BIOLOGICS IN INFLAMMATORY BOWEL DISEASE: HOW MUCH PROGRESS HAVE WE MADE?

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INTRODUCTION

Biologic therapies include: (1) naturally occurring or modified biologic compounds such as vaccines (live, live attenuated, or killed microorganisms), hormone extracts, and blood products; (2) recombinant proteins or peptides—for example, granulocyte macrophage colony stimulating factor and growth hormone; (3) monoclonal antibodies and fusion proteins; and (4) antisense oligonucleotides to nucleic acids. These biologic therapies, which are targeted towards specific disease mechanisms, have the potential to provide more effective and safe treatments for human diseases. Clinical trials have demonstrated that inhibition of the cytokine tumour necrosis factor α (TNF) and inhibition of the selective adhesion molecules α4 integrin and α4β7 integrin are effective in the treatment of various forms of the inflammatory bowel diseases (IBD) ulcerative colitis (UC) and Crohn's disease (CD). It is also clear that drug toxicity related to biologic therapy, including hypersensitivity, serum sickness, autoimmunity, infection, and immunogenicity may occur. This article reviews the progress made to date in the treatment of IBD with biologic therapies, concentrating primarily on the TNF inhibitors infliximab, etanercept, adalimumab, CDP870, CDP571, and onercept, and on the selective adhesion molecule inhibitors natalizumab and MLN-02, but also reviewing other potentially promising therapies targeted towards other mechanisms of action (table 1).

INHIBITION OF TNF

Comparative mechanisms of action for various anti-TNF agents

TNF is elevated in the mucosa of patients with CD,[1] and inhibition of TNF has been an effective treatment strategy.[2] Comparison of various anti-TNF agents with respect to biologic construction, ability to bind soluble and membrane bound TNF, ability to fix complement, ability to mediate antibody dependent cytotoxicity, ability to cause T cell apoptosis, and efficacy in unselected patients versus efficacy primarily in patients with elevated concentrations of C reactive protein (CRP) is shown in table 2. The efficacy of the anti-TNF agent infliximab in unselected patients with CD appears to be linked to the ability of the molecule to induce T cell apoptosis.[3] Other agents with more pure anti-TNF effects appear to be effective primarily in a selected subset of patients with elevated CRP concentrations.

Infliximab

Inflixmab is a chimeric IgG1 monoclonal antibody against TNF-α that is administered intravenously. Infliximab is effective for induction of clinical response and remission in patients with active luminal inflammatory CD and in patients with draining enterocutaneous and perianal fistulas, and for subsequent maintenance of infliximab induced clinical response and remission in these patient groups. Clinical remission rates at week 4 in patients with active luminal inflammatory CD refractory to conventional therapy (aminosalicylates, prednisone, azathioprine, or 6-mercaptopurine) after a single infusion were 4% for placebo, 48% for infliximab 5 mg/kg, and 25% for infliximab 10 mg/kg and 20 mg/kg.[2] The complete fistula closure rates in patients with CD and draining fistulas refractory to conventional therapy (antibiotics, aminosalicylates, prednisone, azathioprine, or 6-mercaptopurine) after three induction infusions at weeks 0, 2, and 6 were 13% for placebo, 55% for infliximab 5 mg/kg, and 38% for infliximab 10 mg/kg.[4] There is a small increase in efficacy when patients with active CD receive three induction doses over six weeks rather than a single induction dose (clinical response rates at week 10 of 65% versus 52%),[5] and multiple induction doses may confer immunological tolerance to the chimeric infliximab antibody (see below). For these reasons, a three dose induction regimen with 5 mg/kg at 0, 2, and 6 weeks is preferred over a single dose induction regimen with 5 mg/kg. Maintenance of clinical remission rates at one year in patients with inflammatory CD who have responded to induction therapy with infliximab were 9% for placebo every eight weeks, 24% for infliximab 5 mg/kg every

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Table 1 Biotechnology compounds that have been or are being evaluated for the treatment of patients with inflammatory bowel disease

