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Biologic Management of Fistulizing Crohn's Disease

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Abstract: Fistulas, occurring in about 20 to 40% of Crohn's disease patients, are usually resistant to conventional therapy of CD. Biologic therapies, which have revolutionary beneficial effects on diseases with an immunologic background, are a new horizon in treating fistulizing CD. The aim of this study was to evaluate the efficacy of biologic agents used to treat fistulizing CD after a brief overview on epidemiology and pathophysiology of fistulizing CD and definition of biologic therapy. Also it focuses on the trials and adverse effects of the biologic agents proved to be effective (Infliximab and CDP571).

Key words: Crohn disease, inflammatory bowel disease, biologic therapy, treatment

INTRODUCTION

Crohn's Disease (CD) is an immune-mediated inflammatory disease that can affect any part of intestinal tract from the mouth to anus. CD is one of the two major entities of Inflammatory Bowel Diseases (IBD) which is usually localized and focal and most commonly affecting the ileum. The incidence of CD is approximately 5 to 10 new cases per 100000 individuals/year. However this incidence has risen progressively since its original description^[1]. Although the exact etiology is unknown both genetical and environmental factors are involved in the pathogenesis

CD and fistula: Fistula is an abnormal communication from one epithelial surface to another. The transmural inflammatory process of CD predisposes to the formation of fistulas. The lifetime risk for the development of a fistula in patients with CD has been reported to be typically between 20 and 40%^[2]. Fistulas have been described as either (1) internal fistulas if they terminate into adjacent organs (e.g., enteroenteric, enterovesical, ileocolic, gastrocolic, or rectovaginal); or (2) external fistulas if they terminate on the surface of the patients body (e.g., enterocutaneous, or perianal). Perianal fistulas comprise the majority of fistulas observed in patients with CD. Frequently external fistulas are associated with local pain, drainage, possible abscess formation and decrease in the quality of life^[3,4] while enteroenteric fistulas alone are usually asymptomatic unless obstructive or septic complications ensue which majorly demand surgical procedures.

Management of a CD patient with a symptomatic fistula is more elusive than a typical obstructing CD patient, as their responses differ to medical therapies. Although widely used in the treatment of fistulas, antibiotics, immunomodulators, and dietary therapies have not been demonstrated to result in sustained closure of fistulas^[5-9]. Certain medications that are useful for the treatment of patients with obstructive CD are believed to be detrimental in fistulizing pattern of CD (e.g. corticosteroids)^[5]. In addition surgical options are limited by the potential for compromise of anal continence and recurrence^[4].

Pathophysiology: Understanding the immunological basis of CD is compulsory for focusing on biologic therapies. Effective barrier of gut which is normal epithelium may be compromised by genetic variation, a response to injury or exogenous agents such as nonstreoidal anti-inflammatory drugs, production of commensal bacteria in the lumen, antigens from dietary source and penetration of bacterial product through the mucosal barrier may cause recurrent intestinal inflammation, which the result is stimulation of the mucosal immune system in patients with Crohn's disease. Activation of especially dendritic cells as antigen-presenting cells promotes the differentiation of type1 helper T cells^[10]. In intestinal mucosa, microbial antigens traversing the epithelium are picked up by antigen-presenting cells and presented to both effectors and regulatory T-cells in the lamina propria. It appears that CD patients have a dysregulated immune response to these antigens and consequently have different cytokine expression than normal^[11].

