1. Introduction

The biologic approach to IBD therapy has developed in recent years as a result of a better understanding of specific immunopathological processes in intestinal inflammation. Advances in the development of biologic drugs were the result of two major findings, in basic research: 1) The ability to dissect immunopathologies in the intestinal mucosa up to the level of single molecules. The best example of such progress is the generation of sophisticated experimental models of inflammatory bowel disease such as knock-out and transgenic mice in which experimental colitis is exacerbated or ameliorated because of the lack or over expression of a single gene. Treatment strategies to decrease/neutralize or increase the concentration or effect of the protein encoded by that gene can be performed. 2) Advances in biotechnology now enable the insertion of genes into viral vectors so that targeted delivery of cytokines is possible, antisense oligonucleotide can be designed to hybridize with target RNA’s thus the expression of specific molecules can be decreased, commercial amounts of growth factors generated and humanized antibodies creating less immunogenicity can be engineered. 

There are several categories of treatments that are relevant to IBD such as 1) Anti-Tumoral Necrosis Factor alfa (TNF-α) antibodies; 2) Selective adhesion blockade; 3) Recombinant cytokines; 4) Growth factors; 5) Immunostimulation; 6) Nucleic acid based therapies; 7) Gene therapy; 8) Autologous bone-marrow transplantation; 9) Helminths, 10) Apheresis.

2. Anti-tnf alpha therapies

TNF-α mediates multiple proinflammatory signals that play a central role in the pathogenesis of IBD, including neutrophil recruitment to local sites of inflammation, activation of both coagulation and fibrinolysis, and induction of granuloma formation. Increased numbers of TNF-α producing cells are present in intestinal biopsy specimens from IBD patients, more frequently in Crohn’s disease tissues than ulcerative colitis [1].

2.1 INFLIXIMAB

Infliximab is a chimeric (75% human / 25% mouse) anti-TNFα monoclonal antibody; TNFα mediates multiple pro-inflammatory processes central to the pathogenesis of IBD.
Infliximab was demonstrated to be effective in both the induction and maintenance therapy for refractory luminal and fistulizing CD. In a randomized double-blind placebo controlled trial, 108 patients with moderate-to-severe CD which is resistant to conventional therapy, were treated with the single intravenous infusion of either placebo or infliximab at a dose of 5 mg/kg, 10 mg/kg or 20 mg/kg.

The rates of the clinical response at 4 week were 81% for infliximab 5 mg/kg, 50% for infliximab 10 mg/kg and 64% for infliximab 20 mg/kg, all of which were significantly higher than that for the placebo-treated group. The clinical remission rate at 4 week was also significantly higher in the infliximab-treated group than in the placebo-treated group (33% vs 4%) [2]. In a randomized, double-blind, placebo-controlled trial for the treatment of fistulizing disease, 94 CD patients with draining abdominal and perianal fistulas refractory to conventional therapy were treated with three intravenous infusions at week 0, 2 and 6 of either a placebo or infliximab at a dose of 5 mg/kg or 10 mg/kg. The response rates were significantly greater in the infliximab 5 mg/kg group (68%) and in the infliximab 10 mg/kg group (56%) than that in the placebo-treated group (26%). The rates of a complete closure of the fistulas were also significantly higher in the infliximab 5 mg/kg and 10 mg/kg group (55% and 38% respectively) compared with the placebo-treated group (13%) [3].

Rutgeerts et al. [4] who described the ACT 1 and 2 trials. These trials enrolled patients with moderate–severe UC refractory to aminosalicylates (ACT 1), corticosteroids, and/or immunosuppressives (ACT 1 and 2). A total of 728 patients were randomized to receive a standard induction schedule of infliximab (5 or 10 mg/kg) or placebo at weeks 0, 2, and 6 followed by every 8 week “maintenance” dosing. Patients were followed for 54 weeks in ACT 1 and 30 weeks in ACT 2. Clinical responses after 8 weeks were reported in 69% and 64% of patients receiving infliximab 5 mg/kg in ACT 1 and 2, and in 61% and 69% of patients who received 10 mg/kg, compared to 37% and 29% of patients who received placebo. In both studies, patients who received infliximab were more likely to have a clinical response at week 30 and by week 54 in ACT 1, 45% and 44% of patients who had received 5 or 10 mg/kg infliximab “maintained” their clinical response compared with 20% of patients randomized to placebo.