Drug	Manufacturer	Indication	Phase of investigation
Infliximab (chimeric IgG1 monoclonal antibody against TNF)	Centocor and Schering Plough	Crohn's disease/ ulcerative colitis	Phase 4/phase 3
CDP571 (humanised IgG4 monoclonal antibody against TNF)	Celltech	Crohn's disease/ ulcerative colitis	Failed phase 3/failed phase 2a
CDP870 (humanised Fab antibody fragment against TNF linked to PEG)	Celltech	Crohn's disease	Phase 3
Etanercept (recombinant human fusion protein comprised of IgG1 Fc antibody fragment linked to soluble p75 receptor to TNF)	Amgen (previously Immunex)	Crohn's disease	Failed phase 2
Onercept (recombinant human p55 soluble receptor to TNF)	Serono	Crohn's disease	Phase 2, failed
Adalimumab (human IgG1 monoclonal antibody against TNF	Abbott	Crohn's disease	Phase 3
Natalizumab (humanised IgG 4 monoclonal antibody to α4 integrin)	Elan Pharmaceuticals and Biogen	Crohn's disease, ulcerative colitis	Phase 3/phase 2a
MLN-02, LDP-02 (humanised IgG1 monoclonal antibody to $\alpha 4\beta 7$ integrin)	Millennium Pharmaceuticals (previously Leukocyte Pharmaceuticals)	Crohn's disease/ ulcerative colitis	Phase 2/phase 2
Alicaforsen, Isis 2302 (antisense nucleic acids against ICAM)	Isis Pharmaceuticals	Crohn's disease/ ulcerative colitis/ pouchitis	Failed phase 3/phase 2/phase 2a
Fontolizumab (humanised anti-interferon γ antibody)	Protein Design Labs	Crohn's disease	Phase 2
J695, ABT-874 (human IgG1 monoclonal antibody to interleukin 12 p40)	Abbott Laboratories (previously Wyeth/Genetics Institute)	Crohn's disease	Phase 2
Interleukin 10	Schering Plough	Crohn's disease/ ulcerative colitis	Failed phase 3/failed phase 2
Interleukin 11	Genetics Institute	Crohn's disease	SQ delivery phase 2, discontinued oral delivery phase 2
CNI-1493 (MAP-kinase inhibitor)	Cytokine PharmaSciences	Crohn's disease	Phase 2
BIRB-796 (MAP-kinase inhibitor)	Boehringer-Ingelheim	Crohn's disease	Failed phase 2
RDP58 (peptide consisting of D-amino acids and glycine which blocks the p38 and JNK MAP kinase pathways and inhibits the synthesis of TNF-α, γ interferon, and interleukin 12)	Proctor & Gamble (previously Genzyme and Sangstat)	Crohn's disease/ ulcerative colitis	Phase 2/phase 2
MRA (humanised anti-interleukin 6 receptor antibody)	Roche (previously Chugai Pharmaceutical Company)	Crohn's disease	Phase 2
Somatropin (recombinant human growth hormone)	Eli Lily	Crohn's disease	Phase 2
Filgrastim (recombinant human granulocyte colony-stimulating factor)	Amgen	Crohn's disease	Phase 2a
Sargramostim (recombinant human granulocyte-macrophage colony stimulating factor)	Berlex (previously Immunex)	Crohn's disease	Phase 3
Daclizumab humanised (anti-interleukin 2 receptor antibody)	Protein Design Labs	Ulcerative colitis	Phase 2
Basiliximab (chimeric anti-interleukin 2 receptor antibody)	Novartis	Ulcerative colitis	Phase 2a
Visilizumab (anti-CD3 antibody)	Protein Design Labs	Ulcerative colitis	Phase 1/2a
Epidermal growth factor	Heber Biotec, a commercial subsidiary of the Center for Genetic Engineering and Biotechnology, Havana, Cuba	Ulcerative colitis	Phase 2
Keratinocyte growth factor 2 (repifermin)	Human Genome Sciences	Ulcerative colitis	Failed phase 2

TNF, tumour necrosis factor; PEG, polyethylene glycol; ICAM, intercellular adhesion molecule 1

Table 2 Comparative mechanisms of action for various anti-tumour necrosis factor (TNF) agents

