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Monoclonal antibody therapy of inflammatory bowel disease

• S.J.H. van Deventer and L. Camoglio

Introduction

Crohn's disease and ulcerative colitis are characterized by relapsing inflammation of the intestinal mucosa. Although the cause of either disease is known, they are likely to have a different pathogenesis. There is substantial evidence for enhanced mucosal T-cell activation in Crohn's disease, whereas in ulcerative colitis specific anti-epithelial antibodies can be demonstrated. Recent data from various animal models of inflammatory bowel disease seem to indicate that the normal mucosal immune response is strictly regulated, and that a lack of specific anti-inflammatory T-cells may lead to uncontrolled activation within the CD4+ compartment. In several T-cell-dependent animal models of inflammatory bowel disease inflammation does not occur in germfree conditions, thus providing evidence for bacterial antigens as the driving force of the ill-controlled immune responses. Whatever the cause of inflammatory bowel disease, there is substantial evidence that mucosal inflammation is mediated by cytokines and chemokines, and by enhanced recruitment of inflammatory cells. Current medical therapy of inflammatory bowel diseases consists of the administration of drugs with poorly defined molecular targets. In fact, it has been argued that in order to be effective in IBD, drugs would need to have a broad range of anti-inflammatory activities. Monoclonal antibodies have been used in a wide range of conditions to block or stimulate very specific targets. Somewhat surprisingly, relatively few interventions using monoclonal antibodies have been published, but in the clinical setting, the results of treatment with two monoclonal antibodies (anti-CD4 and anti-TNF) have now been reported. In this chapter we briefly review the effects of treatment with three classes of potential anti-inflammatory monoclonal antibodies (immunomodulatory, anti-cytokine, and those that prevent mucosal recruitment of leukocytes) in experimental and clinical inflammatory bowel disease.

Immunomodulatory antibodies

The precise mechanism(s) of mucosal inflammation in Crohn's disease and ulcerative colitis are unknown, and both diseases are characterized by recruitment of various inflammatory cells into the intestinal mucosa. Nonetheless, there is reason to believe that, at least in Crohn's disease, activated T-cells within the CD4 compartment are central in the pathogenesis of inflammation. Firstly, various animal models have established the ability of CD45RB^{high} T-cells (Th1 precursors) obtained from healthy mice to induce extensive mucosal inflammation after transfer to SCID mice that lack T-cells. Interestingly, inflammation does not ensue when CD45RB^{low} cells are simultaneously infused [1]. Other mouse models have established that CD8+ cells do not have an important role, and that inflammatory bowel disease may also be induced by T-cells that were educated in an aberrant thymic

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Abstract

Animal models of inflammatory bowel disease have provided insight in the regulation of mucosal inflammation. This has resulted in novel therapeutic approaches that specifically target a single inflammatory mediator. Monoclonal antibody therapy has been used in steroid refractory Crohn's disease patients. Anti-TNF antibody administration induced complete remissions and few side effects were observed. Although these findings need to be confirmed in controlled and long term treatment studies they may guide the development of specific and effective therapies for these diseases.

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environment [2]. In patients with Crohn's disease mucosal CD4+ T-cells have been shown to bear activation markers, and circulating sIL-2 receptor levels correlate with disease activity [3-6]. Finally, cases of severe Crohn's disease that disappeared with the onset of AIDS (and hence a drop of the CD4+ count) have been reported [7 8]. CD4 antibodies have been used in various animal models of autoimmune disease, in particular in rheumatoid arthritis, but the clinical efficacy in this disease had been disappointing [9-11].