### 2.2 ADALIMUMAB

Adalimumab is a subcutaneously administered IgG1 monoclonal antibody that binds with high specificity and affinity to human TNFα and consists of human-derived heavy and light chain variable regions and human IgG1 constant region. Adalimumab is now approved in the US and Europe for the treatment of CD.

The CLASSIC I trial randomized 299 moderate to severe CD patients naïve to anti-TNF therapy to one of three dose combinations administered at week 0 and 2 (160/80 mg, 80/40 mg, or 40/20 mg) or placebo. At week 4, 36% \( (P = 0.001), 24\% \ (P = 0.06), \) and 18\% \ (P = 0.36) in the adalimumab groups, respectively, were in clinical remission compared to 12\% in the placebo group [5]. Fifty-five patients who were in remission at week 4 of CLASSIC were randomized to receive continued adalimumab 40 mg every other week, weekly or placebo for up to one year as part of the CLASSIC trial in which 74\%, 83\% and 44\% of patients, respectively, maintained remission at week 56 [6]. Similar to the ACCENT study with infliximab, immunomodulator therapy again did not alter these results[7]. Finally, the CHARM trial \( (n = 854) \) examined adalimumab induction and maintenance efficacy in patients with moderate to severe active CD. An 80 mg dose at week 0 and 40 mg dose at
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week 2 were administered to all patients, with 499 (58%) achieving clinical response and then randomized to placebo, adalimumab 40 mg every other week, or 40 mg weekly through week 56. Significantly higher rates of remission were seen in the adalimumab groups compared to placebo at both week 26 (40% and 47% vs 17%, \( P < 0.001 \)) and week 56 (36% and 41% vs 12%, \( P < 0.001 \)). The adalimumab groups also had significantly more steroid discontinuation and complete fistula closure. Safety data was comparable to other TNF therapy [8].

2.3 CERTOLIZUMAB

Certolizumab pegol or CDP870 (UCB; Smyrna, GA) is a monoclonal humanized anti-TNF\( \alpha \) antibody Fab’ fragment linked chemically to polyethylene glycol (PEG). In contrast to infliximab and adalimumab the antibody fragment does not induce apoptosis [9]. Certolizumab has been evaluated in both induction and maintenance trials for CD [9,10]. In 92 patients with moderate to severe CD randomized to a single intravenous dose of 1.25, 5, 10 or 20 mg/kg of CDP870 or placebo, the primary endpoints of clinical response or remission after four weeks were not different between treatment groups and placebo, but the remission rate at week 2 was 47% in the 10 mg/kg group compared to 16% in the placebo group (\( P = 0.041 \)) [10]. The PRECISE 1 study compared subcutaneous certolizumab (100, 200 or 400 mg) to placebo administered at week 0, 4, and 8 in 292 patients with moderate-severe CD. While all doses of certolizumab produced significant clinical benefit over placebo at week 2, 400 mg had the strongest effect at all time points, most markedly at week 10 (52.8% vs 30.1%, \( P = 0.006 \)); however, no statistical significance in clinical response was seen at week 12, the primary endpoint. When re-analyzed according to stratification by C-reactive protein level (> 10 mg/L), the 400 mg group had a significantly better response at week 12 (53.1% vs 17.9%, \( P = 0.005 \)) that was attributed to a lower placebo response rate than those patients with a CRP < 10. In the PRECISE 2 trial, patients who responded to a 400 mg induction dose at week 0 and 2 (428/668, 64%) were randomized to receive 400 mg certolizumab or placebo every 4 week for 26 week. Significantly more patients in the certolizumab arm achieved clinical response (62.8% vs 36.2%, \( P < 0.001 \)) and remission (47.9% vs 28.6%, \( P < 0.001 \)) at week 26 [11]. Safety and tolerability were similar to other anti-TNF agents, although patients treated with certolizumab had lower rates of autoantibody formation.