Agent	Description of biologic construction	Binds soluble TNF	Binds membrane bound TNF	Fixes complement	Mediates ADC	Causes T cell apoptosis	Effective in unselected patients	Effective only in patients with elevated CRP
Infliximab	IgG1 chimeric monoclonal antibody	Yes	Yes	Yes	Yes	Yes	Yes	No
Etanercept	Fusion protein comprised of a human IgG1 Fc antibody fragment linked to two human soluble p75 TNF receptors	Yes	Yes	No	No	No	No	?
Adalimumab	Fully human IgG1 monoclonal antibody to TNF	Yes	Yes	Yes	Yes	Yes	?	?
CDP870	Humanised Fab fragment linked to PEG	Yes	Yes	No	No	?	No	Yes
CDP571	Humanised IgG4 monoclonal antibody	Yes	Yes	No	No	?	No	Yes
Onercept	Fully human soluble p55 TNF receptor monomer that binds soluble and membrane bound TNF but does not fix complement	Yes	Yes	No	No	No	No	?

ADC, antibody dependent cytotoxicity; CRP, C reactive protein; PEG, polyethylene glycol.

eight weeks, and 32% for infliximab 10 mg/kg every eight weeks.[6] Median duration of response in these patients was 19 weeks for placebo every eight weeks, 38 weeks for infliximab 5 mg/kg every eight weeks, and >54 weeks for infliximab 10 mg/kg every eight weeks.[6] For patients who initially responded to infliximab and then lost their response during maintenance therapy, it was possible in many instances to regain response by escalating the infliximab dose up to 10 mg/kg[7] or alternatively to shorten the dosing interval. Maintenance of complete fistula closure rates at one year in patients with fistulising CD who have responded to induction therapy with infliximab were 58% for infliximab 5 mg/kg every eight weeks and 38% for placebo every eight weeks.[8] Median time to loss of fistula response was >40 weeks for maintenance infliximab 5 mg/kg every eight weeks and 14 weeks for placebo every eight weeks.

Two pilot controlled trials of infliximab for severe steroid refractory UC have been performed, one with a positive result[9] and one with a negative result.[10] Two large phase 3 trials of infliximab in patients with active UC are underway. Until the results of the ongoing trials are available, the use of infliximab in patients with UC should be considered investigational.

Although infliximab is well tolerated in the majority of patients, serious side effects may rarely occur, including: serious infections (see below); drug induced lupus[11]; acute infusion reactions[12]; delayed hypersensitivity reactions[13]; demyelination[14]; possibly an increased rate of lymphoma[15]; cardiac failure[16]; and death. In clinical trials, infections requiring treatment occurred in 32% of infliximab treated patients versus 22% of placebo treated patients.[17] There was no significant increase in serious infections or sepsis, but pneumonia, sepsis, miliary tuberculosis, and disseminated coccidiomycosis were all observed. In post marketing surveillance, tuberculosis,[18] histoplasmosis,[19] listeriosis, aspergillosis, and pneumocystis pneumonia have all been observed, leading in some instances to death.[20] Reactivation of latent tuberculosis is of particular concern.[18] All patients treated with infliximab should undergo skin testing and chest *x* ray as well as a careful tuberculosis history prior to initiating infliximab therapy.[17 21] A recent study reported the toxicity observed in 500 consecutive patients treated with infliximab at the Mayo Clinic (table 3).[20]

Infliximab is immunogenic and leads to the formation of human antichimeric antibodies (HACA).[2 4 6 7 22–25] The presence of HACA antibodies is clinically important because they are associated with an increased frequency of infusion reactions and with loss of efficacy (fig 1).[24 25] Premedication with 200 mg intravenous hydrocortisone, concomitant treatment with immunosuppressive therapy (azathioprine, 6-mercaptopurine, methotrexate), and administration of three induction doses over six weeks followed by systematic maintenance dosing every eight weeks all appear to be associated with a reduction in the rate of HACA formation.[6 7 24 25]

Regulatory approval for infliximab is limited to patients with moderate to severe CD unresponsive to conventional therapy (USA) or a full and adequate course of corticosteroids and immunosuppressive therapy (Europe) and to patients with actively draining fistulas (fig 2). Patients should routinely receive a concomitant immunosuppressive agent to minimise immunogenicity, and patients who respond to infliximab should generally receive maintenance dosing every eight weeks to minimise both immunogenicity and risk of relapse.

