Current directions of biologic therapies in inflammatory bowel disease

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Abstract: Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases which can be difficult to control with conventional therapies. A greater understanding of their pathophysiology has led to new therapies that target specific molecules of the inflammatory cascade. Three anti-tumor necrosis factor (TNF) monoclonal antibodies have been developed. Infliximab and adalimumab can induce clinical response and sustained remission in CD. Infliximab is also effective in UC. Certolizumab pegol gives good short-term results but long-term efficacy has yet to be determined in other clinical trials. Therapies that target leucocyte trafficking (anti-integrins) have also been developed and are associated with good clinical response in CD. Natalizumab (anti- $\alpha 4$ integrin antibody) is associated with important side effects and is not used anymore in gastroenterology in Europe but is still used in the USA. Vedolizumab (MLN0002), an anti- $\alpha 4\beta 7$ integrin antibody, has a good efficacy and safety profile. Monoclonal antibodies targeting other cytokines are also under development. For example, ustekinumab (CNTO 1275) inhibits interleukins 12 and 23. It is associated with a good clinical response in CD.

Keywords: adalimumab, certolizumab, Crohn's disease, inflammatory bowel disease, infliximab, natalizumab, ulcerative colitis, ustekinumab, vedolizumab

Introduction

Inflammatory bowel diseases (IBD) are chronic relapsing diseases. Crohn's disease (CD) is characterized by a transmural inflammation due to an imbalance between pro- and anti-inflammatory processes [Reimund *et al.* 1996; Reinecker *et al.* 1993; Stevens *et al.* 1992]. Only a small number of affected patients have a less severe disease course with a low prevalence of complications and hospitalizations [Beaugerie *et al.* 2006; Wolters *et al.* 2006; Munkholm *et al.* 1995]. The majority of patients develop complications including strictures, penetration of the bowel wall with obstruction, fistulas, and abscess [Cosnes *et al.* 2002; Louis *et al.* 2002]. Ulcerative colitis (UC) is only a mucosal disease – stenosis and fistula are uncommon. One quarter of such patients develop a chronic active or a rapid fulminating disease course, and 20% require surgery with ileo-anal pouch or stoma [Hoie *et al.* 2007]. Moreover, UC and colonic CD are associated with an increased risk of colon cancer linked to disease extent and chronic uncontrolled inflammation. Treatment goals include steroid-free remission, mucosal healing

and decreases in hospitalization and surgery; as well as sustained clinical remission and sustained mucosal healing with a reduction of colorectal dysplasia and cancer. Steroids are effective short term but fail long term in most patients and are associated with numerous side effects and low rates of mucosal healing [D'Haens *et al.* 2008; Faubion *et al.* 2002]. Mesalazine is not effective in CD but is effective in maintenance of remission in mild UC [Kornbluth and Sachar, 2004]. Immunosuppressive drugs (azathioprine, 6-mercaptopurine, methotrexate) are associated with 40% sustained remission in one year but do not achieve high rates of endoscopic healing and do not modify the natural history of the disease course [Cosnes *et al.* 2005; Lémann *et al.* 2005; Bouhnik *et al.* 1996]. Therefore, chronic active IBD with incomplete mucosal healing under conventional treatment requires the use of biologic treatments. The ideal biologic agent for treating IBD should target a specific event of the inflammatory cascade, induce and maintain a sustained remission, be well tolerated and induce no immunogenicity. A better knowledge of the different inflammatory pathways in IBD has led

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to the development of new targeted therapies with actions that include inhibition of leukocyte trafficking, inhibition of T-cell activation or T-cell polarization, inhibition of pro-inflammatory cytokines. Moreover, thanks to impressive advances in protein engineering, a technique known as humanization was developed which led to the elimination of immunogenic nonhuman peptide sequences from anti-human antibody, and to the development of humanized (95%) and finally fully humanized (100%) antibodies [Hwang and Foote, 2005].

Anti-tumor necrosis factor agents

Development of anti-tumor necrosis factor (TNF) agents dramatically changed the course of IBD. These agents induce and maintain remission in patients with moderate-to-severe IBD. Infliximab, adalimumab and certolizumab pegol are able to block both soluble and membrane TNF but also fix complement. Only infliximab [Van den Brande *et al.* 2003; ten Hove *et al.* 2002] and adalimumab [Shen *et al.* 2006; Shen *et al.* 2005] are able to induce apoptosis of T-cells and monocytes in a caspase-dependent manner. Etanercept is a p75 TNF receptor construct able to bind soluble TNF but failing to induce lysis of cells expressing TNF [Sandborn *et al.* 2001]. Its efficacy has been proven in rheumatoid arthritis but not in IBD, suggesting that molecular mechanisms underlying the effects of anti-TNF are still obscure.