3. Selective adhesion blockade

Many adhesion molecules play an important role in trafficking leukocytes into the inflamed gut wall and they are up-regulated in both CD and UC. \( \alpha_4 \)-integrins, predominantly expressed on lymphocytes, usually exist in combination with a \( \beta \) subunit and interact with adhesion molecules expressed on endothelium. \( \alpha_4 \beta_1 \)-integrin binds to vascular cellular adhesion molecule 1 (VCAM-1) and \( \alpha_4 \beta_7 \)-integrin binds to mucosal addressin cell adhesion molecule 1 (MAdCAM-1). The interaction between \( \alpha_4 \beta_7 \)-integrin and MAdCAM-1 is important in mediating lymphocytes homing to the gut mucosa [12]. Leukocyte function-associated antigen 1 (LFA-1) expressed on leukocytes interacts with intercellular adhesion molecule 1 (ICAM-1), which is constitutively expressed at low levels on vascular endothelial cells and a subset of leukocytes, and they are up-regulated on many cell types in response to pro-inflammatory mediators [13].
3.1 NATALIZUMAB
Natalizumab, a humanized IgG4 anti-α4-integrin monoclonal antibody, inhibits both α4β7-integrin/MAdCAM-1 interaction and α4β1/VCAM-1 binding. It was already approved by Food Drug Administration (FDA) for use in patients with Crohn’s disease in 2007. The mechanism of action consists of natalizumab interrupted lymphocyte trafficking into the intestine [14]. In a large placebo-controlled randomized trial including 248 patients with moderate to severe CD, patients were treated twice at 4 week intervals with 3 or 6 mg/kg of natalizumab or placebo. A significantly higher number of patients achieved remission at week 6 only in the 3 mg/kg natalizumab group compared with the two infusions of placebo group (44% vs 27%) [15]. A larger phase 3 trial of ENACT-1 in 905 patients with moderate to severe CD treated with natalizumab and concurrent immunosuppressive therapies, prior anti-TNF-α therapy or elevated CRP levels showed a significant response rate compared with placebo-treated patients [16]. Three hundred and thirty-nine patients with CD who responded to natalizumab were followed by 12 months (ENACT-2), natalizumab demonstrated a significant superiority over the placebo in its ability to sustain both the response and remission at all consecutive time points over a 6 months period and enabled patients to be successfully withdrawn from steroids [17]. In an uncontrolled short term pilot study in 10 patients with active UC, a single 3 mg/kg intravenous infusion of natalizumab showed a short-term benefit [18]. Natalizumab is efficacious in multiple sclerosis (MS) as well [19,20]. Against these effects of natalizumab in IBD and MS, 3 patients receiving repeated treatment with natalizumab developed JC virus related progressive multifocal leukoencephalopathy (PML) [21-23]. PML, which almost invariably occurs in patients with AIDS or leukemia or in organ-transplant recipients, is a fatal opportunistic infection of the central nervous system caused by the reactivation of a clinically latent JC polyomavirus infection. Two patients with MS had been receiving the concomitant administration of interferon β-1a [21,22] and 1 patient with CD had been treated with natalizumab monotherapy [23].

3.2 MLN-02
MLN-02 is a humanized anti-α4β7-integrin blocks specifically the α4β7-integrin/MAdCAM-1 interaction. A randomized placebo-controlled trial in 185 patients with mild to moderately active UC treated with placebo, 0.5 mg/kg MLN-02 or 2.0 mg/kg MLN-02 intravenously on day 1 and 29 demonstrated that on day 57, 2.0 mg/kg MLN-02 showed significantly greater remission rates over the placebo (36.9% vs 20.7%) [24].
A randomized placebo-controlled trial in 181 patients with moderately active UC treated by two infusions with placebo, 0.5 mg/kg MLN-02, or 2.0 mg/kg MLN-02 intravenously demonstrated that on day 43 the remission rates were significantly higher in the actively treated groups (0.5 mg/kg: 33%, 2.0 mg/kg: 34%) than in the placebo-treated group (15%) [25]. MLN-02 appears to be a generally well-tolerated and effective therapy especially for active UC, but further trials are necessary to confirm these findings.