Table 3 Adverse events occurring in 500 consecutive patients with Crohn's disease treated with infliximab

Adverse event	Frequency
Serious adverse event	43 patients (8.6%)
Serious adverse event attributed to infliximab	30 patients (6%)
Acute infusion reactions	19 patients (3.8%)
Serum sickness-like disease	19 patients (3.8%)
Serum-like disease attributed to infliximab	14 patients (2.8%)
Drug induced lupus	3 patients (0.6%)
New demyelination disorder	1 patient (0.2%)
Any infectious event	48 patients (9.6%)
Any infectious event attributed to infliximab	41 patients (8.2%)
Serious infection	20 patients (4%)
Fatal sepsis	2 patients (0.4%)
Pneumonia	8 patients (1.6%) (2 were fatal)
Viral infections	6 patients (1.2%)
Abdominal abscess requiring surgery	2 patients (0.4%)
Cellulitis of the arm	1 patient (0.2%)
Histoplasmosis	1 patient (0.2%)
Malignant disorder	9 patients (1.8)
Malignant disorder possibly related to infliximab	3 patients (0.6%)
Deaths	10 patients (2.0%)
Deaths possibly related to infliximab	5 patients (1.0%)

Data from Colombel and colleagues.[20]

CDP571

CDP571 is a humanised IgG4 monoclonal antibody against TNF-α that is administered intravenously. A phase 2 dose finding trial demonstrated the short term benefit of CD571 10 mg/kg for inducing a clinical response at two weeks in patients with active CD.[26] A phase 3 trial of CDP571 10 mg/kg again showed short term benefit for inducing clinical response at two weeks in patients with active CD but no significant difference at 28 weeks with every eight week maintenance dosing.[27] A post hoc exploratory analysis of a subgroup of patients with CRP concentrations ⩾10 mg/l demonstrated significantly increased response rates for CDP571 10 mg/kg at both two weeks and 28 weeks.[27] Two controlled trials failed to demonstrate a steroid sparing benefit of CDP571 in patients with steroid dependent CD.[28 29] CDP571 was well tolerated in patients with CD who developed infusion reactions or delayed-type hypersensitivity reactions to infliximab.[30] Further clinical development of CDP571 for the treatment of CD has been discontinued.

CDP870

CDP870 is a humanised TNF-α Fab monoclonal antibody fragment linked to polyethylene glycol that is administered subcutaneously. A phase 2 study of subcutaneous CDP870 at doses of 100, 200, and 400 mg showed significant short term benefits at two weeks for CDP870 in patients with active CD but the difference was not sustained at 12 weeks in patients undergoing four weekly maintenance therapy.[31] A post hoc exploratory analysis of a subgroup of patients with elevated CRP concentrations ⩾10 mg/l demonstrated a significant effect at both two weeks and 12 weeks for all of the CDP870 doses compared with placebo.[31] Another smaller phase 2 study of intravenous CDP870 in patients with active CD failed to demonstrate efficacy.[32] Two large phase 3 studies in patients with CD, primarily targeted towards patients with elevated CRP, are currently underway.

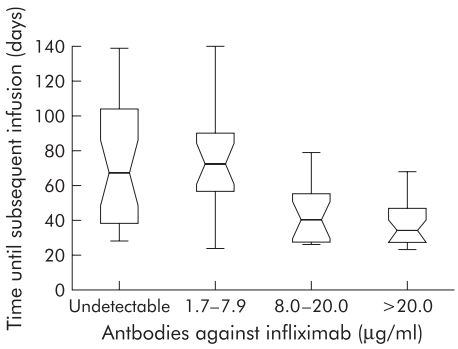

Figure 1 Duration of response according to the concentration of antibodies against infliximab before infusion. Box plots show median values and first and third quartiles in each group. The T bars represent the rest of the data with a maximum of 1.5 times the interquartile range. The four categories can be divided in two groups: the first two categories have concentrations of antibodies against infliximab of <8.0 µg/ml and the second two have concentrations ⩾8.0 µg/ml. Median duration of response in the first two groups differed significantly ($p<0.001$) from the median duration of response in the groups with titres of ⩾8.0 µg/ml. Reprinted with permission from Baert and colleagues.[24]

