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REVIEW

Disruption of inflammatory signals by cytokine-targeted therapies for inflammatory bowel diseases

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Gut inflammation occurring in patients with inflammatory bowel diseases (IBD) is associated with an excessive immune response that is directed against constituents of the normal bacterial flora and results in the production of large amounts of inflammatory cytokines. Anti-cytokine compounds, such as the neutralizing TNF antibodies, have been employed with clinical success in patients with IBD. However, nearly half of IBD patients are refractory to such treatments, response can wane with time, and anti-TNF treatment can associate with severe side effects and/or development/exacerbation of extra-intestinal immune-mediated pathologies. These observations, and the demonstration that, in IBD, the pathological process is also characterized by defects in the production and/or activity of counter-regulatory cytokines, have boosted further studies aimed at delineating novel strategies to combat the IBD-associated tissue-damaging immune response.

Abbreviations

ATI, antibodies to infliximab; CD, Crohn's disease; IBD, inflammatory bowel diseases; JAK, Janus-activated kinase; Stat, signal transducer and activator of transcription; Th cell, T helper cell; T-LPL, T-lamina propria lymphocytes; tmTNF, trans-membrane TNF; UC, ulcerative colitis

Introduction

Inflammatory bowel diseases (IBD) is the general term indicating Crohn's disease (CD) and ulcerative colitis (UC), two chronic inflammatory disorders of the intestine that have different morphological, immunological and clinical characteristics. The aetiology of IBD is unknown, but there is evidence that the liability to develop CD or UC is influenced by a wide range of genetic and environmental factors that promote an exaggerated mucosal immune response that is direct against components of the gut microflora (Kaser *et al.*, 2010). The novel therapeutic strategies for IBD patients are based on inhibiting or modulating the mucosal immune system. In this context, a major effort for researchers is to clarify all the inflammatory pathways of tissue damage in order to optimize the pharmacological interventions. In both CD and UC, the lesion occurs in mucosal areas heavily infiltrated with leucocytes, which through the release of cytokines interact with other immune and non-immune cells thus contributing to the IBD-associated tissue-damaging inflammatory response (MacDonald *et al.*, 1999). In this article, we review the available data justifying the use of compounds that modulate cytokine function in the therapy of IBD.

Anti-TNF therapy

TNF is a cytokine produced by multiple immune and non-immune cells, including macrophages, lymphocytes, mast cells, endothelial cells, fibroblasts and adipocytes, and involved in the regulation of various inflammatory processes (Bazzoni and Beutler, 1996). TNF is primarily produced as a type II transmembrane protein (tmTNF), which can be cleaved by the metalloprotease TNF converting enzyme (TACE) in a soluble form (sTNF) (Black *et al.*, 1997). The biological activity of both tmTNF and sTNF is mediated by

binding to specific receptors, namely TNF-receptor type 1 (TNF-R1) and TNF-R2. While TNF-R1 is expressed in most tissues and by several cell types, TNF-R2 is expressed by immune lineage cells only (MacEwan, 2002). Following interaction with the ligand, TNF-R1 and 2 initiate a cascade of intracellular events culminating in the activation of either mitogen-activated-protein-kinases and NF-κB or death-inducing signals (MacEwan, 2002). TNF is highly produced in the intestine of mice with experimental inflammation (Neurath *et al.*, 1997) and it is supposed to play a major role in driving the pathological process (Kontoyiannis *et al.*, 1999). Indeed, administration of TNF blockers to mice suppresses colitis (Powrie *et al.*, 1994; Neurath *et al.*, 1997). Excessive production of TNF is also seen in the inflamed mucosa of IBD patients (MacDonald *et al.*, 1990), where it targets several immune and non-immune cells and triggers multiple inflammatory pathways (e.g. production of chemokines and cytokines, induction of adhesion molecules on endothelial cells, synthesis of non-specific mediators of inflammation and tissue-degrading proteases) (Efimov *et al.*, 2009). Therefore, neutralization of TNF has been considered as a possible strategy for the treatment of active IBD patients. The first TNF blocker used in IBD has been infliximab, a monoclonal chimeric IgG1 anti-TNF neutralizing antibody that is effective in adult and pediatric patients with active, luminal and perianal CD (Targan *et al.*, 1997; Present *et al.*, 1999), and adult patients with active UC (Rutgeerts *et al.*, 2005). Importantly, clinical benefit seen in infliximab-treated patients associates with healing of the inflamed intestinal mucosa (D'Haens *et al.*, 1999). It has also been shown that scheduled therapy (administration every 8 weeks) can maintain clinical remission up to 1 year (Hanauer *et al.*, 2002). Unfortunately, however, response wanes over time probably due to the development of antibodies to infliximab (ATI), which are reported in high percentages in patients undergoing long-term infliximab therapy, and which neutralize and reduce the circulating levels of the drug. A strong inverse correlation exists between serum trough levels of infliximab and levels of ATI. High trough levels of infliximab have been associated with a more durable maintenance of clinical response, and low trough concentrations with potential loss of response (Baert *et al.*, 2003).