Infliximab

Infliximab is a chimeric monoclonal anti-TNF IgG1 antibody with proven efficacy in induction and maintenance of remission in patients with refractory luminal and fistulizing CD [Hanauer *et al.* 2002; Present *et al.* 1999; Targan *et al.* 1997]. It also causes rapid and profound endoscopic healing. It has been in use since the end of the 1990s. In the ACCENT 1 trial [Hanauer *et al.* 2002], infliximab induced a clinical response at 5 mg/kg administered at weeks 0, 2 and 6. At week 54, with a scheduled treatment every 8 weeks, a remission rate of 29% was observed compared with 5% in the placebo group. Moreover, mucosal healing was obtained in 44% of patients compared with 18% in the placebo group. The ACCENT 2 study proved that infliximab (administered at weeks 0, 2 and 6) improved fistulizing disease in 55% and 38% of patients treated respectively with 10 and 5 mg/kg compared to the placebo group (13% of response) [Sands *et al.* 2004]. At week 54, a

sustained response was observed in 69% and 46% of patients treated respectively with 10 and 5 mg/kg infliximab compared to the placebo group (23%).

Because of its residual murine fragment, some patients developed anti-drug antibodies which could increase the risk of acute and delayed hypersensitivity reactions and induce a secondary loss of response [Hanauer *et al.* 2004; Baert *et al.* 2003]. Thirty to 60% of patients receiving episodic treatment developed anti-drug antibodies compared to 7 to 10% in patients receiving a scheduled treatment [Hanauer *et al.* 2004]. This risk is lower if patients are treated concomitantly with immunosuppressive drugs. ACCENT 1 and 2 trials showed a good tolerability to the drug with a low rate of side effects. Similar rates of infections in placebo and infliximab groups were observed. Development of active tuberculosis in patients with latent tuberculosis was observed [Keane *et al.* 2001], so that the presence of latent tuberculosis has to be evaluated before treatment [Rutgeerts *et al.* 2004]. The TREAT trial showed similar mortality rates in infliximab and placebo groups [Lichtenstein *et al.* 2006]. In this trial, the risk of infections was associated with corticosteroid treatment.

The efficacy of infliximab in inducing and maintaining remission in 110 children with recently diagnosed CD has been demonstrated in the REACH study [Hyams *et al.* 2007] with 88.4% response and 58.9% remission at week 10, and 63.5% response and 55.8% remission after one year of treatment.

Infliximab also showed its efficacy in UC. ACT1 and ACT2 trials studied the efficacy of infliximab at a dose of 5 or 10 mg/kg administered at weeks 0, 2 and 6 in moderate-to-severe UC compared with placebo group during 54 weeks (ACT1) or 30 weeks (ACT2) [Rutgeerts *et al.* 2005]. A clinical response was observed at week 8 in 61% and 69% of patients treated respectively with 5 and 10 mg/kg *versus* 29% and 37% in the placebo group. Clinical response to infliximab in patients with corticosteroid resistance in UC was also assessed and the rate of colectomy was 67% in the placebo group to 27% in the treated group [Järnerot *et al.* 2005].

Adalimumab

Adalimumab is a fully humanized anti-TNF monoclonal IgG1 antibody that may be

given subcutaneously. Its immunogenicity is very low (only 3% of anti-drug antibodies were observed at week 2 compared with 14% with infliximab 5 mg/kg at week 56). The CLASSIC 1 trial [Hanauer *et al.* 2002] was the first multicenter, randomized double-blind controlled trial studying the response to adalimumab by 299 moderate-to-severe CD patients naïve to anti-TNF treatment [Hanauer *et al.* 2002]. At week 4, remission was observed in 36% of patients receiving an induction dose of 160 mg and 80 mg at week 0 and 2 respectively compared with 24% in patients receiving an induction dose of 80 and 40 mg, and 12% in the placebo group. Fifty-five patients from the CLASSIC 1 study were enrolled in the CLASSIC2 trial. The CLASSIC 2 trial showed remission maintained at week 54 in 74%, 83% and 44% of the patients treated respectively with adalimumab 40 mg every 2 weeks, every week and placebo. The CHARM trial evaluated the clinical response to adalimumab in moderate-to-severe CD having received or not received other anti-TNFs previously [Colombel *et al.* 2007]. The remission rate was higher with adalimumab every week and every other week compared to the placebo group at week 26 (respectively 47%, 40%, 17%) and at week 56 (respectively 41%, 36%, 12%). Interestingly, the response rate was higher in patients who had never received other anti-TNFs before.