Etanercept

Etanercept is a fully human fusion protein comprised of two soluble TNF p75 receptors linked to an IgG1 Fc monoclonal antibody fragment that is administered subcutaneously. A phase 2 study of etanercept at a dose of 25 mg twice weekly in patients with active CD failed to demonstrate efficacy.[33] Another unpublished phase 2 controlled trial in patients with active CD was also negative (Amgen, data on file).

Onercept

Onercept is a fully human recombinant soluble TNF p55 receptor administered subcutaneously. A pilot study of onercept in patients with active CD showed a benefit at a higher dose.[34] However, a subsequent phase 2 trial of onercept in patients with active CD was negative (Serono, data on file).

Adalimumab

Adalimumab is a fully human IgG1 monoclonal antibody to TNF-α that is administered subcutaneously. An uncontrolled pilot study demonstrated that adalimumab was well tolerated in patients with CD who lost response, or developed infusion reactions or delayed-type hypersensitivity reactions to infliximab.[35] Three phase 2 and phase 3 trials in patients with CD are currently underway.

INHIBITION OF CELL ADHESION

Mechanisms of action for various antiselective adhesion molecule agents

Lymphocyte trafficking to the gut is an important step in the initiation and perpetuation of intestinal inflammation in patients with IBD,[36 37] and inhibition of lymphocyte trafficking has been an effective treatment strategy.[38] A variety of therapeutic approaches have been used to inhibit lymphocyte trafficking in patients with IBD, including monoclonal antibodies to α4 integrin (natalizumab) and α4β7 integrin (MLN-02, LDP-02), and antisense to intercellular adhesion molecule 1 (ICAM-1) (alicaforsen, Isis 2303). Alpha 4 integrin is expressed at a moderate or high level on almost all lymphocytes and usually exists in combination with either a β1 subunit (that interacts predominantly with the endothelial ligands vascular cellular adhesion molecule 1) or a β7 subunit (that interacts predominantly with the mucosal addressin cellular adhesion molecule (Mad-CAM-1)].[39] The interaction between α4β7 integrin and Mad-CAM-1 is important in mediating leucocyte homing to gut mucosa.[40]

Natalizumab

Natalizumab is a humanised IgG4 monoclonal antibody to α4 integrin. Two phase 2 studies of intravenous natalizumab at doses of 3 mg/kg, 3 mg/kg every four weeks ×2 doses, and 6 mg/kg every 4 weeks ×2 doses showed significant short

