Translational Medicine
ISSN: 2161-1025

Uchiyama et al., Transl Med 2012, S:2
DOI; 10.4172/2161-1025.S2-004

Review Article Open Access

Clinical Studies of Molecular Targeted Therapies for Inflammatory Bowel Disease

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Abstract

Therapeutic strategies for inflammatory bowel disease (IBD), particularly biological therapies, have been developed recently. The pathogenesis of IBD is based on complicated cytokine-mediated signaling pathways, which represent future drug targets. Recent data have shown that these pathways induce intestinal T-cell activation, which is a central process in disease pathogenesis, via inflammatory mediators. These inflammatory mediators, including cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-12/IL-23, and IL-10, may play important roles in disease pathogenesis, and therefore represent potential therapeutic targets. These strategies may lead to new therapeutic drugs that are more effective and less toxic in IBD.

Keywords: Ulcerative colitis; Crohn's disease; Molecular target; T cell

Introduction

Inflammatory bowel disease (IBD) is defined as chronically relapsing inflammations of the gastrointestinal tract that are not caused by identified pathogens [1,2]. IBD is generally thought to develop as a result of an abnormally active intestinal immune system that results from host-microbial interactions in a genetically susceptible individual [3]. Ulcerative colitis (UC) and Crohn's disease (CD) are the 2 major forms of IBD that markedly influence the health-related quality of life in patients and are expensive to manage[4-6]. UC is characterized by a superficial, continuous inflammation, which is limited to the large intestine, and its symptoms are primarily diarrhea with bleeding. CD is a multifocal, transmural inflammatory process that can affect any part of the digestive tract, and is complicated by deep ulcerations that have the potential to form fistulae and abscesses. Infectious agents, environmental factors, genetic predisposition, and mucosal imbalance with ongoing activation of the intestinal immune system have been implicated in the pathogenesis of IBD [7]. Interestingly, some genes are common to both disorders, suggesting that a part of CD and UC have common genetic and pathophysiologic mechanisms of illness and are not 2 distinct disease entities.

As the exact pathogenic mechanisms are still incompletely understood, therapeutic strategies have been limited to mostly evidence-based principles. Corticosteroids and immunosuppressive agents such asazathioprine, which ameliorate nonspecific inflammatory processes, have been used as conventional treatment for IBD. However, fora majority of IBD patients, corticosteroids are insufficient treatment, as population-based studies have shown that a significant proportion of corticosteroid-treated CD patients develop steroid dependency or even steroid-refractory illness [8], while the need for surgical intervention has apparently remained unchanged [9]. This insufficient therapeutic effect and the potentially severe side effects of corticosteroids have demonstrated the necessity for a more specific therapeutic response, which can only result from a more comprehensive approach of targeting critical points in the signal transduction pathways involved in the inflammatory cascade [10]. Several factors, such as genetic and immunologic abnormalities, are involved in the pathogenesis of IBD. In the context of environmental triggers, these factors lead to the common end result of increased intestinal inflammation and provide multiple potential targets for pharmacotherapeutic intervention. These targets include aberrant host-microbial interactions at the luminal-epithelial-cell interface, antigen processing by macrophages and antigen presentation to T cells, T-cell activation, T-cell signaling and T-cell differentiation, cytokine production, and leukocyte trafficking (Figure 1).

Recent understanding of immunopathogenic mechanisms in IBD has led to the development of biological therapies, which selectively inhibit crucial mediators of the inflammatory process. There is a conception that uncontrolled activation of central effector cells in the gut is the pivotal pathogenic mechanism underlying the initiation and perpetuation of the inflammatory reaction [11,12]. In IBD, CD4+ T cells have been reported to be the main type of activated immune

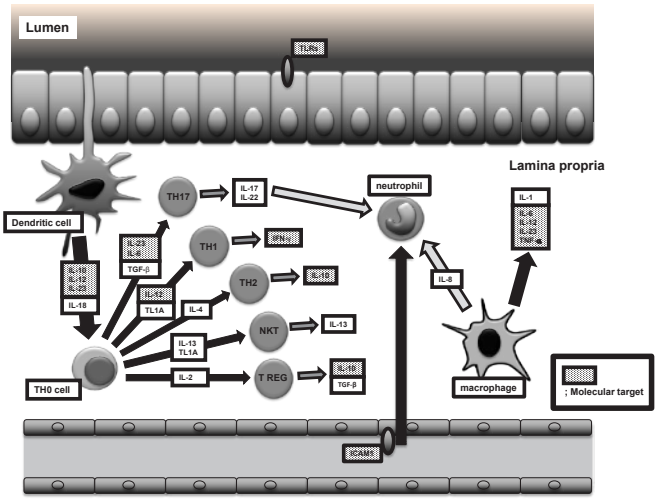

Figure 1: Therapeutic targets for ulcerative colitis and Crohn's disease. IBD is included these complicated immunologically driven interactions. These cascades might be targets for biologic therapies.