There is no prospective randomized placebo-controlled trial studying adalimumab in fistulizing CD but the presence of a fistula was not an exclusion criteria in the CHARM study and *post hoc* data have been published. In this trial, a complete closing of fistula was observed in 36% of patients treated with adalimumab every other week, 46% in patients treated every week, and 14% in the placebo group [Rutgeerts *et al.* 2005].

Interestingly, the GAIN study [Sandborn *et al.* 2007b] showed remission in 301 patients who were secondary nonresponders or intolerant to infliximab at week 4 in 21% of patients treated with adalimumab, at an induction dose of 160/80 mg and then with 40 mg every other week, compared with only 7% in the placebo group. A decrease in C-reactive protein (CRP) levels was also observed – elevated CRP may be considered prognostic of good response to adalimumab therapy. The safety of adalimumab was comparable to that of infliximab.

Preliminary data from open-label trials showed efficacy of adalimumab in mild-to-moderate UC with loss of response or poor tolerability to infliximab [Trinder and Lawrance, 2009, Peyrin-Biroulet *et al.* 2007]. These data should be confirmed by a large ongoing prospective trial.

Certolizumab pegol

Certolizumab pegol (CDP-870) is a PEGylated Fab fragment of a humanized anti-TNF antibody. It has shown efficacy in patients with refractory CD. The addition of two polyethylene glycols to the antibody fragment enhances its plasma half-life and permits its subcutaneous administration every 4 weeks. The preliminary placebo-controlled phase II study by Schreiber and colleagues studied certolizumab pegol at different doses (100, 200, 400 mg) at weeks 1, 4, 8 in patients with moderate-to-severe CD [Schreiber *et al.* 2005]. All doses produced clinical benefit over placebo, mainly at week 2. At week 10, the optimal dose was 400 mg. The PRECISE 1 [Sandborn *et al.* 2007a] and PRECISE 2 [Schreiber *et al.* 2007] trials used an induction dose of 400 mg at weeks 0, 2 and 4 and then a scheduled treatment every 4 weeks. The trial showed response by two-thirds at week 6 as compared with placebo but no significant improvement in remission at weeks 6 and 26.

Inhibitors of leucocytes trafficking

The number of inflammatory cells in the bowel wall depends on cell proliferation, apoptosis and also on leukocyte recruitment. Adhesion molecules, mainly integrins ($\alpha 4\beta 7$, $\alpha 4\beta 1$), located at the surface of endothelial cells, play a crucial role in the migration of leukocytes from blood vessels to intestinal tissue in IBD.

Natalizumab

Natalizumab is a humanized IgG4 monoclonal antibody directed against $\alpha 4$ -integrin inhibiting the adhesion and migration of leukocytes into inflamed tissues [Sandborn and Yednock, 2003]. Different pilot studies have suggested that natalizumab may be effective in CD without major adverse effects [Ghosh *et al.* 2003; Gordon *et al.* 2001]. The ENACT1 trial included 905 patients receiving either placebo or 300 mg natalizumab at weeks 0, 4 and 8. Similar response rates were observed at week 10 in treated and placebo groups (56% and 49% of response and 37% and 30% of remission, respectively), which suggested no benefit of natalizumab as an induction treatment in moderate-to-severe CD.

The patients who responded to the induction treatment were enrolled in the ENACT2 study (354 patients treated with natalizumab and 74 patients treated with placebo). Continuing natalizumab resulted in a higher rate of sustained response (61% *versus* 28%) and remission (44% *versus* 26%) at week 36. Although data from the clinical trial indicate that natalizumab seems to be safe, it has been associated with progressive multifocal leukoencephalopathy (PML). PML is a fatal opportunistic infectious, demyelinating brain disorder induced by the JC virus [Van Assche *et al.* 2005]. This complication has also been described in six patients treated with natalizumab for multiple sclerosis. A follow up of 3100 patients who received natalizumab in different clinical trials showed no additional cases. A pilot study of natalizumab in UC showed no major adverse effects [Gordon *et al.* 2002]. There are now seven cases of PML associated with the use of natalizumab. The incidence of PML is estimated at one per thousand [Yoursy *et al.* 2006]. However, the medication is now FDA approved for patients who have failed anti-TNF therapy.