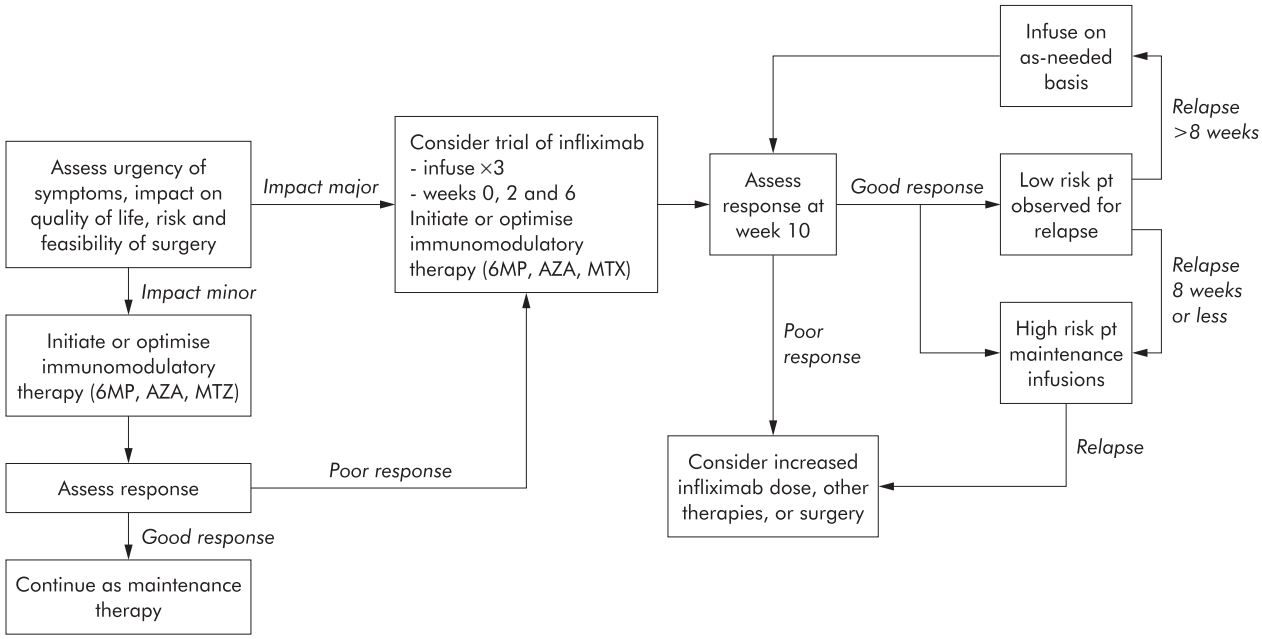

Figure 2 Suggested treatment algorithm for managing patients with refractory Crohn's disease. 6MP, 6-mercaptopurine; AZA, azathioprine; MTX, methotrexate. Modified with permission from: Sands BE. Therapy of inflammatory bowel disease. *Gastroenterology* 2000;**118**:S68–82.

term benefit for natalizumab in patients with active CD.[38 41] A large phase 3 study in patients with active CD failed to show a benefit for natalizumab 300 mg every four weeks ×3 doses, primarily due to an unexpectedly high placebo response rate.[42] A post hoc exploratory analysis of a subgroup of patients with CRP concentrations elevated above the normal range demonstrated a significant effect for natalizumab compared with placebo.[42] Patients who responded to natalizumab in the phase 3 induction study were re-randomised to maintenance therapy with nazalizumab 300 mg or placebo every four weeks through six months (natalizumab withdrawal study). This maintenance study demonstrated a highly significant maintenance benefit, with the difference between the treatment groups at six months exceeding 30%.[43] An additional phase 3 induction study in patients with active CD is currently being initiated. A pilot study of natalizumab in patients with active UC suggested clinical benefit.[44]

MLN-02 (LDP-02)

MLN-02 is a humanised IgG1 monoclonal antibody to α4β7 integrin that selectively inhibits leucocyte adhesion in the gastrointestinal mucosa. Fc receptor recognition and binding has been deleted thus eliminating complement fixation and cytokine release. A phase 2 trial of intravenous MLN-02 in patients with active CD failed to achieve the primary end point of clinical improvement but did show efficacy for remission at the highest dose studied.[45] A phase 2 trial of intravenous MLN-02 for active UC demonstrated efficacy for both clinical and endoscopic end points.[46]

Alicaforsen (Isis 2302)

Alicaforsen (Isis 2302) is a 20 base phosphorothioate oligodeoxy nucleotide designed to hybridise to a sequence in the 3′ untranslated region of the human ICAM-1 message. The oligonucleotide-RNA heterodimer so formed serves as a substrate for the ubiquitious nuclease RNase-H with subsequent cleavage and reduction in cellular specific message content and consequent reduction in ICAM-1 expression. A phase 2 trial indicated that intravenous alicaforsen had a beneficial effect in active CD[47] but a phase 3 trial failed to demonstrate efficacy.[48] Another phase 2 trial failed to show efficacy of subcutaneous alicaforsen for active CD.[49] Subgroup analysis of the phase 3 trial suggested that patients with high blood levels of alicaforsen responded better[48] and a dose ranging pilot study identified a higher dose of intravenous alicaforsen that could more consistently achieve high blood levels.[50] Two phase 3 trials of high dose intravenous alicaforsen in patients with active CD are underway (Isis Pharmaceuticals press releases, 2002). A phase 2 study of alicaforsen enemas suggested a beneficial effect at the highest dose in patients with active distal UCs. A phase 3 study in active UC is underway.[51] A phase 2a study suggested a possible benefit of alicaforsen enemas for chronic pouchitis.[52]