Shortening the infusion intervals (i.e. administration every 4 weeks) and/or increasing the dose of the drug (from 5 $mg \cdot kg^{-1}$ to 10 $mg \cdot kg^{-1}$ body weight) are useful strategies for increasing trough levels of infliximab and restoring the response to the drug (D'Haens *et al.*, 2011). At the same time, the concomitant administration of immunosuppressive drugs (i.e. thiopurines or methotrexate) could help prevent ATI development (Baert *et al.*, 2003). The spectrum of TNF-neutralizing drugs has recently been enriched by the commercialization of adalimumab, a fully human monoclonal IgG1 anti-TNF antibody, and certolizumab pegol, a monovalent Fab anti-TNF antibody fragment covalently linked to polyethylene glycol (Figure 1). Indications for both adalimumab and certolizumab pegol include induction and maintenance of remission in adult patients with luminal and perianal CD (Schreiber *et al.*, 2005; Colombel *et al.*, 2007). Administration of adalimumab or certolizumab is accompanied by a reduced production of anti-drug antibodies as compared with infliximab (Anderson *et al.*, 2005), confirming that chimeric antibodies are generally more immunogenic than humanized or human antibodies. No study has been yet carried to compare clinical efficacy of the three commercially available TNF antagonists in patients with IBD, but data from clinical trials suggest that they have similar efficacy and adverse-event profiles. The exact mechanism by which anti-TNF drugs reduce intestinal inflammation is not fully understood. The three compounds seem to have high binding affinities for both soluble (s) and tmTNF, but they differ in their ability to activate specific cellular pathways. For example, infliximab and adalimumab are able to bind FcγR, a natural receptor for antibodies, fix complement and induce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity (Arora *et al.*, 2009) Infliximab and adalimumab enhance also the rate of caspase-dependent apoptosis in lamina propria lymphocytes, a mechanism mediated by tmTNF-activated reverse signalling (ten Hove *et al.*, 2002). Certolizumab lacks these effector functions because it has no Fc region (Weir *et al.*, 2006), and does not induce apoptosis (Fossati and Nesbitt, 2005) probably because it is not able to crosslink tmTNF.

Because TNF is involved in the host defence against pathogens, particularly intracellular bacteria, it is not surprising that some patients can develop serious infections (Bongartz *et al.*, 2006) and have reactivation of opportunistic infections and latent tuberculosis following anti-TNF therapy (Keane *et al.*, 2001). Long-term therapy with infliximab can induce serum sickness and allergic-like infusion reactions, which have been linked to circulating ATI (Vermeire *et al.*, 2003). Moreover, infliximab and adalimumab therapy has been associated with *de novo* emergence of autoimmune conditions, such as drug-induced lupus or psoriasis (Wollina *et al.*, 2008). The reason by which anti-TNF therapy causes/exacerbates these immune-mediated pathologies is not known, even though studies in experimental models of psoriasis have shown that blockade of TNF can enhance T helper (Th)17 cell responses (Ma *et al.*, 2010), which are supposed to be pathogenic in the skin. By contrast, no increased risk of developing tumours has been documented in IBD patients receiving TNF blockers (Biancone *et al.*, 2006), even if a recent meta-analysis has demonstrated that these drugs can dose dependently increase the risk of malignancies in patients with rheumatoid arthritis (Bongartz *et al.*, 2006).

