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Lecture

Anti-TNF Treatment in Inflammatory Bowel Disease

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INTRODUCTION

Crohn's disease and ulcerative colitis are chronic inflammatory disorders of the gastrointestinal tract. Although the primary etiological defect stil remains unknown, in the last decade impotant progress has been made concerning the immunological basis of the disease. Genetic, environmental and microbial factors result in repeated activation of mucosal immune response. Tumor necrosis factor alpha (TNF-alpha) is one of the central cytokines in the underlying pathogenesis of mucosal inflammation in inflammatory bowel disease (IBD) and has been the primary target of biologic therapies.

Role of TNF-alpha in pathogenesis of inflammatory bowel disease

TNF-alpha is produced by activated macrophages and T lymphocytes. Other proinflammatory cytokines including interleukin (IL)-1, IL-6 and are stimulated by TNF-alpha. It also increases leucocyte migration by inducing expression of adhesion molecules by endothelial cells and leucocytes.

TNF-alpha mediates multiple proinflammatory signals that play a central role in the pathogenesis of IBD, including neutrophil recruitment to local sites of inflammation, activation of both coagulation and fibrinolysis, and induction of granuloma formation.[1] Increased numbers of TNF-alpha producing cells are present in intestinal biopsy specimens from IBD patients, more frequently in Crohn's disease than ulcerative colitis.[2] Moreover, enhanced secretion of TNF-alpha from lamina propria mononuclear cells has been found in the intestinal mucosa of IBD patients.[3] In Crohn's disease tissues, TNF-alpha positive cells have been found deeper in the lamina propria and in the submucosa, whereas TNF-alpha immunoreactivity in ulcerative colitis is, mostly, located in subepithelial macrophages.[4] There may be insufficient increased release of soluble TNF receptor from lamina propria mononuclear cells of patients with IBD in response to enhanced secretion of TNF-alpha.[5] TNF-alpha in the stool have also been found from children with active IBD,[6] and elevated levels of TNF-alpha have been found increased in the serum of children with active ulcerative colitis and Crohn's colitis.[7]

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Anti-TNF antibodies and fusion proteins:

We certainly have many ways to block TNF-alpha. Different therapeutic approaches have been focused on inhibition of TNF-alpha in patients with IBD. Monoclonal antibodies such as; infliximab, adalimumab, certolizumab (CDP870) and CDP571; the p 75 soluble TNF receptor fusion protein etanercept and p55 soluble TNF receptor onercept are most studied ones. Some of them have failed in clinical studies and clinical studies in different phases are still ongoing for some of them.

Infliximab

Infliximab is a murine-human chimeric IgG1 monoclonal antibody containing approximately 75% human protein and 25% murine protein.[8] It is the most studied anti-TNF antibody with poven efficacy. Infliximab binds to both the transmembrane and soluble form of TNF-alpha,[9,10] paradoxically increasing its half-life but decreasing its activity.[11] Infliximab is specific to TNF-alpha and does not bind to TNF-beta.

Infliximab neutralizes the biologic activity of TNF-alpha by inhibiting binding to its receptors, and results in blokage of proinflammatory signals or molecules that are up-regulated by TNF-alpha. The main mechanism of ac-

tion is the destruction of activated effector cells through apoptosis. A key effect is the disappereance of inflammatory cells from the previously inflamed mucosa through lysis of inflammatory cells carriying membrane-bound TNF-alpha. Treatment with infliximab at therapeutic concentrations resulted in monocyte apoptosis in patients with chronic active Crohn's disease.[12] Infliximab also induces cell lysis through complement-dependent cellular cytotoxicity.[13] A potent anti-inflammatory effect is the natural result of these biological activities.

Clinical use of infliximab

Infliximab therapy is effective for the induction and maintenance of clinical remission; closure of enterocutaneous, perianal and rectovaginal fistulas; maintenance of fistula closure; and corticosteroid sparing in patients with Crohn's disease.[14-17]

ACCENT I[14] and ACCENT II[16] were two important multicenter, randomized, double blind, placebo controlled trials, upon which the approval of the drug for Crohn's disease was based in 1998.