MISCELLANEOUS AGENTS

Fontolizumab (anti-interferon γ)

Increased production of interferon γ by Th1 cells is part of the process of polarisation towards a Th1 immunological response seen in patients with CD. Fontolizumab is a humanised monoclonal antibody to interferon γ. A small phase 2a study of fontolizumab in patients with active CD did not show a clear benefit.[53] A larger phase 2 study of fontolizumab at subcutaneous doses of 1.0 mg/kg or 4.0 mg/kg in 196 patients with active CD did not demonstrate efficacy.[54] A second phase 2 study using larger intravenous doses of 4.0 mg/kg and 10 mg/kg failed to demonstrate efficacy in 133 patients with active CD at week 4 but a post hoc exploratory analysis of 96 patients who received a second 4.0 mg/kg or 10 mg/kg dose of fontolizumab did demonstrate efficacy.[54] Additional studies of fontolizumab for induction and maintenance of remission in patients with CD are anticipated.

Anti-interleukin 12

Interleukin 12 plays a central role in promoting Th1 responses and is critical in the regulation of differentiation and activation of helper T lymphocytes. J695 (ABT-874) is a human IgG1 monoclonal antibody to interleukin 12 p40 that has been genetically modified in its variable region so that it has a high affinity for human interleukin 12. A phase 2 dose finding trial with in patients with active CD demonstrated efficacy.[55]

Interleukin 10

Interleukin 10 is a T helper type 2 cytokine that suppresses the production of interleukin 2 and interferon γ by T helper type 1 cells and decreases interleukin 12 production. A phase 2a study of intravenous interleukin 10 in patients with active CD suggested benefit.[56] Phase 2 trials of subcutaneous interleukin 10 in patients with mild to moderately active CD[57] and postoperative remission,[58] and phase 3 trials in patients with chronically active CD[59 60] did not demonstrate efficacy. A phase 2 trial of interleukin 10 in patients with active UC did not demonstrate efficacy.[61]

Interleukin 11

Interleukin 11 is a cytokine produced by cells of mesenchymal origin whose biologic effects include thrombocytopoiesis and enhancement of the barrier function of intestinal mucosal. Two placebo controlled trials of subcutaneous interleukin 11 in patients with active CD did not demonstrate clearcut efficacy.[62 63] Interleukin 11 is stable in the gastrointestinal lumen and an oral formulation has been developed.[64] A phase 2 study of oral interleukin 11 in patients with active CD is underway.

CNI-1493

CNI-1493 is a guanylhydrazone small molecule that inhibits the mitogen activated protein kinases (MAP kinases) JNK and p38, resulting in indirect inhibition of TNF-α production. A small phase 2 study of intravenous CNI-1493 suggested a benefit for active CD.[65] A larger phase 2 trial of intravenous CNI-1493 for active CD is underway.

BIRB-796

BIRB 796 is a small molecule inhibitor of the MAP kinase p38 that can be administered orally.[66] A large phase 2 trial of BIRB-796 in patients with active CD failed to demonstrate efficacy.

RDP58

RDP58 is an anti-inflammatory peptide consisting of nine D-amino acids and glycine which was developed by computer aided rational design using artificial intelligence. RDP58 blocks the p38 and JNK MAP kinase pathways and inhibits the synthesis of TNF-α, interferon γ, and interleukin 12 in animal models. RDP58 is not systemically bioavailable. A phase 2 trial of RDP58 in patients with active CD failed to

demonstrate efficacy.[67] A phase 2 trial of RDP58 for active UC demonstrated efficacy for a clinical remission end point.[68]

MRA (anti-interleukin 6 receptor antibody)

Interleukin 6 is a cytokine with a central role in immune regulation and inflammation that correlates with CRP and is elevated in patients with CD. MRA is a humanised IgG1 monoclonal antibody to interleukin 6 receptor. A phase 2 study of MRA in patients with active CD demonstrated efficacy.[69]