Abrogation of IL-6 signalling with a neutralizing IL-6 receptor antibody

IL-6 can be produced by many cell types, but major sources of this cytokine are monocytes and macrophages during acute inflammation and T cells in chronic inflammation (Nishimoto and Kishimoto, 2006). IL-6 biological activity is mediated by binding of IL-6 with a non-signalling membrane-bound receptor, termed IL-6 receptor (IL-6R)α. This interaction facilitates the recruitment of homodimers of the signal-transducing receptor gp130, with the downstream effect of activating the protein kinase JAK1 and Stat3, a transcription factor involved in the growth and resistance of cells to apoptotic stimuli as well as in the differentiation of Th17 lymphocytes (Atreya *et al.*, 2006). An alternative IL-6 signalling pathway, known as

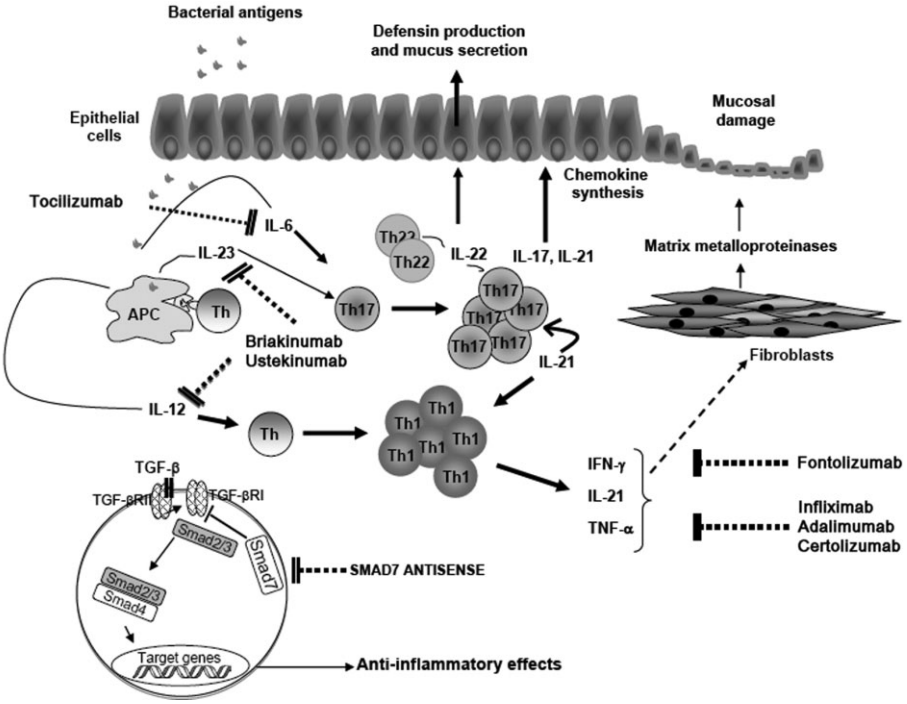

Figure 1

Schematic view of potential targets and site of action of some biologics in IBD. Following stimulation with bacterial products/components, antigen presenting cells (APCs) produce IL-12, which facilitates the differentiation of Th1 cells. Moreover, APCs make IL-23 and IL-6, which contribute to the polarization and expansion of Th17 cells. Briakinumab and ustekinumab, two monoclonal antibodies directed against p40, a subunit shared by IL-12 and IL-23, could interfere with the activation of both Th1 and Th17 cells. Commitment of naive T cells along the Th17 cell pathway and survival of such cells could also be inhibited by tocilizumab, an antibody blocking IL-6 signalling. The biological activity of IFN-γ, a typical Th1 cytokine, can be suppressed by fontolizumab, while anti-TNF antibodies include infliximab, adalimumab and certolizumab. Th17-derived cytokines, such as IL-17A and IL-21, contribute to amplify the ongoing mucosal inflammation by stimulating epithelial cells to make chemokines, thus enhancing the recruitment of inflammatory cells to the intestinal lamina propria. TNF and IL-21 can also stimulate fibroblasts to synthesize MMPs, a family of enzymes that play a major role in the mucosal degradation and tissue damage occurring in IBD. Moreover, IL-21 enhances the production of IFN-γ by Th1 cells, thereby expanding Th1 cell responses. Attenuation of the mucosal inflammation could be obtained using IL-22, a cytokine made by both Th17 cells and Th22 cells, which targets epithelial cells and stimulates the production of defensins and mucins. In IBD, there is