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Received February 27, 2012; **Accepted** March 26, 2012; **Published** March 26, 2012

Citation: Uchiyama K, Takagi T, Naito Y (2012) Clinical Studies of Molecular Targeted Therapies for Inflammatory Bowel Disease. Transl Med S2:004. doi:10.4172/2161-1025.S2-004

cells, characterized by enhanced proliferation and trafficking into the intestinal mucosa [13]. Alterations in cytokine production elicited by this aberrant T-cell activation lead to a disturbed balance between pro- and anti-inflammatory cytokines [14]. Profiles of these cytokine are currently the main focus of not only basic but also clinical research in IBD because of the development of new therapeutic strategies.

Tumor Necrosis Factor-α (TNF-α)

In IBD, activated macrophages and lymphocytes produce various pro inflammatory cytokines. One of them, TNF-α plays an important role in IBD. TNF-α exists as a transmembrane protein (membrane-bound TNF [mTNF]), from which the soluble form (sTNF) is released via proteolytic cleavage by the TNF-α-converting enzyme, and secreted TNF-αexerts its biological functions via 2 distinct cell surface receptors, TNF receptor 1 (TNFR1) and TNFR2 [15,16]. Several studies have demonstrated that the production of TNF-α is elevated in the intestinal mucosa and serum of IBD patients [17-19]. Therefore, this cytokine has been reported to be an important target for the treatment of IBD, and several anti-TNF-α agents have been developed. Among them, infliximab, adalimumab, and certolizumabpegol have proven their therapeutic effects in several studies in CD patients [20-25]. The efficacy of anti-TNF-α agents is based on multiple effects, but the precise molecular mechanism of action is still unclear. It has been reported that infliximab can block both soluble TNF-α and mTNF-α in vitro [22]. Given that the pathogenesis of CD depends more on effects mediated via mTNF-α, the neutralization of soluble TNF-α is not the only therapeutic modality of anti-TNF-α agents [26]. Several studies on the mechanism of action of infliximab in IBD have demonstrated that it induces apoptosis in a Fas-independent manner via caspase activation in circulating peripheral blood monocytes from CD patients. Mitochondrial release of cytochrome *c* and transcriptional activation of the proapoptotic proteins Bax and Bakhave also been reported [27]. The apoptotic effect of infliximab on lamina propria T cells at the site of intestinal inflammation was demonstrated in biopsy samples [28]. Intestinal biopsies were taken from macroscopically inflamed areas in CD patients before and 24h after a single infusion of infliximab, and T-cell apoptosis was examined. Infliximab also induced apoptosis in a Fas-independent manner in cultured intestinal T cells from CD patients [29,30]. These data suggest that anti-TNF-α antibodies induce apoptosis in lamina propria mononuclear cells, explaining their clinical efficacy in the treatment of CD. Van den Brande et al. [31] demonstrated the apoptotic effect of infliximab in the lamina propria T cells of patients with active CD and showed that induction of intestinal T-cell apoptosis was related to the clinical efficacy of anti-TNF-α treatment in these patients. These data substantiate the hypothesis that induction of intestinal T-cell apoptosis is one of the central molecular mechanisms of action of anti-TNF-α agents in IBD, and that this effect also explains the clinically visible rapid induction of remission after anti-TNF-α antibody administration. However, these data are not enough to explain the molecular mechanism of action of anti-TNF-α antibodies in IBD because the clinically effective anti-TNF-α agent certolizumab does not induce apoptosis in intestinal T cells.

TNF-α antibody treatment has been reported to contribute colonic mucosal healing of UC and CD patients. Schnitzler et al. [32] reported that long-term maintenance of TNF-α antibody treatment induce mucosal healing and is associated with the avoidance for major abdominal surgeries. Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC Study) revealed that the treatment with infliximab-based strategies resulted in significantly higher rates of mucosal healing at week 26 among patients with active Crohn's disease [33]. Recent study showed the effect of infliximab about mucosal healing with UC patients [34,35].

TNF-α antibody treatment is the standard strategy to control active CD and UC. However, a large proportion of refractory IBD patients do not respond to TNF-α antibody treatment and the long-term use of these agents are hampered by immunogenicity and the risk of severe infectious complications. Therefore, for specific groups or subgroups of IBD patients, alternative compounds will be necessary to control intestinal inflammation.