We have completed a small and non-controlled study using anti-CD4 treatment in 12 patients with steroid-refractory Crohn's disease. This study was designed as a phase I dose-escalating study, using the mouse-human chimeric antibody M-T412. This antibody cross-reacts with CD4 molecules from healthy blood donors, and previously had been shown to deplete CD4 cells *in vivo*. The three doses of MT-412 used were 10, 30 and 100 mg daily as an intravenous infusion for seven consecutive days. The first infusion of M-T412 resulted in systemic release of TNF, both types of soluble TNF receptors and interleukin-6, and caused a febrile reaction in most patients, but in general the side effects were minor [12]. A dose-dependent decrease in circulating CD4+ cell counts was observed, with low CD4+ counts (about 25% of baseline) persisting for three months after the first infusion. No significant permanent changes in the CD8+ or CD19+ (B-cell) counts were observed. At ten weeks the CDAI had significantly decreased by 24% and 52% in the two highest dose groups [13]. In all but one patient the abnormal expression of HLA-DR by the intestinal epithelium had disappeared [14]. Because HLA class II expression by mucosal epithelial cells is regulated by interferon- this observation strongly suggested a downregulation of mucosal T-cell activation. However, these data should be cautiously interpreted because this study was uncontrolled, and not designed to primarily assess the efficacy of M-T412 treatment.

Various mechanisms may explain the effects of CD4 targeted monoclonal antibody therapy. Although the mechanisms of action are not completely understood treatment with anti-CD4 monoclonal antibodies may induce immunological tolerance, and recently it has been shown that apoptosis may result from crosslinking of CD4 [15]. Finally, some anti-CD4 antibodies (including M-T412) cause a reduction in the number of circulating T-cells.

In conclusion, anti-CD4 antibody therapy was demonstrated to be relatively safe, despite prolonged reductions in the number of circulating CD4+ T-cells. No controlled studies have been conducted using this treatment modality, but a few patients responded with prolonged remissions. Nonetheless, in view of the recently characterized role of specific T-cell subsets within the CD4+ compartment (*vide infra*) with some CD4+ T-cells being regulatory, a reduction of *all* CD4 T-cells would no longer seem to be a primary goal of immunotherapy. On the other hand, it is possible that some of the biological effects of anti-CD4 antibody therapy can be obtained using more specific approaches. Inappropriate T-cell activation can be inhibited by blocking co-stimulatory signals, for example by administration of CTLA4-Ig, and various

ways of inducing apoptosis of activated T-cells are presently under investigation [16 17].

Anti-cytokine antibodies

The inflamed mucosa produces a wide range of pro- and anti-inflammatory cytokines, that orchestrate the inflammatory reaction as well as tissue remodelling and fibrosis. Many of these locally released cytokines remain compartmentalized within the mucosa, and with the exception of interleukin-6, the serum concentration of most pro-inflammatory cytokines is not strikingly increased in active inflammatory bowel disease. Traditionally, the production of various cytokines has been attributed to specific cell types, leading to the discrimination of 'T-cell' and 'monocyte/macrophage'-type cytokines. It now is clear that within the gut mucosa epithelial cells importantly contribute to cytokine production, in particular by secreting large amounts of chemokines such as IL-8, MIP-1 / and RANTES [18 19]. It should also be noted that some secreted cytokines, such as TNF, also exist in a membrane-bound form on T-cells and monocytes, and in this conformation they are likely to modulate the function of other cells during cell-cell contact. Finally, neither the rate of production nor the tissue concentration of a particular cytokine seems to predict a central role in the pathogenesis of mucosal inflammation. Therefore the only way to definitively demonstrate the pathogenic importance of various cytokines would be to silence genes that encode the specific cytokines, or to block their biological effects, i.e. using monoclonal antibodies. A major problem in developing cytokine-directed clinical intervention strategies is the choice of the targets. In fact, it has been argued that, in view of the complex interactions and redundancy within the cytokine system, blocking the biological activity of a single cytokine would unlikely cause beneficial clinical effects.