3.3 ALICAFORSEN (ISIS 2302)
ISIS 2302 is a 20 base phosphorothioate oligodeoxynucleotide designed to specifically hybridize to the 3'-untranslated region of the human ICAM-1 mRNA. Treatment of ISIS 2302 in vitro resulted in a highly specific reduction in ICAM-1 mRNA and, consequently, a marked decrease in ICAM-1 protein expression [26].
A pilot trial in patients with moderate CD (including 15 patients treated with 13 intravenous infusions of 0.5, 1.0 or 2.0 mg/kg ISIS 2302 vs 5 patients with placebo over 26 day) demonstrated a higher remission rate in ISIS 2302-treated group compared with the placebo-treated group on day 33 (47% vs 20%) [27, 28]. Another larger randomized placebo-controlled trial also failed to show any benefit of ISIS 2302 for active CD [29]. Two hundred and ninety-nine patients with moderately active, steroid-dependent CD received placebo or ISIS 2302 (2 mg/kg intravenously three times a week) for 2 or 4 week in month 1 and 3. There were no differences in the steroid-free remission rates at week 14 between the ISIS 2302-treated groups (2 week: 20.2%, 4 week: 21.2%) and the placebo-treated group (18.8%). This suggested that ISIS 2302 may be effective when given in adequate doses. In another study patients were infused with high dose ISIS 2302 (250 mg to 350 mg) intravenously three times a week for 4 week, showed a 41% remission rate [30]. A randomized placebo-controlled trial in 40 patients with mild to moderately active distal UC treated with 60 mL alicaforsen enema (0.1, 0.5, 2, or 4 mg/mL or placebo) once daily for 28 consecutive days showed a beneficial effect at the highest dose [31]. An open-label, uncontrolled study in 12 patients with chronic unremitting pouchitis treated with 240 mg alicaforsen enema nightly for 6 week demonstrated a significant improvement in the pouchitis disease activity index and an endoscopic mucosal appearance at week 6 [32].

4. Recombinant cytokines

MRA (Anti-IL-6 receptor antibody)

IL-6 is one of the major inflammatory cytokines. IL-6 can transduce signals into cells without IL-6 receptor expression when IL-6 binds to soluble IL-6 receptor. The expression of IL-6 and soluble IL-6 receptor increases in patients with active CD [33, 34]. A pilot randomized double blind placebo-controlled trial of a humanized anti-IL-6 receptor monoclonal antibody that included thirty-six patients were randomized biweekly to receive either a placebo, 8 mg/kg MRA or MRA/placebo alternately for 12 week. The clinical remission rate with biweekly MRA was significantly higher than with placebo (80% vs 31%) [35].

4.1 FONTOLIZUMAB (Anti-interferon-γ antibody)

Interferon-γ is a key cytokine that enhances the development of a Th1 immune response. Fontolizumab is a humanized monoclonal antibody directed against interferon-γ. A phase 2 study of fontolizumab at intravenous doses of 4 mg/kg or 10 mg/kg in 133 patients with moderate to severe active CD did not demonstrate efficacy at day 28. However, exploratory analyses based on 91 patients who received a second dose of fontolizumab at day 28 did demonstrate efficacy. This effect was most prominent in patients with elevated baseline concentrations of CRP [36]. An additional phase 2 study of fontolizumab at lower subcutaneous doses of 1.0 mg/kg or 4.0 mg/kg in 196 patients with active CD did not demonstrate efficacy at day 28 [37]. These results indicate that a single dose may not be sufficient to achieve a significant improvement. Further clinical studies of fontolizumab for the induction and maintenance of remission in patients with CD are required.

4.2 ANTI-IL2 Receptor (CD25) Antibodies

Daclizumab: IL-2 is a major T cell growth factor, which is secreted by activated T cells and acts via the high-affinity IL-2 receptor on T cells themselves to promote cell survival and proliferation. The IL-2 receptor α-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. An open label pilot study of daclizumab suggested that it was beneficial for patients with active UC [38]. However, a recent placebo-controlled phase 2 trial of daclizumab at intravenous doses of 1 mg/kg twice with a 4-week interval or 2 mg/kg every 2 week for a total of four doses in 159 patients with active UC failed to show any efficacy [39].