a defective activity of TGF-β1, a powerful anti-inflammatory cytokine, due to high Smad7. Smad7 is an inhibitor Smad that interacts with type I TGF-β receptor and prevents Smad3/3 phosphorylation, a phenomenon that is induced by activated type I TGF-β receptor following binding of TGF-β1 to type II TGF-β receptor. Inhibition of TGF-β-induced Smad2/3 phosphorylation by Smad7 prevents the interaction of Smad2/3 with Smad4 and subsequent migration of the complex to the nucleus, where Smad2/3+Smad4 inhibit the expression of many inflammatory genes. Therefore, inhibition of Smad7 with a specific antisense oligonucleotide could restore TGF-β1 activity and facilitate the resolution of the inflammatory process.

IL-6 trans-signalling, is triggered by interaction of IL-6 to the soluble form of IL-6Rα (sIL-6Rα) and subsequent binding of this complex to membrane-bound gp130 (Rose-John *et al.*, 2006). IL-6 trans-signalling is responsible for the majority of IL-6 biological effects during chronic inflammatory processes and blockade of this signalling with an IL6R neutralizing antibody enhances mucosal T cell apoptosis and attenuates experimental colitis in mice (Atreya *et al.*, 2000). Expression of IL-6, sIL-6Rα and gp130 is up-regulated in IBD (Hyams *et al.*, 1993; Gustot *et al.*, 2005), and there is preliminary evidence indicating that administration of tocilizumab, formerly known as MRA, a humanized monoclonal antibody against IL-6R, to CD patients associates with higher clinical response and remission and induction of intestinal T cell apoptosis as compared with placebo (Ito *et al.*, 2004) (Figure 1). Nonetheless, tocilizumab does not seem to attenuate the endoscopic and histologic lesion (Ito *et al.*, 2004). It is thus conceivable that blockade of IL-6 signalling is not sufficient to fully inhibit the ongoing inflammation perhaps due to the existence of IL-6-independent inflammatory pathways that sustain the mucosal damage in patients treated with tocilizumab (Figure 1).

What do we need to effectively block inflammatory Th cell response in IBD?

As previously pointed out, CD and UC are immunologically distinct diseases. In particular, it has been long recognized that CD bears the stigmata of a T helper type 1 (Th1)-related disease, characterized by excessive production of IL-12, the major inducing factor of Th1 cell response in humans, and IFN-γ (Fuss *et al.*, 1996; Monteleone *et al.*, 1997). Consis-