In the ACCENT I trial, the aim was to asses the efficacy and safety of repeated infusions of infliximab in patients who improved after an initial infusion, also corticosteroid sparing effects and safety in a large number of patients. The results showed that patients with Crohn's disease who respond to an initial dose of infliximab are more likely to be in remission at weeks 30 and 54, to discontinue corticosteroids, and to maintain their response for a longer period of time if infliximab therapy is maintained every six weeks. Maintenance infliximab treatment was safe and genarally well tolerated.

ACCENT II trial also included adults with Crohn's disease who had had single or multiple draining abdominal or perianal fistulas, of at least three months duration. ACCENT II evaluated the efficacy and safety of repeated infusions of infliximab in maintaining closure of draining fistulas among patients who had a response to a three-dose induction regimen of infliximab. Among patients with fistulizing Crohn's disease whose fistulas closed after infliximab induction therapy, continued infliximab infusions at fixed intervals maintained closure for a longer period than placebo infusions. Today infliximab has become the drug of choice in fistulizing patients.

There are few small studies and case reports of infliximab in patients with active ulcerative colitis that have showed conflicting results.[18-22] Two randomized, double-blind, placebo-controlled studies − the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2, respectively) − evaluated the efficacy of infliximab for induction and maintenance therapy in adults with ulcerative colitis.[23] Clinical response or clinical remission with discontinuation of corticosteroids at week 30 in both studies and at week 54 in ACT 1, a clinical remission and mucosal healing at weeks 8 and 30 in both studies and at week 54 in ACT 1, and a clinical response at week 8 in patients with a history of disease refractory to corticosteroids were assessed. In each study, 364 patients with moderate-to-severe active ulcerative colitis despite treatment with concurrent medications received placebo or infliximab (5 mg or 10 mg per kilo gram of body weight) intravenously at weeks 0, 2 and 6 and then every eight weeks through week 46 (in ACT 1) or week 22 (in ACT 2). Patients were followed for 54 weeks in ACT 1 and 30 weeks in ACT 2. In both studies, patients with moderate-to-severe active ulcerative colitis treated with infliximab at weeks 0, 2, and 6 and every eight weeks thereafter were more likely to have a clinical response at weeks 8, 30, 54 than those receiving placebo.

ACT 2 also helped us to undestand the pathogenesis of ulcerative colitis. Ulcerative colitis is believed to result from an immune response of type 2 helper T cells in the colonic mucosa, whereas Crohn's disease is accepted as an immune disease of type 1 helper T cells, which would suggest that TNF-alpha is not a potent mediator in ulcerative colitis. The study showed that TNF-alpha plays an important role in the disease process and targeting this cytokine is an effective therapy for ulcerative colitis. The mechanism of action of infliximab in ulcerative colitis also includes the induction of apoptosis of inflammatory cells expressing membrane-bound TNF-alpha, as in Crohn's disease.[24]

Based on the results of ACT 1 and ACT 2, infliximab has recently been approved for maintaining clinical remission and mucosal healing in patients with moderately to severely active ulcerative colitis, who have had an inadequate response to conventional therapy.

There are few studies for treatment of indeterminate colitis with infliximab. In a retrospective, multicenter study, patients with indeterminate colitis were found more refractory to infliximab.[25] Papadakis et al, reported that the results of infliximab therapy in indeteminate colitis were much better than the previous study. Fourteen of 20 patients (70%) had a complete response to infliximab 5 mg/kg, 2 patients had a partial response. Four of the 14 responders had to step up to 10 mg/kg of infliximab because of fading of response to 5 mg/kg. It was striking that 10 patients who were in the course of follow-up were classified as Crohn's disease and 2 as ulcerative colitis.[26]