Basiliximab is a chimeric monoclonal antibody against CD25, which 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 UC [40, 41]. A large randomized controlled trial is required to confirm the therapeutic benefit of this antibody.

4.3 VISILIZUMAB
Visilizumab, an anti-CD3 monoclonal antibody is undergoing evaluation in severe UC. In an open-label phase I trial, 79% and 54% of steroid-refractory UC patients treated with 10 mcg/kg per day (n = 24) for two consecutive days experienced response and remission respectively at day 30, and 100% of those treated with 15 mcg/kg per day (n = 8) achieved both clinical response and remission [42]. Sixty-three percent of patients receiving the higher dose remained in remission at one year. Almost two-thirds of patients experienced symptoms of cytokine release syndrome 1-3 hr post-infusion, including nausea, chills, fever, headache and arthralgias [43].

5. Growth factors
Growth factors may restore the protective and reparative foundation of the colon, and therefore represent a possible therapeutic option for UC. Growth factors that have been identified as potentially beneficial in treating UC include transforming growth factor β (TGF-β), epidermal growth factor (EGF), keratinocyte growth factor-1 and 2 (KGF-1 or 2, also known as fibroblast growth factor 7 or 10). Repifermin is a truncated, purified KGF-2 expressed in Escheria coli, and induces the proliferation of intestinal and colonic mucosa and reduces intestinal ulcers and inflammation in animal models [44]. Intravenously administered repifermin (1-50 μg/kg) for five consecutive days did not yield different rates of clinical response or remission at week 4 compared to placebo in patients with active UC [44].

EGF is a mitogenic peptide produced by salivary and duodenal Brunner’s glands, topical application is beneficial in wound healing and systemic EGF is useful in treating neonatal necrotizing enterocolitis [45]. An 83% remission rate was demonstrated in patients with mild to moderate left-sided UC (n = 24) randomized to daily EGF enemas for 2 week compared to 8% in the placebo group (P < 0.001); disease activity, endoscopic and histologic scores remained significantly better in the EGF group through 12 week [45]. It aids mucosal healing by stimulating local prostaglandin synthesis and epithelial cell regeneration via up-regulation of EGF and its receptor, neutrophil suppression, and decreased production of inflammatory cytokines stimulated by NSAIDs and/or H pylori [46]. A small open-label trial in which twice daily Rebamipide enemas were given to patients with UC proctitis for one month demonstrated significant clinical, endoscopic and histopathologic improvement [47].
6. Immunostimulation

The greatest evidence supporting the use of colony-stimulating factors in intestinal inflammation comes from studies conducted in patients with active Crohn’s Disease (CD): sargramostim and filgrastim.

6.1 GM-CSF

Initial findings suggested that patients treated with sargramostim (GM-CSF) (Immunex Corporation, Seattle, WA, USA) in active CD had a high rate of clinical response and remission, with limited side effects [48]. This 8-week, open-label, dose-escalating study, was conducted on 15 patients with Crohn’s Disease Activity Index (CDAI) greater than 220 but lower than 475. Among them, 80% achieved clinical response (decrease in CDAI >70 points) and 53% achieved remission (CDAI <150). The response rate was 75%, 85%, and 75% in the 4, 6, and 8 µg/kg per day dose groups. The only patient with fistula had complete clinical closure of a chronic recto-vaginal fistula. Treatment with sargramostim also improved quality of life.

Lastly, the Sargramostim in Crohn’s Disease Study Group [49] conducted a multicenter, randomized, placebo-controlled trial, where 124 patients were included. Patients were randomly assigned in a 2:1 ratio to receive sargramostim (6 µg per kilogram of body weight) or placebo subcutaneously daily for 56 days. The primary end point was clinical response and other end points included changes in disease severity, quality of life, and adverse events.