tently, CD4+ T cells isolated from the inflamed gut of CD patients over-express the IL-12Rβ2 chain necessary for IL-12 signalling, and contain high levels of active Stat4 and T-bet (Parrello *et al.*, 2000; Neurath *et al.*, 2002), two transcription factors necessary for driving and sustaining Th1 cell responses. IL-12 is a heterodimeric cytokine produced by macrophages/dendritic cells mostly in response to bacterial stimulation and shares the p40 subunit with IL-23, another dendritic cell-derived cytokine involved in the regulation of both Th1 and Th17 cell responses (Trinchieri, 2003) (Figure 1). The nature of antigen(s) eliciting IL-12 production in CD remains unknown, but interactions between genes and components of the enteric flora may favour the shift of T cell responses towards the Th1 subtype. Studies in mice with lack or mutations of NOD2 (CARD15), a gene linked to CD and implicated in the response to bacteria, have shown that NOD2 activation is necessary to negatively regulate the production of IL-12 following to Toll-like receptor (TLR)-2 stimuli (Watanabe *et al.*, 2004). These studies raise the intriguing possibility that high IL-12 production and Th1 cell activation in CD may be secondary to a failure of NOD2 to inhibit TLR2 signalling, and that blockade of Th1-associated cytokines/transcription factors or inhibitors of TLR2 could be useful for attenuating the CD-associated Th1-driven inflammatory response. This hypothesis is supported by the demonstration that, *in vivo* in mice, administration of a neutralizing IL-12/p40 antibody reduces the ongoing Th1 cell response and ameliorates CD-like colitis induced by intrarectal administration of 2,4,6-trinitrobenzene sulfonic acid (Neurath *et al.*, 1995). Unfortunately, however, results of clinical studies testing the efficacy of two distinct neutralizing monoclonal anti-IL-12p40 antibodies (briakinumab, formerly known as ABT-874 and ustekinumab) in patients with moderate-to-severe active luminal CD were quite disappointing, as these antibodies were only slightly superior to placebo in inducing clinical remission (Mannon *et al.*, 2004; Sandborn *et al.*, 2008) (Figure 1). However, ustekinumab appeared more effective than placebo in inducing clinical response in patients who had previously received anti-TNF therapy, suggesting the possibility that anti-IL-12/p40 can be used in patients who failed or are resistant to TNF blockers (Sandborn *et al.*, 2008).

Similarly, no significant clinical response has been documented in active CD patients treated with fontolizumab, an anti-IFN-γ antibody (Hommes *et al.*, 2006; Reinisch *et al.*, 2006, 2010), as well as in patients receiving apilimod mesylate, an oral inhibitor of IL-12/IL-23 synthesis (Sands *et al.*, 2010) (Figure 1). The reason why anti-Th1 cytokine therapy has failed in CD remains unknown. A possible explanation is that these therapeutic approaches block the ongoing Th1 cell-related inflammation but leave unchanged or enhance further pathways of tissue damage. Indeed, it is now well known that the gut of CD patients contains high numbers of Th17 cells, another subset of Th cells that secrete IL-17A, IL-17F, IL-22 and IL-26, whose production/activity is not inhibitable by anti-IL-12/p40 antibodies or fontolizumab (Brand, 2009). If so, one could speculate that compounds targeting simultaneously both Th1 and Th17 cells rather than a targeted approach aimed exclusively at one or the other are more useful for combating CD-related inflammation. A strategy to reach this goal is to inhibit the expression/activity of IL-21, because this cytokine is produced in excess in the inflamed gut of CD patients (Monteleone *et al.*, 2005) and controls positively the production of both Th1 and Th17 cytokines (Monteleone *et al.*, 2005; Fina *et al.*, 2008). Moreover, preclinical studies have shown that IL-21-deficient mice are resistant against Th1/Th17-cell-driven colitis and administration of an antagonist IL-21 receptor fusion protein to mice suppresses experimental colitis (Fina *et al.*, 2008). The inflammatory role of IL-21 in the gut is also supported by the ability of this cytokine to enhance the synthesis of chemokines by epithelial cells (Caruso *et al.*, 2007) and secretion of MMPs by stromal cells (Monteleone *et al.*, 2006) and to make effector CD4+ T cells resistant to regulatory T cell-mediated immunesuppression (Peluso *et al.*, 2007) (Figure 1).