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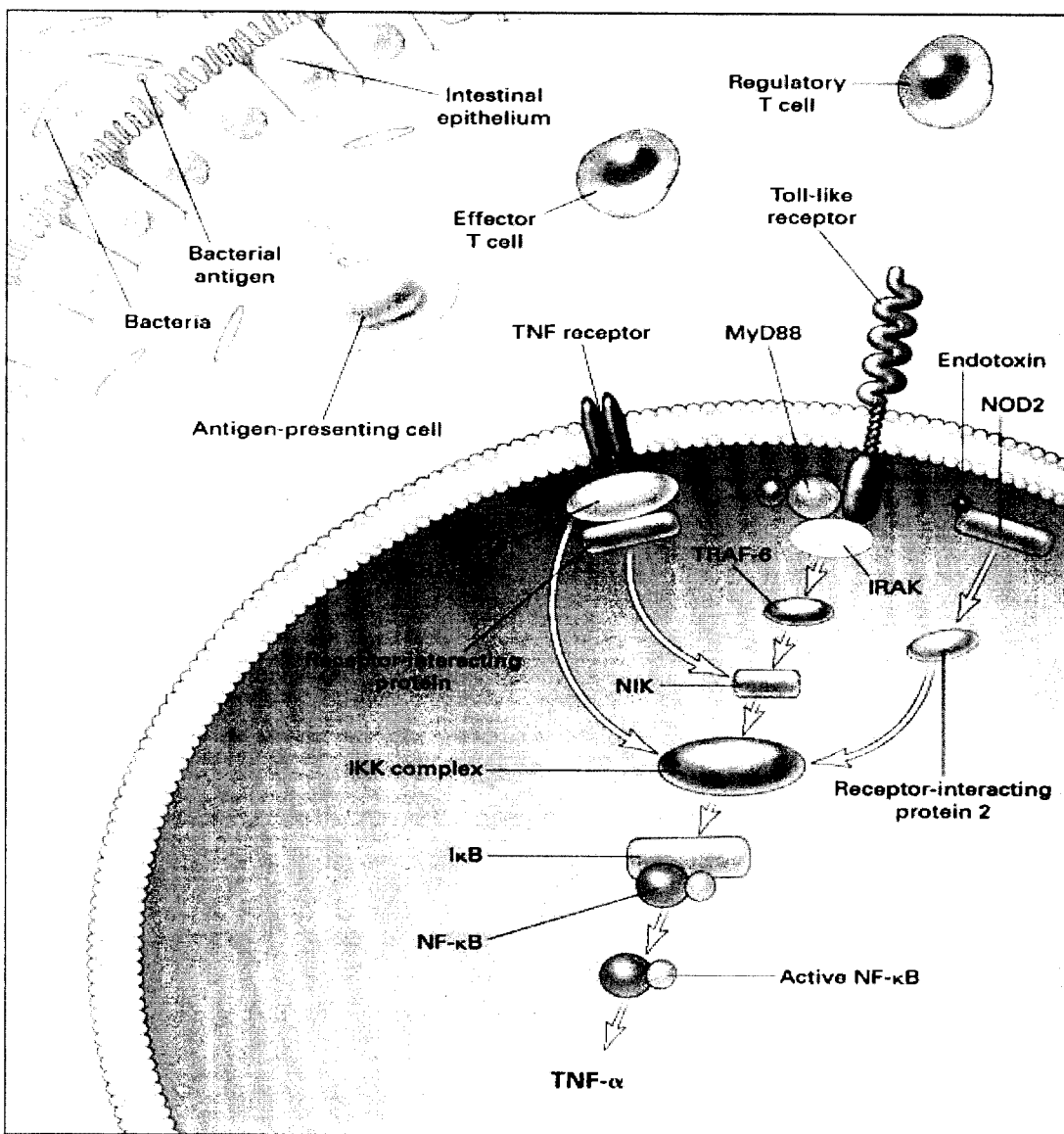


Fig. 1: Pathways of microbial–host interactions in the intestine

TRAF denotes TNF-receptor–associated factor, IRAK interleukin-1 receptor–associated kinase, NIK NF- κ B–inducing kinase, IKK inhibitor of κ B kinase and MyD88 myeloid differentiation factor 88. Obtained with permission from Elson *et al.*^[11]. Authors wish to thank Dr. Elson and N. Engl. J. Med. editorial office for their kind assistance and permission for using this figure in this study

