Strategies targeting tumor necrosis factor in Crohn's disease

W. J. Sandborn

Inflammatory Bowel Disease Clinic, Division of Gastroenterology and Hepatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, U.S.A.

Abstract

Tumor necrosis factor plays an important role in mediating the inflammation of Crohn's disease. Strategies aimed at reducing tumor necrosis factor in patients with Crohn's disease include the mouse/human chimeric monoclonal antibody infliximab, the humanized monoclonal antibody CDP571, the human recombinant tumor necrosis factor receptor fusion protein etanercept, and the small molecule thalidomide. Infliximab is effective for treating active Crohn's disease, maintaining remission, and closing fistulas. Side effects occurring in patients treated with infliximab include human anti-chimeric antibodies, infusion reactions, formation of autoantibodies, and rarely drug induced lupus. CDP571 is effective for treating active Crohn's disease, steroid sparing, and possibly for closing fistulas and maintaining remission. Side effects occurring in patients treated with CDP571 include anti-idiotype antibodies, infusion reactions, and formation of autoantibodies. Pilot studies have suggested that etanercept and thalidomide may also be beneficial. Anti-tumor necrosis factor therapies are effective for the treatment for Crohn's disease. (Acta gastroenterol. belg., **2001**, 64, **170-172**).

Introduction

Tumor necrosis factor (TNF) is elevated in the blood, stool, and intestinal tissue of patients with Crohn's disease (1-3). Therapeutic strategies targeted towards reducing TNF have been effective in the treatment of active Crohn's disease and for maintaining remission (4,5). A variety of biotechnology and small molecule approaches have been utilized to reduce TNF in humans. This article reviews anti-TNF strategies that have been utilized to target TNF in patients with Crohn's disease.

Therapeutic agents with anti-TNF activity

Therapeutic agents with anti-TNF activity which have been utilized in patients with Crohn's disease include infliximab, CDP571, etanercept, and thalidomide. Infliximab is a mouse/human chimeric monoclonal antibody which is approximately 75 percent human and 25 percent murine (6). The murine portion of the antibody is the variable or antigenic recognition region. CDP571 is a humanized monoclonal antibody which is approximately 95 percent human and 25 percent murine. The murine portion of antibody is the complimentarity determining regions (CDR) within the variable or antigenic recognition region. Etanercept is a completely human fusion protein that is comprised of an Fc portion of a human antibody linked to a human soluble receptor to tumor necrosis factor (p75). Thalidomide is a small molecule with anti-TNF properties.

There are some variations in the potential mechanisms of action for these different anti-TNF inhibitors (6). Infliximab acts to neutralize both soluble and transmembrane TNF alpha and in addition causes lysis of TNF producing cells via complement fixation and antibody dependent cytotoxicity. Infliximab also appears to lead to apoptosis of T lymphocytes. CDP571 acts to neutralize both soluble and transmembrane TNF alpha. Etanercept has a more limited function and simply acts to neutralize soluble TNF alpha. The clinical relevance of these possible differences in mechanisms of action with respect to the efficacy of anti-TNF therapy for Crohn's disease is unknown.

Efficacy of infliximab for the treatment of Crohn's disease

To date, three placebo-controlled studies have been performed with infliximab in patients with Crohn's disease. The first study, led by Targan and colleagues, reported on 108 patients with active Crohn's disease treated with infliximab at doses of 5, 10, or 20 mg/kg or placebo (7). At 4 weeks, 48 percent of patients receiving infliximab 5 mg/kg, 25 percent each of patients receiving 10 or 20 mg/kg and only 4 percent of placebo treated patients were in complete clinical remission. The differences were statistically significant for the infliximab 5 mg/kg versus placebo comparison. Any patients who failed to respond in this initial study were treated with open label infliximab 10 mg/kg. Seventy three patients who responded in either the initial blinded study or the open label crossover study were then re-randomized into a second study at 12 weeks and treated with infliximab 10 mg/kg or placebo every 8 weeks through week 36, with follow-up through week 48 (8). During the re-treatment phase of the study, approximately 60 percent of patients receiving repeated doses of infliximab maintained remission compared with approximately 20 percent of placebo treated patients. Between weeks 44 and 48 (8-12 weeks after the final infliximab dose administered at week 36) the majority of infliximab treated patients relapsed, suggesting that the duration of benefit for infliximab in many patients is approximately 8 weeks. In the third study, 94 patients with actively draining perianal or abdominal fistulas were randomized to treatment with infliximab 5 or 10 mg/kg or placebo administered at weeks 0, 2, and 6 (9). Complete closure of all fistulas maintained for at least 4 weeks occurred in