In UC, the T cell response is less polarized, even though UC T-LPL produces more IL-5 and IL-13, two Th2-related cytokines, as compared with normal controls (Fuss *et al.*, 2004). Consistently, studies in the oxazolone model of colitis, which shows striking similarities with UC, indicate that an excessive Th2-cell response contributes to the pathogenesis of the intestinal inflammation. Oxazolone-induced colitis is mediated by CD1-reactive natural-killer T (NKT) cells that make high levels of IL-13 (Heller *et al.*, 2002). Indeed, elimination of NKT cells or neutralization of IL-13 prevents the development of colitis. Overall, these data suggest that IL-13 is a potential therapeutic target for controlling mucosal inflammation in UC.

Like CD, UC is characterized by enhanced production of IL-17A and IL-21 (Fujino *et al.*, 2003; Monteleone *et al.*, 2005). Therefore, it is conceivable that simultaneous blockade of Th2 and Th17 cytokines could be useful for inhibiting UC-associated immune-inflammatory response.

Enhancing the activity of counter-regulatory cytokines as a novel approach to treat IBD

In recent years, a considerable amount of work has been produced to show that IBD-associated immune response is marked by a defective production and/or activity of counter-regulatory cytokines. Furthermore, preclinical studies have shown that restoring/enhancing the activity of such molecules is useful to suppress gut inflammation. The first example of such defects involves the intracellular pathway triggered by TGF-β1, a powerful immune-regulatory cytokine, which is able to target multiple immune and non-immune cell types and suppress inflammatory pathways (Gorelik and Flavell, 2002). The anti-inflammatory properties of TGF-β1 are largely dependent on activation of an intracellular signal program, which is triggered by binding of the cytokine to a heterodimeric membrane-bound receptor and promotes phosphorylation (activation) of Smad2/3, two intracellular proteins that interact with and are activated by TGF-β receptor (Heldin *et al.*, 1997). Although TGF-β1 is highly produced in IBD tissue (Babyatsky *et al.*, 1996), activation of Smad2/3 is defective due to the abundance of Smad7. Smad7 is an inhibitor Smad that binds the TGF-β receptor and prevents TGF-β driven Smad2/3 activation (Monteleone *et al.*, 2001). Consistently, knockdown of Smad7 with a specific antisense

Table 1

Side-effects associated with the use of anti-cytokine antibodies in patients with inflammatory bowel diseases

Compound	Route of administration	Patients	% of patients with side effects	Severity of side effects	Side effects	References
Infliximab	Intravenous	CD/UC	0.1–20	Potentially severe	Allergic-like infusion reactions, serum sickness, infections including TB reactivation, worsening of cardiac decompensation, demyelinating disease, hepatosplenic T cell lymphoma (rare), psoriasiform eruptions	Targan *et al.*, 1997 Hanauer *et al.*, 2002 Peyrin-Biroulet *et al.*, 2008
Adalimumab	Subcutaneous	CD/UC	0.1–10	Potentially severe	Injection site reactions, headache, infections including TB reactivation, worsening of cardiac decompensation, demyelinating disease, hepatosplenic T cell lymphoma (rare), psoriasiform eruptions	Hanauer *et al.*, 2006 Colombel *et al.*, 2007 Peyrin-Biroulet *et al.*, 2008
Certolizumab pegol	Subcutaneous	CD	0.1–5	Potentially severe	Injection site reactions, allergic reactions, headache, perianal abscess, bleeding, infections including TB reactivation	Schreiber *et al.*, 2005 Schoepfer *et al.* 2010
Tocilizumab (anti-IL-6R)	Intravenous	CD	9	Mild to moderate	Gastrointestinal bleeding	Ito *et al.*, 2004
Fontolizumab (anti-IFN-gamma)	Intravenous	CD	5–8	Mild	Dry skin, rash, sinusitis	Reinisch *et al.*, 2006 Reinisch *et al.* 2010 Hommes *et al.*, 2006
Ustekinumab (anti IL-12/p40)	Intravenous, subcutaneous	CD	16	Potentially severe	Pruritus, anxiety, infusion reactions (pyrexia, flushing), viral gastroenteritis (1 case), disseminated histoplasmosis (1 case)	Sandborn *et al.*, 2008
ABT-874/J695 (anti IL-12/p40)	Subcutaneous	CD	10–88	Mild	Injection site reactions, headache, bronchitis, urinary tract infections	Mannon *et al.*, 2004

oligonucleotide restores TGF-β1-induced Smad2/3 activation- (Monteleone *et al.*, 2001), thereby suppressing inflammatory cytokine production and experimental colitis in mice (Boirivant *et al.*, 2006) (Figure 1). Studies are now ongoing to assess the efficacy of Smad7 antisense oligonucleotide in patients with active CD.