The primary end point was not proven, this was achieved in 54% in the sargramostim group and 44% in the placebo group (P = 0.28), but a clinical response defined by a decrease from baseline of at least 100 points in the CDAI score was significantly higher in the sargramostim group than in the placebo group (48% vs 26%, P = 0.01), as well as the remission rate (40% vs 19%, P = 0.01). The improvement, including remission rates, was also superior in the sargramostim group thirty days after treatment. In patients in whom the validated Crohn’s Disease Endoscopic Index of Severity was assessed, the median post-treatment scores were significantly lower in the sargramostim group, but the median decrease between the two groups was not. Draining fistulae was eliminated in 4 of 8 of patients in the treatment group and in 2 of 5 in the placebo group. Only 1 of 78 patients had detectable neutralizing antibodies at day 57, and no association was observed with adverse events. Treatment with GM-CSF may provide effective synergistic or single-agent treatment alternatives to immunosuppression for IBD [50], but evidence that supports its recommendation as treatment remains weak.

6.2 G-CSF

Dejaco et al [51] performed an open-label pilot study with filgrastim (Neupogen®, Amgen Inc, Thousand Oaks, CA, USA) in 5 CD patients with severe endoscopic postoperative recurrence, but with clinically inactive CD (CDAI <150). Patients received 300 µg of filgrastim subcutaneously, three times weekly for a total of 12 weeks, for the primary objective of evaluating safety and efficacy in this group of patients. Efficacy was evaluated by ileocolonoscopy, including histopathological examination according to Rutgeerts’ rating for postoperative recurrence, which was performed before treatment and within 1 week after the end of treatment. Four patients had stricturing and one had penetrating behavior. Complete mucosal healing occurred in 2 patients after treatment (1 patient after 12 weeks of
therapy and in 1 patient 9 months after treatment cessation), and all other patients had no response. In 1 patient closure of perianal fistulas was noted. This study suggested that despite the small number of patients filgrastim seems to be safe, well tolerated, and might provide efficacy in CD.

Korzenik et al [52] conducted a 12 week open-label trial with filgrastim (Neupogen®, Amgen Inc, Thousand Oaks, CA, USA) that offered preliminary evidence that is a safe and potentially effective therapy for the treatment of active CD and fistulious complications. Twenty CD patients with a CDAI >220 and ≤450 were enrolled. Primary end point was a decrease in the CDAI of >70 points and remission was considered to be a CDAI <150 points. All patients received filgrastim daily for 12 weeks at an initial dose of 300 µg subcutaneously. The absolute neutrophil count (ANC) was monitored weekly and was targeted between 25 and 35 × 10^9. The dose was adjusted downward by 100 µg if ANC exceeded this range, and after a subsequent reduction to 100 µg/day, the dose was lowered to 75 µg/day. Five patients (25%) achieved remission during the study, 11 (55%) demonstrated a decrease of at least 70 points, and 3 of 4 (75%) patients with fistulae had a positive response (defined as closure of more than 50% of fistulae). Among responders at week 12, 4 of 11 patients (36%) maintained response for additional 4 weeks after completion of therapy and the others had an increase in disease activity.

7. Nucleic acid based therapies

Nucleic acid based therapies have focused on the use of antisense phosphorothioate oligonucleotide to the p65 subunit of NF-κB and ICAM-1 antisense oligonucleotide (Alicaforsen, ISIS-2302). In a pilot study 11 steroid-refractory or resistant IBD patients were given a single dose of rectal antisense NF-κB p65 oligonucleotide. An improvement in clinical, endoscopic and histologic scores was seen at day 7 in 71% of the treatment group compared with 25% of the placebo group [53].

ISIS-2302 is a 20-base pair complementary nucleotide chain that hybridizes with ICAM-1 mRNA that is thus degraded by RNase-H and the message and expression of ICAM-1 is therefore decreased. In patients treated with doses between 300-350 mg infused 3 times weekly for 4 weeks, it seemed to have higher benefit in those with active CD [54]. Immunostimulatory DNA sequences, ISS-DNA, also known as CpG DNA, are unmethylated CpG dinucleotides within consensus sequences present in bacterial and viral genomes. ISS-DNA and their synthetic analogues activate innate immunity via Toll-like receptor 9. ISS-ODN (Liposomal immunostimulatory DNA sequence) was shown to prevent and ameliorate the severity of colitis in animal models [55] and therefore may be effective also in the treatment of human IBD. Clinical trials to test their efficacy are underway.