Although infliximab is well tolerated in the majority of patients, serious side effects may rarely occur, including serious infections, drug induced lupus,[27] acute infusion reactions,[28] delayed hypersensitivity reactions,[29] demyelination,[30] possibly increased rate of lymphoma,[31] cardiac failure[32] and death. The rate of infection is higher in infliximab-treated patients (36%) than in those receiving placebo (26%).[33] Upper respiratory tract infections and urinary tract infections are frequently reported. In post marketing surveillence, tuberculosis,[34] histoplasmosis,[35] listeriosis, aspegillosis, and pneumocystis carini pneumonia have all been observed, leading in some instances to death.[36] Active screening for these micoorganisms is not advised, except for tuberculosis. Reactivation of latent tuberculosis is of particular concern. Any changes in symptoms should be assesed carefully, tuberculosis skin testing (PPD) should be done routinely. All PPD positive patients or patients who have received tuberculosis immunisation (bacillus Calmette-Gurin), should undergo chest X-ray. If chest X-ray is negative with a PPD positive patient, latent tuberculosis treatment should be administered before infliximab. If chest X-ray is positive, the patient should be treated for active tuberculosis before infliximab therapy.

Recently TREAT registry reported the long-term safety data for infliximab in Crohn's disease. Multivariate analysis of factors associated with mortality showed that, mortality rates were similar between infliximab and non-infliximab treated patients. The increased risk for serious infections observed with infliximab likely was due to disease severity and coricosteroid use.[37]

Approximately 28% of infliximab-treated patients develop human antichimeric antibodies.[38] Infusion reactions are more common in patients who developed antibodies.[33] Concomitant therapy with corticosteroids, methotrexate, azathiopurine or 6-mercaptopurine reduces the incidence of antibody formation and rate of infusion reactions; possibly related to impaired humoral response induced by immunosupression.[39,40] But the multiple immunosuppresive drug use on the other hand might increase infectious complications.

Adalimumab

Adalimumab is a fully human IgG 1 monoclonal antibody to TNF-alpha that is administered subcutaneously and has a long half life. It binds to human TNF-alpha, thereby interfering with binding to TNF-alpha receptor sites and subsequent cytokine-driven inflammatory processes.[41] It has been approved for use in rheumatoid arthritis and psoriatic arthritis.

Most of the antibodies that develop against infliximab are presumably directed towards the murine portion of the molecule and will not cross react with the fully human adalimumab. The rate of formation of antibodies to adalimumab observed in clinical trials of Crohn's disease has been very low (approximately 3%).[42] Adalimumab side effects are similar to infliximab. Infusion reactions seen with infliximab do not occur with adalimumab, although the injections can be temporarily painful.

Sandborn et al demonstrated that, adalimumab has short-term benefits in Crohn's disease and is tolerated and effective in patients who have lost their response to infliximab.[43]

A previous phase 3 study (CLASSIC [Clinical assesment of Adalimumab Safety and efficacy Studied as an Induction therapy in Crohn's] I) demonstrated that adalimumab is effective for induction of clinical response and remission when administered as a loading dose in patients with moderately to severely active Crohn's disease who were naive to infliximab and other anti-TNF therapy.[42]

CLASSIC II was a subsequent pilot maintenance trial which demonstrated that adalimumab administered at doses of 40 mg every other week and 40 mg weekly was effective in maintaining remission in patients with adalimumab-induced clinical remission.[44]

More recently, phase 3 double blind, placebo controlled trial – CHARM (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance) study – demonstrated the safety and efficacy of adalimumab administered 40 mg weekly vs every other week for maintenance of clinical remission in patients who had responded to induction therapy with adalimumab.[45] Hanauer and colleagues, reported additional results of CHARM and showed that maintenance adalimumab therapy allowed significant percentages of patients to maintain steroid-free remission (off steroid therapy $\geq$ 90 days).[46] Adalimumab was also found to be effective in sustaining clinical remission in Crohn's disease regardless of whether patients received concomitant immunosupressive therapy with azathiopurine, 6-mercaptopurine or methotrexate, and regardless of whether patients had previously been exposed to anti-TNF therapy with infliximab.[47] Additional results of CHARM study showed that adalimumab is effective in the healing of draining fistulas in patients with Crohn's disease.[48]

GAIN (Gauging Adalimumab efficacy in Infliximab Nonresponders), is the most recent trial reported during the 2006 ACG meeting.[49] This double-blind placebo-controlled study was conducted to determine the efficacy and safety of adalimumab in the induction of response and remission in patients with Crohn's disease who had previously respond-

ed to therapy with infliximab and then lost response or became intolerant (secondary failure). Induction of clinical remission at week 4 was significantly higher in the adalimumab-treated group vs placebo-treated group.