The pattern of cytokines expressed by the lamina propria lymphocytes of patients with CD are consistent with a T-helper-1 immune response; Th1 response is characterized by increased expression of interferon- γ , interleukin IL-2, IL-12, and IL-18 followed by subsequent increased proinflammatory cytokines of TNF (Tumor necrosis factor) and IL-1 β , and then NF- κ B, as well as a compensatory increase in the T- helper- 2

mediated anti-inflammatory cytokine IL-10 and transforming growth factor- β ^[9,12]. Figure 1 shows a schematic feature of this process which leads to production of TNF- α ^[6,11].

Biologic therapy (definition and its use in CD): Knowledge regarding the human and rodent immune systems has led to an understanding of a variety of

immunologic pathways and mechanisms and consequently the ability to intervene these processes by biotechnology agents. Biologic therapies are treatments to stimulate or restore the ability of the immune system to struggle diseases. The task therefore is to restore, replace and boost body defense systems.

Generally biologic therapies include: (1) innate biologic isolates such as vaccines containing live, attenuated or killed microorganisms; (2) recombinant proteins such as growth hormone, erythropoietin and so on; (3) antibody-based and nucleic acid-based therapies and (4) cell and gene therapies^[7].

Each of the immunologic pathways mentioned in the previous part could be targeted for biologic therapy; hence, numerous biologic compounds have been tested for CD. In an effort to reduce immunogenicity, fully human or humanized anti-TNF- α therapies have been developed, including a fully human TNF p75 soluble receptor fusion protein (etanercept), a fully human TNF p55 soluble receptor monomer (onercept), a pegylated humanized Fab antibody fragment (CDP870), a humanized IgG4 monoclonal antibody (CDP571) and a fully human IgG1 monoclonal antibody (adalimumab). Other human or humanized anti-TNF- α therapies, including etanercept, CDP870 and CDP571, which are more pure TNF- α inhibitors that do not lead to lymphocyte apoptosis, have either been ineffective for Crohn's disease (etanercept) or effective only in a subgroup of patients with Crohn's disease who have elevated baseline concentrations of C-reactive protein (CDP870 and CDP571)^[13-16].

Since 1998, after introduction of infliximab, a chimeric monoclonal antibody targeting tumor necrosis factor (TNF)- α , as a medical therapy for Crohn's disease, more effort have been done to produce different biomedical treatment in control of the exaggerated immune responses observed in these chronic inflammatory conditions. In the following, some of these efforts have been reported.

Human monoclonal anti-TNF antibody strategies: Adalimumab is a fully human IgG1 antibody that binds to circulating and membrane-bound TNF- α in a manner similar to infliximab, but which has the potential for less immunogenicity and the possibility for self-administration by patients.

Similar to infliximab, adalimumab induces apoptosis of monocytes and T cells^[17]. Induction of apoptosis of membrane TNF-positive cells has been proposed as a likely mechanism of action for these IgG1 antibodies, a mechanism different from that of other antibody subclasses and the soluble TNF receptors, etanercept and onercept^[18]. These other humanized anti-TNF- α therapies,

although effective in rheumatoid arthritis, have not been observed to be effective in Crohn's disease.

Cytokine inhibition: Mannon *et al.*^[19], described the results of a safety and efficacy trial involving a fully human anti-interleukin (IL)-12 antibody (ABT-874) in 79 patients with active Crohn's disease. IL-12 is an important cytokine that is produced in excess in the mucosa of patients with Crohn's disease; it drives T cells towards a T-helper-1 response. Inhibition of IL-12 has been shown to ameliorate inflammation in several animal models of IBD. This monoclonal antibody reacts with the p40 subunit of the IL-12 heterodimer and therefore has some cross-reactivity with the newly identified IL-23, which has an identical p40 subunit.