8. Gene therapy

Gene therapy strategies using plasmid IL-10 vectors or an adenovirus IL-10 constructs seem to be a potent approach for the treatment of IBD. Barbara et al [56] reported that gene transfer was achieved by intraperitoneal injection of non-replicating human adenovirus bearing IL-10 gene, either 24 hr before or 1 hr after intrarectal administration of TNBS
(trinitrobenzenesulfonic acid) in rats. IL-10 gene transfer prior to colitis improved colitis macroscopically and histologically.

9. Allogenic bone-marrow transplantation

Allogenic bone-marrow transplants in CD patients were noted to induce prolonged disease remission, providing evidence of the role of bone-marrow T cells in this disease. The goal of autologous haematopoietic stem-cell transplantation (HSCT) is resetting T cell responses by eliminating all circulating T cells. A phase I study in 12 patients with refractory CD showed that 11 patients entered a sustained remission (CDAI <150). After a median follow-up of 18.5 months, only one patient has developed a recurrence of active CD, which occurred 15 month after HSCT [57].

10. Helminths

Helminthic colonization has been theorized to be protective against the development of IBD based both on epidemiologic and animal model data. Another strategy for resetting the T-cell repertoire has been proposed based on the helminths. The immune system has evolved with the presence of these helminths, which functions to expand the T regulatory cell population, enhancing IL-10 production and shifting a Th1 type process more towards Th2 [58]. An RCT of Trichiuris suis, a pig worm, using 2,500 Trichiuris suis ova administered orally once every two weeks, in UC has shown a response of 44% of the treatment group versus 14% of receiving placebo group [59]. An open label study of 29 patients with active CD identified high rates of response (79.3%) and remission (72.4%).

11. Apheresis

Selective apheresis of leukocytes, including the targeted removal of monocytes, granulocytes, and lymphocytes is a growing area of research in the treatment of UC. Review of leukocyte apheresis studies shows efficacy in inducing remission across various UC populations in small open trials [60], but the inherent process of apheresis makes controlled studies difficult to conduct. Two larger trials have demonstrated that leukocyte apheresis \((n = 76)\) and granulocyte/monocyte apheresis (Adacolumn®) \((n = 69)\) are equally or more effective than steroids in the induction of remission [61, 62], with fewer adverse events [61] and greater steroid-sparing effects [62]. In the only controlled trial to date, 19 patients with moderate to severe UC treated with five weekly sessions of either leukocyte sham apheresis (followed by every other week for 4 wk) or sham apheresis demonstrated that the leukocyte apheresis group had significantly greater clinical improvement (80%) than the sham group (33%)[63]. Maintenance of remission after apheresis has been equivocal: in one study of 71 patients with active UC treated with leukocyte apheresis, only 27% of those with an initial response \((n = 53)\) maintained remission for more than six months; rapid response to treatment was the only factor correlated with long-term response in multivariate analysis [64]. In another study, however, 26 of 33 patients maintained remission at one year after 11 weekly sessions of granulocyte/monocyte apheresis [65]. Apheresis may be effective in other settings as well, including a small group of patients with toxic megacolon [66], acute pouchitis [67] and a patient with pyoderma gangrenosum [68].
12. Conclusion

Several biological agents are already approved and in evaluation for treatment of IBD patients who had no response to conventional treatment (5-ASA, steroids, immunomodulators). These antibody-based therapies consisting of monoclonal antibodies directed against several cytokines (anti-TNFα, IL6, IL-2R, Interferon γ) and selective adhesion molecules (Natalizumab, MLN-02, Alicaforse). In addition to the cytokine treatment as near- to middle-term additions to therapeutic options, therapies directed to receptors involved in T-cell activation such as Abatacept (CTLA4-Ig) targeting the recruitment of inflammatory cells will soon be important for the care of IBD patients unresponsive to other modalities. However, there are new potential therapies directed to enhance the innate immune system (Sargramostin, filgastrin) and miscellaneous such as nucleic acid based therapies (ISS-DNA), allogenic bone-marrow trasplants, helminths, apheresis and gene therapy.

13. References


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