Vedolizumab

Because of the major adverse effects of natalizumab, represented by the JC-induced PML, new selective adhesion molecule-inhibiting agents are in development. Vedolizumab (MLN0002, MLN-02) is a recombinant humanized IgG1 monoclonal antibody to the $\alpha 4\beta 7$ integrin. Two randomized control trials evaluating the efficacy and safety of vedolizumab in 181 active UC patients [Feagan *et al.* 2005] and 185 CD patients with moderate-to-severe CD showed no serious adverse effects. Clinical remission rates in UC at week 6 were 33, 32 and 14% in the groups receiving 0.5 mg/kg vedolizumab, 2 mg/kg vedolizumab and placebo, respectively. For the minority of patients who developed vedolizumab antibody titers greater than 1/250, no benefit of treatment was observed because of incomplete saturation of the $\alpha 4\beta 7$ receptor on circulating lymphocytes. Data from a phase II study using vedolizumab [Feagan *et al.* 2008] were recently published. The primary endpoint was clinical response on day 57 and the secondary endpoints were the number of patients with clinical remission and with an enhanced clinical response. Clinical response rates at day 57 were 53%, 49% and 41% in the 2.0 mg/kg vedolizumab, 0.5 mg/kg vedolizumab and placebo groups, whereas clinical remission rates at day 57 were

37%, 30% and 21%, respectively. No major adverse effects were reported except one hypersensitivity reaction.

Anti IL-12/IL-23 antibodies

Interleukin (IL)-12 is a key cytokine that drives the inflammatory responses in CD. IL-12 is found at high concentrations in the bowel wall of CD patients, is mainly produced by antigen-presenting cells and takes a crucial role in the Th1 orientation of the lymphocyte system [Berrebi *et al.* 1998; Gately *et al.* 1998; Monteleone *et al.* 1997]. Mice with trinitrobenzene sulfonate-induced colitis have a Th1-mediated gut inflammation characterized by greatly increased production of IL-12, interferon (IFN) gamma and TNF alpha. Neutralization of endogenous IL-12 in CD mucosal cell cultures resulted in significant decreases in the number of IFN gamma producing cells [Parronchi *et al.* 1997]. Administration of recombinant anti-IL-12 in mice can resolve the induced colitis or prevent its development if given at the time of induction [Davidson *et al.* 1998; Neurath *et al.* 1995]. IL-12 is a heterodimeric cytokine constituted by two linked subunits, p35 and p40 [Mattner *et al.* 1993]. IL-12 and IL-23 share a common p40 subunit and, therefore, IL-23 biological activity is fully inhibited by the recombinant anti-IL-12p40. The role of IL-23 in T-cell response and its increased expression in CD has been described more recently [Schmidt *et al.* 2005]. The IL-23-driven inflammation appears to be mediated by the production of IL-17 and IL-6. Moreover, administration of IL-23 can increase the development of colitis lymphocyte-deficient recombinant mice [Yen *et al.* 2006]. Two fully humanized IgG1 monoclonal antibodies targeting the IL-12/IL-23 p40 subunit have been developed: ABT-874 (Abbott) and CNTO 1275 (Ustekinumab, Centocor). A randomized, controlled study of 79 moderate-to-severe CD patients treated with ABT-874 (1 or 3 mg/kg) was performed. This study proved the efficacy of anti-IL-12/IL-23 p40 in the induction of response at week 7 in the group receiving the higher dose with 75% of response compared to 25% in the placebo group [Mannon *et al.* 2004]. A high proportion of patients receiving the drug developed injection-site reactions. Only three out of 79 patients developed anti-drug antibodies. More recently, a double-blind crossover trial studied the efficacy of ustekinumab against the subunit p40 of IL-12, IL-23 [Sandborn *et al.* 2008].

Clinical response rates for the combined groups given ustekinumab and placebo were 53% and 30%, respectively at weeks 4 and 6, and 49% and 40%, respectively at week 8. In a subgroup of 49 patients who were previously given infliximab (neither primary nor secondary nonresponders), clinical response to ustekinumab was significantly greater than in the group given placebo ($p < 0.05$) through week 8.