Fontolizomab, a humanized anti interferon gamma antibody, was reported by Hommes *et al.*^[20], for the treatment of moderate to severe Crohn's disease according to baseline C-reactive Protein (CRP) levels. The antibody was well tolerated when administered in 2 infusions, with all but 1 adverse reaction (sudden death of a 65-year-old man in his sleep) attributed to the underlying Crohn's disease. This early-phase trial will require additional support to demonstrate the appropriate dosing, timing, concurrent therapies, and patient selection to determine the ultimate role for interferon-gamma inhibition in Crohn's disease.

MRA, a humanized monoclonal antibody to IL-6, was reported by Ito H and colleagues for treatment of Crohn's disease in recent pilot study^[21] and 80% of the patients given biweekly MRA achieved a clinical response (a decrease in the CDAI score of 70 points or more) compared with 31% of the placebo-treated patients (P=.019). Moreover 20% of the patients given biweekly MRA achieved remission (a CDAI score of less than 150 points) compared with 0% of the placebo group.

Selective adhesion molecule inhibition: Gosh *et al.*^[22] reported Natalizumab, a humanized monoclonal IgG4 antibody to α -4 integrin, as a treatment for Crohn's disease. This agent, disrupts adhesive interactions between leukocytes and vascular endothelium and inhibits recruitment and migration of α -4-expressing leukocytes into gut tissue, but natalizumab variations in dose and dosing regimens still need clarification.

Anti-CD3 monoclonal antibody: Plevy *et al.*^[23] described remarkable initial results with visilizumab, a humanized anti-CD3 monoclonal antibody administered to patients with severe, steroid-refractory ulcerative colitis. This antibody, transiently depletes T cells and may allow a reset population of unprimed or regulatory T cells to

proliferate and replace the "autoreactive" cells that likely contribute to ongoing inflammation.

Other biologic agents: There is another hypothesis that Crohn's disease may result from deficiency in innate immunity rather than from an overactive immune system. Sargramostim (GM-CSF), an immune system stimulator originally developed as an anticancer drug, was studied in moderate to severe CD patients (mean baseline CDAI score: 300 points) by Dieckgraefe *et al.*^[24] and patients given sargramostim (6 mcg kg⁻¹ SC daily for 8 weeks) achieved clinical remission (a CDAI score of 150 points or less) compared with patients given placebo (40% vs 19%, respectively; P=.014)

Low-tech biologics: A group of investigators from the University of Iowa has been exploring the potential of helminth therapy to ameliorate IBD^[25]. Helminth colonization is linked to down regulation of immune responses, and indeed, IBD is prevalent in areas where parasitic helminths are scarce.

Summer's and colleagues^[26,27] in two different articles described the results of *trichuris suis* (a pig whipworm that does not produce disease in humans) for the treatment of ulcerative colitis, but these result must be confirmed in larger controlled trials, and assessment of dose-response requires testing.

The present study pays more emphasis on anti TNF antibodies (infliximab and CDP571) which have been shown beneficial in treating fistulizing CD.

Infliximab: Infliximab (Remicade, CA2) is a genetically engineered IgG1 chimeric monoclonal antibody against TNF- α containing approximately 75% human protein and 25% murine protein^[8].

The local production of tumor necrosis factor α (TNF- α) is thought to have a key role in the initiation and propagation of Crohn's disease^[28-30]. Production of TNF- α in the intestinal mucosa is increased in patients with Crohn's disease^[30-32]. Neutralization of TNF- α has been suggested as a therapeutic intervention in inflammatory diseases, such as inflammatory bowel disease and rheumatoid arthritis^[28,33].

Infliximab (formerly known as cA2) is a genetically constructed IgG1 murine-human chimeric monoclonal antibody that binds both the soluble subunit and the membrane-bound precursor of TNF- α ^[34,35]. Infliximab inhibits a broad range of biologic activities of TNF- α , presumably by blocking the interaction of TNF- α with its receptors, and it may also cause lysis of cells that produce TNF- α ^[35,36].