Somatropin (growth hormone)

Growth hormone is a regulatory protein that increases amino acid and electrolyte absorption by the intestines, decreases intestinal permeability, induces expression of insulin-like growth factor I, and decreases intra-abdominal fat.[70] The rationale for the use of growth hormone in CD is to reverse the catabolic process associated with inflammation and to reduce the intra-abdominal (mesenteric) fat associated with CD. A small placebo controlled trial of somatropin (recombinant human growth hormone) plus a high protein diet in patients with active CD demonstrated a greater decrease in mean Crohn's disease activity index scores for somatropin treated patients than for placebo treated patients (remission rates were not reported).[71]

Sargramostim (granulocyte-macrophage colony stimulating factor) and filgrastim (granulocyte colony stimulating factor)

Genetic syndromes resulting in neutrophil dysfunction such as glycogen storage diseases, Chediak-Higashi syndrome, and chronic granulomatous disease, which commonly manifest intestinal inflammation that has a phenotype similar to CD, have successfully been treated with filgrastim (recombinant human granulocyte colony stimulating factor) and sargramostim (recombinant human granulocyte-macrophage colony stimulating factor).[72 73] Based on these observations, phase 2a studies were conducted in patients with CD which suggested that filgrastim and sargramostim may be of benefit in patients with active and fistulising CD, possibly via an immunostimulant effect on neutrophils.[74 75] A phase 2 trial with sargramostim in patients with active CD demonstrated efficacy.[76]

Daclizumab

Interleukin 2 is produced by Th1 cells after interleukin 12, interferon γ, and interleukin 18 induce differentiation of naïve T helper cells to Th1 cells. Daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor, blocks the binding of interleukin 2 to the interleukin 2 receptor. A phase 2a study of daclizumab suggested benefit in patients with refractory UC.[77] A large phase 2 dose finding trial in patients with active UC is underway.

Basiliximab

Basiliximab is a chimeric monoclonal antibody to the interleukin 2 receptor that blocks the binding of interleukin 2 to the interleukin 2 receptor. A phase 2a study of basiliximab suggested benefit in patients with steroid dependant UC.[78]

Visalizumab

Visilizumab is a humanised monoclonal antibody to CD3. A phase 1/2a dose finding study in hospitalised patients with UC failing intravenous corticosteroids has shown promising preliminary results, with no serious toxicity observed to date.[79]

Epidermal growth factor enemas

Human epidermal growth factor is a potent mitogenic peptide produced by salivary and duodenal Brunner's glands which stimulates cell proliferation in the gastrointestinal tract. A phase 2 study of recombinant epidermal growth factor enemas demonstrated efficacy in patients with active distal UC.[80]

Repifermin

Keratinocyte growth factor 1 (also known as fibroblast growth factor 7) is a potent stimulant of intestinal epithelial cells. Repifermin (keratinocyte growth factor 2 also known as fibroblast growth factor 10) is a homologue of keratinocyte growth factor 1. A phase 2 study of recombinant intravenous repifermin in patients with active UC failed to demonstrate efficacy.[81]

CONCLUSION

Infliximab is effective for induction and maintenance of remission in patients with inflammatory and fistulising CD. The optimal treatment regimen appears to be three induction doses of 5 mg/kg at 0, 2, and 6 weeks, followed by systematic maintenance dosing every eight weeks. Infliximab should be coadministered with an immunosuppressive agent to minimise the formation of HACA. Adverse events observed with infliximab include drug induced lupus, acute infusion reactions, delayed-type hypersensitivity reactions, demyelination, serious infections including reactivation of latent tuberculosis, possibly non-Hodgkin's lymphoma, and death. The role of the humanised and human anti-TNF therapeutic alternatives to infliximab (CDP870 and adalimumab) in patients with CD remains to be determined. The antiselective adhesion molecule agents natalizumab and MLN-02 appear to have beneficial effects for CD and UC. Other promising agents include anti-inteleukin 12, sargramostim, daclizumab, visalizumab, and epidermal growth factor enemas.

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