Interleukin-6 (IL-6)

It has been reported that the proinflammatory cytokine IL-6 plays an important role in the pathogenesis of IBD. Serum IL-6 levels were substantially elevated in patients with active CD [36-38]. Given that the concentration of IL-6 is related to the activity of CD, serum IL-6 levels are considered to be a clinically relevant parameter [39]. IL-6 mRNA levels are also elevated in the intestinal mucosa of CD patients [40]. In addition, intestinal IL-6 production highly correlates with the severity of endoscopic and histopathologicsigns of inflammation in CD [41,42]. Other studies showed that the main producers of IL-6 in intestinal mucosa are lamina propria T cells [43] and macrophages [44]. In studies on a murine model of dextran sulfate sodium-induced colitis, IL-6-deficient mice showed reduced signs of intestinal inflammation [45]. These results indicate that IL-6 plays an important role in the pathogenesis of IBD.

IL-6 exerts its effects by binding to a soluble form of its corresponding receptor (sIL-6R), which is generated by limited proteolysis of the membrane-bound form on the surface of macrophages [46]. An antibody against IL-6R was tested in diverse murine models of chronic intestinal inflammation. The inflammatory activity was reduced in all models by anti-IL-6R antibody treatment, thereby confirming the role of IL-6-mediated trans-signaling in mucosal inflammation in vivo [43,47]. The anti-IL-6R antibody has been tested in a pilot clinical study [48,49] and analysis of CDAI scores revealed that the antibody was effective in active CD patients compared to the placebo control. However, endoscopic and histologic scores revealed no differences between the anti-IL-6R antibody and placebo groups, suggesting that there is no effect of this antibody on mucosal healing.

IL-12/IL-23

Genome-wide association scans have identified more than 50 susceptibility genes and protective genes for CD and several genes for UC [50-52]. Many of these genes encode proteins associated with inflammatory pathways. Multiple genetic variants in the IL-12/IL-23 pathway that are already known to be associated with CD have been identified by a novel gene pathway analysis [53]. IL-12 and IL-23 are structurally similar heterodimeric cytokines that share a common subunit, p40 (the product of IL-12B). Multiple stages of the immune response and differentiation of naïve CD4+ T cells are modulated by these cytokines. IL-12 promotes the differentiation of CD4+ cells into Th1 cells, which secrete IFN-γ and TNF-α; IL-23 enables the differentiation of CD4+ cells into Th17 cells, which are important in inflammatory regulation [3]. Therefore, the IL-12/IL-23 pathway and the IL-17 pathway are targeted for early phase clinical trials in both CD and UC. Antibodies against IL-12, p40, IL-17 receptor, JAK3, and IL-23 receptor are included in the strategy to control IBD. Antibodies against IL-12 and IL-23 have been evaluated in early phase II studies and these agents have demonstrated efficacy in subpopulations of patients with CD. In a phase III study, ustekinumab, which is a parenteral formulation of IL-12 and IL-23 antibodies and targets the

p40 subunit common to both IL-12 and IL-23, was shown to be highly effective in the treatment of patients with psoriasis [54]. The phase II study of ustekinumabin moderate-to-severe CD patients demonstrated efficacy primarily in patients who had previously received the anti-TNF-α antibody infliximab [26]. Another anti-IL-12/anti-IL-23 antibody apilimodmesylate is an oral compound that suppresses the transcription of IL-12 and IL-23. However, a phase II randomized controlled study showed that this compound was not more effective than placebo for the treatment of active CD [55].

IL-10

A European genome-wide association study identified IL-10 genevariants as susceptibility genes for UC [51]. The anti-inflammatory cytokine IL-10 prevents intestinal inflammation, and genetically deficient IL-10 knockout mice spontaneously develop colitis [56]. Based on these observations, subcutaneous administration of IL-10 was evaluated in CD clinical trials. AlthoughIL-10 administration was not effective in CD patients [57], this drug should be evaluated for UC treatment; an early phase clinical trial is currently underway for the assessment of this product both as an oral pill and a rectal enema formulation.

INF-γ

In patients with CD, it has been reported that the production of IL-12 and IL-18 results in a Th1 polarized immune response, which is thought to be one of the important processes in the pathogenesis of CD. Therefore, it is reasonable to treat CD using agents that block INF-γ, a representative Th1 cytokine. In a CD clinical trial evaluating fontolizumab, an anti-INF-γ-antibody, the active CD group comprising 201 patients exhibited greater improvement in CD activity index scores and C-reactive protein (CRP) levels compared to the placebo group [58]. Although a strong clinical response to fontolizumab in CD was not observed in that phase II study, CRP levels in fontolizumab-treated CD patients were significantly reduced. Two other clinical trials of fontolizumab were conducted on 133 and 45 active CD patients, respectively [59,60]. These studies also demonstrated higher rates of clinical response and remission in the fontolizumab groups compared to the placebo groups. Given the bioactivity of the INF-γ antibody in CD treatment, further large scale clinical trials will be necessary to establish clinical efficacy in CD.