Proposed mechanisms of action for infliximab include neutralization of both soluble and transmembrane TNF, as well as lysis of TNF producing cells via complement fixation, antibody dependent cytotoxicity and apoptosis of T-lymphocytes caused by the IgG1 Fc portion of the antibody^[8,9,37]. The down-regulation of T helper-1 cytokine-producing cells within the lamina propria after successful treatment with infliximab has been demonstrated^[38]. This apoptogenic effect carries a great importance as if etanercept, which is a fusion protein that permanently binds free TNF- α to its receptor, has all the abilities of infliximab except the induction of apoptosis in T-cells, has been shown to have no value in CD management^[13,37].

Four controlled trials have evaluated the effect of infliximab on fistulizing CD^[4,39-41]. In the recent multi center trial^[4], 306 eligible patients (included men and women (patients 18 years of age or older) with Crohn's disease who had single or multiple draining fistulas, including perianal fistulas and enterocutaneous fistulas, for at least three months. Women with rectovaginal fistulas were included if they had at least one other enterocutaneous draining fistula^[42]. Concurrent therapies for Crohn's disease, including stable doses of 5-aminosalicylates, oral corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil, methotrexate, and antibiotics, were permitted. Patients were excluded from the study if they had a stricture or abscess for which surgery might be indicated or if they had previously been treated with infliximab. For induction therapy, of 306 patients enrolled, 282 received 5 mg kg⁻¹ of infliximab intravenously on weeks 0, 2 and 6. About 69% of patients responded to infliximab on week 14. A response was defined as a reduction of at least 50 percent from base line in the number of draining fistulas at consecutive visits four or more weeks apart^[39]. The 195 patients with a response were randomly assigned at week 14 to receive placebo maintenance (99 patients) or infliximab maintenance (96 patients) to evaluate the efficacy of infliximab maintenance therapy, the median time to the loss of response was 14 weeks in the placebo maintenance group in comparison to more than 40 weeks in the infliximab maintenance group (p<0.001). The remaining 87 patients, who had no initial response to infliximab administration were also randomly assigned to receive placebo maintenance (44 patients) or infliximab maintenance (43 patients). At week 54, 23% of patients in the placebo maintenance group still had a response (23 of 98), as compared with 46% of patients in the infliximab maintenance group (42 of 91, p=0.001). Among 87 patients who had no response at the time of randomization, 7 of 44 who subsequently received placebo, had a

response (16%), as compared with 9 of 43 patients who subsequently received infliximab (21%).

By including the other three studies^[39-41], it seems that fixed 8-week-interval maintenance therapy after induction (weeks 0, 2 and 6) of infliximab (5 mg kg⁻¹) provides a revolutionary treatment for fistulizing CD and induces remission in about 2/3 of the patients.

Toxic effects: Short- and long-term infliximab therapy is generally well tolerated. However, clinicians and nursing staff must be vigilant for the occurrence of infrequent but serious events, including serum sickness-like reaction, opportunistic infection and sepsis, and autoimmune disorders. Among infrequent but serious toxicities related to tumor necrosis factor-neutralizing therapies, important concerns are infectious complications, autoimmune disorders and the theoretical risk of cancer and lymphoma. However it should be noted that there are no published data regarding the use of infliximab for more than 1 year or more than 8 doses in patients with CD. The rate of serious adverse events reasonably related to the drug is 6-7%^[43,44]. Acute infusion reactions, defined as adverse events that occur during or within 2 hours following an infusion, occur in 5-22% of the patients^[45,46]. Most infusion reactions include symptoms of urticaria, dyspnea, and/or hypotension. In the combined safety data from all clinical trials with infliximab, only 2.6% of patients had infusion reactions leading to discontinuation^[45]. Serum sickness-like disease, characterized by myalgias, arthralgias, fever, and rash occurring within 1-14 days of infusion, was seen in 2-3% of patients^[43,44].