Various cytokine knock-out mice models have been described that have inflammatory bowel disease as a major phenotype [20]. We will not review these experiments in detail, but in conjunction with CD4+/CD45 T-cell subset transfer experiments in SCID mice, the data seem to indicate that normal homeostasis within the gut mucosa depends on active suppression by specific CD4+ T-cells. CD4+/CD45RB^{high}-induced inflammatory bowel disease in SCID mice is characterized by mucosal expression of high levels of TNF and IFN mRNA, and can be prevented by repeated administration of neutralizing anti-TNF and anti-IFN antibodies. In this model, as well as in IL-10 knockout mice, administration of IL-10 also decreases disease activity [21]. Hence, these data would support the use of anti-TNF or anti IFN antibody treatment in Crohn's disease. We have recently completed an open-label phase I study using the chimeric mouse/human monoclonal antibody cA2 in patients with steroid-refractory Crohn's disease [22 23].

In this uncontrolled study, a single intravenous infusion of the antibody caused a complete remission in nine out of ten patients studied. A very rapid (within days) drop in the circulating IL-6 and CRP levels was observed, and in most patients a remarkable healing of mucosal ulcerations was recorded. Anti-

TNF treatment resulted in a marked downregulation of mucosal chemokine expression, in particular of RANTES and MIP-1. The median duration of the induced remissions was three months, and all patients had relapsed at six months after the infusion. These data indicate that TNF has a central position in the mucosal inflammatory reaction in Crohn's disease, and suggest the possibility of anti-TNF treatment of steroid-refractory patients. However, many questions remain, and need to be answered in studies that are presently ongoing. It is unknown whether repeated administration of anti-TNF antibodies will continue to be effective and safe. Importantly, the exact mode of action of anti-TNF antibody treatment is unknown.

It has been well documented that neutralization of TNF can downregulate the expression of neutrophil-adhesion molecules by activated endothelial cells [24]. TNF is a potent inducer of the extrinsic route of coagulation activation, and can activate the transcription of a wide range of other cytokines. Nevertheless, the half-life of cA2 in humans (about two weeks) is much shorter than the duration of the remissions observed, and this suggests an immunomodulatory activity rather than simple neutralization. It is tempting to speculate that anti-TNF antibodies bind to membrane-expressed TNF on the source cells (monocytes, macrophages, T-cells), causing either killing (by activation of complement or ADCC) or modulation (by yet unknown mechanisms). Elucidation of the mechanism of action of anti-TNF antibody treatment could lead to the definition of novel therapeutic targets in IBD and therefore should have a high priority.

Instead of blocking pro-inflammatory cytokines, it might be feasible to influence the development of T-cells into the Th1 and Th2 subsets, and the importance of various cytokines (IL-4, IL-10, IL-12) in this process is now well established *in vitro*. Neutralization of IL-12 would also be expected to prevent NK-cell activation, and IL-12 antibody therapy reduced Th1-mediated chronic intestinal inflammation caused by the hapten reagent TNBS in mice. In this study, the presence of IL-12 was essential to maintain TNBS-induced colitis and the persistent local Th1 cytokine response, while even a delayed anti-IL-12 treatment had beneficial effect. These data suggest that anti-IL-12 antibodies might have a potential therapeutic effect in Crohn's disease. This hypothesis is also supported by the recent finding that IL-12 p35/p40 (p70) heterodimer expression (the active functional form) is increased in the colon of patients with CD compared to that in normal colon [25].

Interference with recruitment of inflammatory cells

The normal gut mucosa is populated by a large number of potential inflammatory cells, and in active UC and Crohn's disease additional leukocytes are recruited from the circulation. Endothelial adhesion and transmigration of leukocytes depends on the expression of endothelial adhesion molecules that recognize specific ligands on leukocytes, and on the polarized expression of chemotactic factors such as platelet-activating factor and the chemokines. The molecular interactions leading to neutrophil-endothelial cell adhesion have been well characterized, and consist of