IBD patients exhibit defects in the colonic production of IL-25 and thymic stromal lymphopoietin, two cytokines synthesized constitutively by epithelial cells and able to suppress the production of inflammatory cytokines (Caruso *et al.*, 2009; Iliev *et al.*, 2009). Importantly, administration of IL-25 prevents and cures experimental models of colitis, raising the possibility that IL-25-based therapy can enter into the therapeutic armamentarium of IBD patients in the next future (Caruso *et al.*, 2009).

Another cytokine with regulatory function is IL-22, a T cell-derived cytokine which is essential for the integrity of the intestinal epithelial barrier (Ouyang, 2010) (Figure 1). We have recently shown that intestinal production of IL-22 can be enhanced by activation of aryl hydrocarbon receptor (Monteleone *et al.*, 2011), a finding that well fits with the demonstration that the therapeutic effect of aryl hydrocarbon receptor ligands in murine models of colitis is preventable by neutralization of IL-22.

Another approach to potentate anti-inflammatory signals in the gut is to use IL-10, a cytokine, which inhibits the development of Th1-type responses, suppresses Th2 cell-mediated allergic reactions and macrophage/dendritic cell activation, and enhances the differentiation of regulatory T cells (Moore *et al.*, 2001). Additionally, IL-10 can target stromal cells and inhibit the production of tissue-degrading proteases (Pender *et al.*, 1998). IL-10-null mice spontaneously develop bacteria-induced IL-12-driven enterocolitis, thus confirming the key role of this cytokine in preventing detrimental inflammatory responses in the gut (Sellon *et al.*, 1998). Germline mutations in IL-10R genes have been documented in some patients with early-onset and severe IBD, raising the possibility that defects in IL-10 activity may have a key role in sustaining the IBD-related pathogenic response (Glocker *et al.*, 2009). Unfortunately, however, subcutaneous administration of recombinant human IL-10 to patients with active and steroid-dependent CD was not effective in inducing clinical response/remission (Schreiber *et al.*, 2000). It is conceivable that the failure of these clinical studies relies on the fact that IL-10 did not reach therapeutic concentrations in the gut following systemic administration (Braat *et al.*, 2006). To overcome this issue, IL-10-encoding probiotics have been developed. Despite an encouraging phase I trial in CD patients (Braat *et al.*, 2006), studies testing the therapeutic effect of IL-10-secreting lactobacilli in IBD patients have not yet published.

Conclusions

In the last decades, studies in various experimental models of IBD have advanced our understanding of the contribution of cytokines in the pathogenesis of gut inflammation. It has also become evident that distinct subsets of inflammatory cytokines can be produced at the same time in the same patient. Therefore, targeting simultaneously two or more of these signals could be more advantageous than inhibiting selectively single cytokine pathways. Various approaches for inhibiting cytokines that govern Th cell polarization and/or activity have already been developed and tested in IBD patients. Other compounds are now ready to move into the clinic. However, in designing clinical interventions around inflammatory cytokines, we should take into consideration that many of these molecules are involved in the host response against infective agents and neoplasias. Therefore, the use of cytokine blockers could associate with severe side effects (Table 1). In this context, a more advantageous approach could consist in restoring/enhancing the production/activity of counter-regulatory cytokines, which are defective in IBD. As it is highly plausible that no drug will work in all IBD patients, further experimentation will be however needed to ascertain whether and which patient could benefit from specific cytokine-based therapies.

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Conflict of interest

GM has filed a patent entitled 'A treatment for inflammatory diseases' (patent No. 08154101.3), while the remaining authors have no conflict of interests to disclose.

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