Similar to other humanized monoclonal human antibodies, parenteral infliximab (with 25% murine protein) is associated with the development of antibodies. The incidence of these antibodies is about 10-15% with the standard induction therapy (weeks 0, 2 and 6)^[4,39,43]. In contrast to the controversy of the association between antibody status and efficacy, it is accepted that patients who are positive for antibodies to infliximab are two to three times as likely to have infusion reactions as those who were negative or who had inconclusive results. Infliximab inclines patients to autoantibody formation such as antinuclear antibodies (ANA) and anti-double-stranded DNA antibodies which rarely may lead to features of drug-induced lupus^[4,43,45,47]. Limited data have been presented linking anti-tumor necrosis factor α therapy in patients with CD with new-onset multiple sclerosis-like syndromes. The mean time to symptom onset from initiation of therapy was 5 months but ranged from 1 week to 15 months. In most cases, patients experienced partial or complete resolution of their

symptoms following discontinuation of therapy^[48]. Physicians should be aware of this adverse effect and should monitor for neurologic symptoms throughout infliximab therapy. Patients who develop new neurologic symptoms should undergo evaluation by magnetic resonance imaging. The most frequent cause of serious adverse events associated with use of infliximab is infection. In clinical practice, infliximab has been associated with definite occurrence of unexpected infections however in clinical trials, no statistically significant increase in serious infections or sepsis was observed in infliximab-treated patients compared with placebo-treated patients^[45]. In the post marketing experience, in a follow up on 271,000 patients, the rate of pulmonary complications was 0.29%. Tumor necrosis factor- α is an inflammatory cytokine which has two type of receptors TNRF1 and TNRF2^[49]. These receptors induce apoptosis and the activation of nuclear factor-kB which can influence the production of cytokines and the expression of adhesion molecules^[50]. One of the mechanism by which TNF mediate successful host response to Mycobacteria is apoptosis of macrophages after bacillary infection^[12,51]. Serious concern should be paid when active tuberculosis is suspected, treatment with infliximab should be stopped until the diagnosis has been ruled out or the infection has been treated with antituberculosis agents. As a suggestion before commencement of infliximab, every effort should be made to determine whether the patient has latent tuberculosis infection^[52]. Cases of histoplasmosis, varicella-zoster virus infections, and candida esophagitis have been observed. In postmarketing experience, opportunistic infections including pneumocystis carinii, listeriosis, aspergillosis, coccidioidomycosis, cytomegalovirus infections, cryptococcosis, and systemic candidiasis have all been described and in some instances have led to patient death^[45]. Data from large treated populations generally concur with the conclusion that although theoretically it is possible, a causal association between infliximab and risk of malignant disease is unlikely. Finally, the mortality rate possibly related to infliximab observed in these large case series was about 0.5-1%^[43,44].

CDP571: CDP571 is a "humanized" chimeric monoclonal antibody to human TNF- α (Celltech, Slough, England). CDP571 neutralizes both soluble and transmembrane TNF, by the IgG4 Fc portion of the antibody^[8]. CDP571 contains approximately 95% human protein and 5% murine protein, and thus theoretically is less immunogenic than infliximab. Two placebo-controlled trials have concerned CDP571 showing significant greater rate of fistula closure in CDP571 treated patients comparing with placebo group;

25% vs. 0% reported by Feagan *et al.*^[53] and 50% vs. 15% reported by Sandborn *et al.*^[54].

CONCLUSION

Although the etiology of CD still remains unknown but in the recent years some developments in the roles of some cytokines like epidermal growth factor and the nitric oxide system have occurred^[55]. Biologic therapies have made new horizons in the management of severe CD. With little adverse effects, infliximab as the core agent of this revolution can induce remission incomparable with previous treatments in fistulizing CD. However, there still remain many areas that are in need of further research and intense investigation.

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