
- GM-CSF
Azathioprine and 6-mercaptopurines have been studied in various trials and have been found to be beneficial in active disease and maintenance of remission. The scope and breadth of the use of other agents is beyond the scope of this article.

**GM-CSF (SARGRAMOSTIM)**

Defective functioning of intestinal innate immune defense is thought to play a role in the pathogenesis of Crohn's disease (2). Breakdown of the intestinal defensive barrier, consisting of neutrophils and macrophages, may permit persistent exposure of lamina propria cells to luminal microbes and microbial products, resulting in a chronic inflammatory process mediated by T cells. Thus, treatment directed at augmenting the intestinal innate immune defense system rather than suppressing a secondary inflammatory response may be effective in Crohn's disease. GM-CSF, a myeloid growth factor, plays a pivotal role in the development and function of phagocytic cells. GM-CSF is used in glycogen storage disease type Ib, where neutropenia and IBD-like disease are dominant. A randomized placebo-controlled trial assessing GM-CSF (sargramostim) in 124 patients with moderate to severe active Crohn's showed no significant difference in the rate of clinical response defined by a decrease of at least 70 points in the Crohn's Disease Activity Index score on day 57, but it did show significantly decreased disease severity and improved quality of life in patients with active Crohn's disease (39).

**PREBIOTICS AND PROBIOTICS**

*Prebiotics*

Prebiotics are non-digestible dietary carbohydrates that stimulate the growth of endogenous protective enteric bacteria. This includes inulin and oligofructose. Randomized, placebo-controlled, double-blind crossover clinical trials have been done in patients with pouchitis and ulcerative colitis (40)(41). Taken together, the results support the hypothesis that prebiotics can offer an opportunity to prevent and mitigate intestinal inflammatory lesions in Crohn’s disease, ulcerative colitis and pouchitis (42).

*Probiotics*

Probiotics are living microorganisms or components of microbial cells which affect the host beneficially. This benefit may be direct or indirect, including enhanced barrier function, modulation of the mucosal immune
system, and alteration of the intestinal microflora and the production of antimicrobial agents.

The evidence for the use of probiotics in IBD is strongest in the case of pouchitis, particularly for the use of VSL#3. In addition, E. coli Nissle 1917 appears to be at least equivalent to 5-aminosalicylic acid treatment in UC and may be useful in the form of enemas for distal disease. However, studies of probiotics in CD have been disappointing, and a recent Cochrane systematic review (Rolfe et al. 2006) has concluded that their use could not be recommended on the available evidence. Prebiotics are frequently evaluated as part of a synbiotic combination, making it difficult to isolate their individual effects. However, few adverse events have been reported for either probiotics or prebiotics in any of these studies, confirming the safety of these treatments. At present, there is some evidence to support the use of probiotics and prebiotics in IBD, although large trials using standardised methodology are required to confirm this evidence. However, the investigation of the therapeutic application of these treatments increases understanding of the role of the gastrointestinal microbiota in the pathogenesis of IBD. With improved knowledge of the mechanisms by which the gastrointestinal microbiota determine gut immune responses, clinical research will be better focused to select appropriate investigational probiotic treatments and patient groups, and trial outcomes can be more meaningfully translated into clinical practice (43).

GROWTH HORMONE

Growth hormone has been studied in 18 patients with Crohn’s disease. The study demonstrated that growth hormone may be beneficial in the treatment of patients with chronically active Crohn's disease. However the study did not study whether growth hormone therapy would be beneficial at the onset of Crohn's disease (44).

CONCLUSION

The medical options available for treatment of inflammatory bowel disease is rapidly changing and newer therapies are being developed. There are many aspects of therapy with these agents for which the data is lacking or inadequate. Our aim as gastroenterologist is to improve treatment efficacy, reduce adverse effects and improve the quality of life of patients.
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