Toll-like Receptors (TLRs)

All experimental animal colitis models require enteric bacteria for the development of intestinal inflammation, and fecal diversion has been accepted as a treatment for distal intestinal inflammation [61]. The recognition of various pathogen-associated molecular patterns, such as lipopolysaccharide, peptidoglycan motifs, and bacterial flagellins, are included in the innate immune system between intestinal flora and intestinal epithelial cells [62]. Toll-like receptors (TLRs) recognize and respond to these bacterial components and induce various intracellular cascades, such as proinflammatory cytokine production [63]. In colonic inflammation, the expression of TLRs on colonic epithelial cells are abnormal, and genetic variants in TLR2, TLR4, TLR5, and TLR9 have been reported to be associated with CD [64-67]. TLR4 induces continuous proinflammatory cytokine production in the presence of Gram-negative bacteria and is up regulated in the colonic mucosa of IBD patients [68]. TLRs are essential for host-microbe interactions and represent potential targets for future biological therapies to limit such interactions. Currently, there are no active trials using TLR agonists or antagonists to disrupt aberrant bacterial-host interactions in IBD patients.

Adhesion Molecules

Several endothelial adhesion molecules, such as E-select in, ICAM-1, ICAM-2, VCAM-1, and the mucosal address in Mad-CAM-1, could enhance inflammation by modulating leukocyte trafficking and recruiting immune cells into the gut. These molecules interact with integrins on leukocytes, inducting their migration from blood vessels into the site of inflammation in the pathogenesis of IBD. Some of these adhesion molecules represent attractive targets for the development of new drugs for reducing and preventing the recurrence of inflammation, and for long-term control of disease [69]. A selective inhibitor of the human α_4-subunit, natalizumab, which inhibits both the VCAM-1/α4β1 and MAdCAM-1/α4β7 pathways of leukocyte adhesion and transmigration, respectively, has been approved for the treatment of patients with moderate-to-severe CD. The therapeutic effect of natalizumab was superior to that of placebo, demonstrating early and sustained efficacy of the drug as induction therapy in patients with active CD [70]. The monoclonal antibody MLN-02 recognizes α4β7 integrin and selectively inhibits leukocyte adhesion in the gastrointestinal mucosa. The clinical study showed higher clinical remission rates at day 57 (53%) in active CD patients in the MLN-02 group compared to the placebo group, suggesting a beneficial effect of the drug on clinical remission [71]. MLN-02 has also been shown to have beneficial effects in UC patients [72]. Anti-ICAM-1 therapy, using an antisense ICAM-1 (CD54) oligonucleotide that is specifically designed to inhibit ICAM-1 expression, could be useful in the treatment of IBD patients. Although systemic treatment in CD patients revealed no significant results, topical application in the form of enemas has demonstrated some effect in secondary outcomes, and initial studies in pouch it is are promising [73].

Growth Factors

The downstream effects of human growth factors are associated with cellular functions, including epithelial healing in response to injury [74]. As previously reported, impaired epithelial repair is an important pathophysiological event in IBD. Several growth factors, such as epidermal growth factor, keratinocyte growth factor, growth hormone, teduglutide, and GM-CSF/G-CSF have emerged as potential tools for the modulation of intestinal inflammation and tissue repair. GM-CSF did not reveal benefits over placebo in patients treated with 5-ASA; however, steroid-dependent CD patient sexhibiteda higher rate of steroid-free remission compared to patients on placebo [75]. G-CSF has been shown to prevent postoperative recurrence of CD [76,77]. However, evidence relating to other growth factor treatments in CD patients is limited. The phase II trials of keratinocyte growth factor-2 and epidermal growth factor, in particular, did not show efficacy in CD or UC patients [78,79].

Conclusion

The pathogenesis of IBD is complicated and therapeutic target cells include not only immune cells, such as T cells and macrophages, but also colonic epithelial cells. A number of molecules are also associated with the pathogenesis of IBD. Increased understanding of the immune mechanisms in IBD has facilitated the development of clinically effective biologics target such molecules. Future biological agents, therefore, carry an enormous potential for optimized therapeutic efficacy in patients with IBD.

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This article was originally published in a special issue, **Clinical Studies of Molecular Targeted Therapies** handled by Editor(s). Dr. Junya Kuroda, Kyoto Prefectural University of Medicine, Japan