According to the results of three randomized, double-blind, placebo-controlled trials −GAIN, CLASSIC and CHARM− FDA has granted Priority Review to adalimumab. Adalumimab is certainly one o the most promising drugs for the near future and it seems that it will be on the market soon.

Certolizumab Pegol

Certolizumab pegol is a humanized anti-TNF Fab' fragment linked to polyethylene glycol that is also administered subcutaneously, which is a huge advantage. It has a two-week plasma half-life. In conrast to the IgG1 antibodies, certolizumab does not appear to induce apoptosis. A previous phase 2 study demonstrated that certolizumab pegol may be efficious in the induction of clinical response and remission when administered at a dose of 400 mg at weeks 0, 4 and 8 in patients with moderately to severely active Crohn's disease.[50] Although all certolizumab doses produced significant clinical benefit over placebo at all time points, clinical response rates were highest for 400 mg doses when compared 100 and 200 mg doses.Therefore, at week 12, no significant statistical benefit was found over placebo.

PRECISE (Pegylated antibody fragment evaluation in Crohn's disease safety and efficacy) 1 is the phase 3 study to evaluate the efficacy in induction of response.[51] PRECISE 2 was conducted to evaluate the maintenance response.[52] The results showed that clinical response and clinical remission rates were significantly higher than placebo. CRP levels, which have been a post hoc predictor of response to anti-TNF and other biologic agents, are reduced by anti-TNF treatment. In post-hoc analysis, those individuals with an elevated CRP demonstrated a higher response rate.

Etanercept

Etanercept is a fully human fusion protein comprised of two soluble TNF p75 receptors linked to an IgG1 Fc monoclonal antibody fragment that is administered subcutaneously. Although etanercept is a TNF-alpha blocker, it is not approved and marketed for inflammatory bowel disease. A randomized, controlled trial showed that etanercept was no better than placebo in inflammatory bowel disease.[53] Higher doses may be required for Crohn's disease or there might be a difference in the mechanism of TNF-alpha blockage. Both etanercept and infliximab neutralized TNF-alpha, but only infliximab bounds to T lymphocytes and induces apoptosis of these cells.[54] Further in vitro and in vivo studies are required to sort out these important issues.

Onarcept

Onercept is a fully human recombinant soluble TNF p55 receptor administered subcutaneously. A clinical benefit was observed in a pilot study involving 12 patients with active Crohn's disease.[55] However a subsequent placebo-controlled, phase 2 trial found no significant benefit for clinical response or induction of remission.[56]

Natalizumab

Natalizumab, a humanized monoclonal antibody to alpha-4 integrin, is administered intravenously. It had been approved for use in the treatment of multiple sclerosis and has been evaluated for treatment of Crohn's disease.[57,58] The report of 3 cases of multifocal leucoencephalopathy caused by the human polyoma JC virus in patients with multiple sclerosis and Crohn's disease treated with this agent, led to an estimated risk of 1:1000.[59-62] As a result marketing of the drug was suspended.

Conclusion

TNF blockage has been the fundamental advance in management of inflammatory bowel disease. Infliximab, adalimumab and certolizumab all seems to be effective in Crohn's disease. Infliximab is the only anti-TNF agent currently approved for Crohn's disease ulcerative colitis. Adalumimab and Certluzimab Pegol seem like two most promising drugs for the near future. And certainly there will be other biological treatment options available in next decade. Safety is an important concern that must be carefully balanced against efficacy. Since inflammatory bowel disease is a chronic and life-long disorder, we need more long-term efficacy and safety data with maintenance therapy. Patients should be informed properly about important side effects and careful follow-up is mandatory. Targeting TNF has been an important breakthrough in the management of inflammatory bowel disease. In future new targets in the pathogenesis of mucosal inflammation such as inhibition of cell adhesion, NF-kB and T cell activation should be evaluated.

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