Anti-CD3 antibodies

The activation of the CD3 complex on T-cells leads to a severe cytokine-release caused by T-cell activation. A humanized anti-CD3 monoclonal antibody binding the Cd3 chain of the T-cell receptor expressed on activated T-cells has been tested in UC. An open-label phase I trial studied 32 severe steroid-refractory patients with UC who received visilizumab at a dose of 10 or 15 $\mu\text{g/kg}$, administered intravenously on 2 consecutive days. The drug demonstrated an acceptable safety profile at the 10 $\mu\text{g/kg}$ dose level, a clinical benefit (66% remission and 87% clinical response) and a rapid decrease in circulating CD4(+) T-cell counts [Plevy *et al.* 2007]. Transient elevation of blood EBV-DNA (EBV, Epstein -Barr Virus) was also observed. Development of this compound, however, has been halted.

Anti-IL-6 antibodies

IL-6 is released mainly by antigen-presenting cells and produces its immunological effects mainly by binding to its soluble receptor. This cytokine plays a critical role in the apoptosis resistance of T-cells in CD by enhancing the expression of anti-apoptotic genes like BclXL and by inhibiting the expression of pro-apoptotic genes like Bax. IL-6 acts in synergy with IL-12 and IL-23 leading respectively to a Th1 and to a Th17 orientation of the lymphocyte system [Yen *et al.* 2006; Schmidt *et al.* 2005]. In animal models, administration of recombinant anti-IL-6 leads to a regression of colitis by inhibiting the release of pro-inflammatory cytokines, decreasing leukocyte migration and increasing the apoptosis of T-cells. Tocilizumab (namely MRA), a humanized anti-IL-6 receptor monoclonal antibody is under development for the treatment of inflammatory autoimmune diseases such as rheumatoid arthritis [Ding and Jones, 2006]. Tocilizumab showed efficacy at week 12 both in induction of response and remission in 36 patients with moderate-to-severe CD in a phase II study. The drug was administered intravenously at a dose of 8 mg/kg every 2 weeks and every 4 weeks. The response was higher

in the group treated every 2 weeks [Ito *et al.* 2004]. No major adverse effects were observed.

Recombinant human IL-10

IL-10 is an anti-inflammatory cytokine whose production is reduced in CD. IL-10 suppresses inflammation by various mechanisms including decreasing secretion of IL-2, IL-1, IL-8 and TNF alpha [Moore *et al.* 2001]. IL-10-deficient mice develop transmural inflammation of the gut which can be prevented by administration of recombinant IL-10 [Kühn *et al.* 1993]. However, the clinical efficacy of recombinant IL-10 for the treatment of CD has been disappointing. High doses of recombinant IL-10 caused a reduction in TNF alpha production but also an upregulation of IFN-gamma production by peripheral lymphocytes. No clinical efficacy was observed and many side effects occurred [Fedorak *et al.* 2000; Schreiber *et al.* 2000].

Epidermal growth factor and granulocyte-macrophage colony stimulating factor

Problems caused by epithelial permeability have been implicated in the physiopathology of CD. During intestinal inflammation, significant damage to the bowel wall and the epithelial barrier are observed with increased intestinal permeability. Epidermal growth factor (EGF) has been involved in the preservation of mucosal integrity and the regeneration of damaged mucosa [Beck and Podolsky, 1999]. Recombinant EGF has been tested in 24 patients with moderate-to-severe UC in a randomized double-blind placebo-controlled trial [Sinha *et al.* 2003] – it achieved disease remission in 83% of patients *versus* 8% in the placebo group.

Granulocyte-macrophage colony stimulating factor (GM-CSF) is able to stimulate the innate immune system and is used for the treatment of disorders due to neutrophil dysfunction. A phase II study in 124 patients with CD evaluated the efficacy of sargramostin (GM-CSF) and showed efficacy for the secondary endpoint of remission. The precise mechanism of GM-CSF's action in CD is still unclear [Korzenik *et al.* 2005].

Conclusion

A better knowledge of the physiopathology of CD and UC has led to the development of specific treatments against specific steps of the inflammatory cascade taking place in IBD. Anti-TNFs were the first biologic agents used in CD, and

then in UC. New therapies have been developed including drugs inhibiting other cytokines, drugs against leukocyte migration, and drugs promoting leukocyte apoptosis. These recent advances in IBD treatment give us new opportunities to treat IBD refractory to conventional treatment or resistant to biologic agents by switching from one biologic agent to another.

Conflict of interest statement

None declared.

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