a weak interaction, which is dependent on the expression of L-selectin by neutrophils, and results in 'rolling' of the neutrophil along the endothelial surface [26-28]. Subsequently, neutrophils become activated, the α_2 -integrins are upregulated and switched on and L-selectin is shedded. The endothelial contribution to neutrophil adhesion consists of the induced expression of P-selectin (early) and E-selectin (late) that are involved in mediating the early phase of neutrophil binding, and the constitutive expression of ICAM-1, that binds the α_2 integrin CD11b/CD18 [29]. In addition, the activated endothelium expresses the membrane-bound platelet-activating factor, as well as heparan-sulphate-associated interleukin-8, that are both involved in the process of transendothelial migration of neutrophils [30-31]. Hence, one can envisage prevention of neutrophil recruitment by interference with either early or late phases of neutrophil/endothelial cell interaction, or by blocking the biological signalling that results in transmigration. Indeed, using either knockout mice or blocking monoclonal antibodies, proof of efficacy for all these interventions has been shown in various animal models of infection, inflammation or ischemia/reperfusion injury. Surprisingly, in only two studies neutrophil-targeted antibodies have been tested for efficacy in experimental inflammatory bowel disease. Pretreatment with the anti-CD18 antibody IB-4 markedly suppressed mucosal neutrophil infiltration in trinitrobenzene sulphonate-induced colitis, and this resulted in a reduction in epithelial injury [32]. We have recently demonstrated that a blockade of CD11b, using a recombinant protein named neutrophil inhibitory factor (NIF), resulted in a reduction of mucosal neutrophil infiltration in immune complex-induced colitis in rabbits, and this coincided with a reduction of mucosal LTB₄ and TXB₂ production, while PGE₂ release remained unchanged [33]. Hence, these two studies indicate that in different models of experimental inflammatory bowel disease reduction in neutrophil infiltration is feasible and may result in a reduction in tissue injury. The relevance of these findings for the therapy of (severe) inflammatory bowel disease remains unknown, and a complete blockade of neutrophil transmigration may seriously impair the host defense response. Nevertheless, the outcome of the two animal studies discussed would justify a more detailed analysis of the therapeutic efficacy of prevention of neutrophil influx into the bowel mucosa in IBD.

The factors that mediate lymphocyte recruitment in the gut mucosa have been only partially elucidated, and it is not known what proportion of these cells is recruited through high endothelial venules vs. direct recruitment into the mucosa. Adhesion of lymphocytes and monocytes is mediated by the expression of VCAM-1 by endothelial cells that has VLA-4 as its natural ligand. Treatment of spontaneous colitis in cotton-top tamarins with two different mouse monoclonal antibodies against human E-selectin did not ameliorate disease activity, but administration of antibodies against the α_4 subunit of VLA-4 was highly effective [34]. It should be noted that the α_4 VCAM-1 subunit is not only involved in monocyte-lymphocyte/endothelial cell interactions, but also in lymphocyte recirculation through mesenteric lymph nodes

and Peyer patches [35]. Furthermore, modulation of VLA-4 by antibody-mediated crosslinking may potentially alter the function of lymphocytes. Nonetheless, the most likely explanation for the beneficial effect of anti-CD4 antibodies is interference with recruitment of monocytes and lymphocytes into the mucosa.

Conclusion

The studies discussed in this review have demonstrated that a blockade of specific inflammatory pathways may ameliorate experimental inflammatory bowel disease. Two monoclonal antibodies, anti-CD4 and anti-TNF, have been used in small clinical studies, and few side effects were observed. Anti-TNF treatment seemed to markedly improve disease activity in patients with steroid-refractory Crohn's disease, but these findings need to be confirmed in controlled clinical trials. Hence, treatment of inflammatory bowel disease using monoclonal antibodies is feasible, and may be effective. However, treatment of chronic human diseases with mouse/human chimeric antibodies may have disadvantages. Many, if not all, monoclonal antibodies clinically tested induce human-anti-chimeric antibody (HACA) responses, that may interfere with the activity of the monoclonal antibody, or induce side effects. Monoclonal antibody therapy is currently very expensive, and would in most cases require repeated intravenous administration. Finally, some of these antibodies are potentially very immunosuppressive, and long-term treatment may be complicated by opportunistic infections or malignancy. Nevertheless, monoclonal antibodies have proved to be exciting tools that enable a relatively rapid resolution of the inflammatory mechanisms in Crohn's disease and ulcerative colitis and the results of these interventions may guide the development of specific and effective therapies for these diseases.

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