Corresponding author : Sandborn W. J., Gastroenterology & Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, U.S.A.

55 percent of the infliximab 5 mg/kg group, 38 percent of infliximab 10 mg/kg group, and only 13 percent of the placebo treated group. The difference between infliximab 5 mg/kg and placebo was statistically significant. In addition, a soon-to-be published study from the Mayo Clinic reported a steroid sparing benefit in patients with Crohn's disease treated with infliximab (10). In this study, 44 of 100 consecutive patients treated with infliximab were receiving corticosteroids. Corticosteroid tapering was attempted in 40 of 44, and total corticosteroid withdrawal patients was achieved in 29 of 40 patients (73 percent). In another recent pilot study, our group at the Mayo Clinic demonstrated a beneficial effect when infliximab was administered to patients with Crohn's disease involving an ileoanal pouch (11).

Toxicity associated with infliximab

Human anti-chimeric antibodies (HACAs) have been reported in 13 percent of patients treated with infliximab (10 percent frequency in patients receiving corticosteroids or immunosuppressive medications and 23 percent in patients not receiving corticosteroids or immunosuppressive medications) (12,13). Patients with human anti-chimeric antibodies appear to develop infusion reactions more frequently. Overall, infusion reactions occurred in 16 percent of infliximab treated patients and six percent of placebo treated patients. In addition, a syndrome of delayed hypersensitivity has been reported in up to 25 percent of patients retreated with infliximab after a drug holiday of 2-4 years. Formation of new autoantibodies such as new ANA antibodies (increase from 24 percent at baseline to 36 percent at last follow-up) or anti-double stranded DNA antibodies (nine percent) also occurred. Rarely, these patients may develop features of drug-induced lupus. Non-Hodgkin's lymphoma appears to be relatively rare but has been reported in two patients with Crohn's disease and at least three patients with rheumatoid arthritis (12,14).

Efficacy of CDP571 for the treatment of Crohn's disease

Three placebo-controlled trials with CDP571 have been conducted in patients with Crohn's disease. The first study in 31 patients with active Crohn's disease demonstrated that CDP571 5 mg/kg resulted in a greater decrease in the mean Crohn's disease activity index score at week 2 compared with placebo (15). In a second larger study, Sandborn and colleagues reported on 167 patients with active Crohn's disease treated with CDP571 at doses of 10 or 20 mg/kg or placebo (16). At two weeks, 54 percent of patients receiving CDP571 10 mg/kg and 37 percent of patients receiving CDP571 20 mg/kg had a clinical response compared to only 27 percent of placebo treated patients. The differences were statistically significant for the CDP571 10 mg/kg versus placebo. Subsequently, patients in this study were retreated every 8 or 12 weeks with CDP571 10 mg/kg or placebo for one or two doses respectively, and then followed through week 24. There were trends towards a greater rate of clinical remission in patients receiving retreatment (maintenance therapy) with CDP571 but the differences compared with placebo were not statistically significant. In this study, there was also a trend towards a greater rate of fistula closure in patients with draining perianal fistulas in patients treated with CDP571 as compared to placebo (50 percent closure rate versus 15 percent closure rate). In the third study, 71 patients with steroid dependent Crohn's disease were treated with CDP571 20 mg/kg at baseline followed by 10 mg/kg at week 8 or placebo at baseline and again at week 8, and then followed through week 16 (17). Corticosteroids were tapered over 10 weeks. At week 16, 44 percent of CDP571 treated patients had successfully discontinued steroids while remaining in clinical remission compared with only 22 percent of placebo treated patients. The Kaplan Meier survival estimate of time to relapse was statistically greater for the CDP571 treated patients. In this study, there was a trend towards a greater rate of fistula closure in patients with draining perianal fistulas among patients treated with CDP571 as compared with placebo (25 percent versus zero percent).

Toxicity associated with CDP571

Anti-idiotype antibodies occurred overall at a rate of 5.3 percent in patients receiving treatment with CDP571 (6,16,17). Infusion reactions occurred in 12.7 percent of CDP571 treated patients compared to 7.7 percent of placebo treated patients. Anti double stranded DNA antibodies occurred and 5.3 percent of CDP571 treated patients and zero percent of placebo treated patients (concomitant immunosuppressive therapy was not related to the development of anti-double stranded DNA antibodies). To date, there have been no cases of delayed hypersensitivity reactions, drug-induced lupus, or non-Hodgkin's lymphoma.

Pilot efficacy data of etanercept for the treatment of Crohn's disease

A small pilot study of etanercept in patients with active Crohn's disease was reported as an abstract in 2000 (18). D'Haens and colleagues treated 10 patients with active Crohn's disease with etanercept 25 mg administered subcutaneously twice weekly for 12 weeks. At week 2, clinical response occurred in 60 percent of the patients. Forty seven patients have been enrolled in a placebo controlled trial of etanercept 25 mg twice weekly, follow up is complete, and the results are pending.

Toxicity associated with etanercept

Human anti-human antibodies occur at a rate of 16 percent in etanercept treated patients (6). Injection site

reactions occurred frequently (37 percent of patients). New anti nuclear antibodies occurred in 11 percent of etanercept treated patients as compared to five percent of placebo treated patients. Similarly, new anti double stranded DNA antibodies occurred in 15 percent of etanercept treated patients compared to four percent of placebo treated patients. Delayed hypersensitivity reactions and drug-induced lupus have not been reported with etanercept to date. One patient with Hodgkin's lymphoma was reported in the original safety data set submitted to the United States FDA, and additional non-Hodgkin's lymphoma have been reported in post market surveillance.

Pilot efficacy data of thalidomide for the treatment of Crohn's disease

Two pilot studies have been conducted using thalidomide to treat active inflammatory and fistulizing Crohn's disease. Vasiliauskas and colleagues (19) used thalidomide 50 to 100 mg/day for 12 weeks in patients with active inflammatory Crohn's disease and reported response rates of 67 percent and remission rates of 0-33 percent. Ehrenpreis and colleagues (20) used thalidomide 200-300 mg/day for 12 weeks in patients with active inflammatory and fistulizing Crohn's disease. Eighty percent of patients with fistulizing disease had fistula closure, and 50 percent of patients with active inflammatory disease had a clinical response.

Toxicity associated with thalidomide

Peripheral neuropathy may have occurred in up to 33 percent of patients receiving thalidomide at doses of 50-100 mg/day (19). The frequency of peripheral neuropathy for patients receiving higher doses of thalidomide was not carefully investigated (20). Other side effects included rash, constipation, seborrhea, and the possibility of teratogenicity.

Unresolved issues in anti-TNF therapy for Crohn's disease

A number of issues remain unresolved with respect to anti tumor necrosis factor therapy. First, for infliximab treated patients, is an initial induction regimen of three doses at 0, 2, and 6 weeks necessary ? Second, for infliximab treated patients, is concomitant immunosuppressive and required ? Third, for infliximab treated patients, is pre-medication required ? Fourth, for infliximab treated patients, is intermittent dosing after months to years safe ? Finally, what is the relative balance of efficacy and toxicity for infliximab versus CDP571, etanercept, and thalidomide ?

Conclusions

In conclusion, infliximab is safe and effective and should probably be used more frequently in patients with Crohn's disease. DP571 and etanercept will likely be safe and effective, the relative trade-offs for efficacy and safety between infliximab versus CDP571 and etanercept are unclear. Preliminary studies suggest that thalidomide may be effective, but it is probably not practical from a safety perspective for the majority of patients.

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