PRELIMINARY EXPERIENCE OF INFLIXIMAB TREATMENT IN CROHN'S DISEASE

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ABSTRACT

Objective: This is a preliminary study of resistant Crohn's disease treated with Infliximab (Remicade), a monoclonal antibody to Tumor necrosis factor alpha (TNF). The aim of the study was to determine the efficacy of Infliximab in patients with moderate to severe active Crohn's disease.

Material and Methods: The Prospective open label observational study was conducted in the department of Medicine and Gastroenterology Al Hammadi Hospital Riyadh Saudi Arabia from December 2000 to December 2001. Ten Patients with confirmed Crohn's disease of the bowel who had less than satisfactory response to conventional treatment were given Infliximab. Amongst the 10 patients 6 had luminal crohn's disease (60%) and 4 had fistulizing crohn's disease (40%). Three patient had an associated extra intestinal manifestation of the disease, two having arthritis and an another had erythema nodosum.

Results: Out of 10 patients, 8 cases showed improvement in their disease (80%). All the 4 cases with fistulising disease showed improvement in their disease with disappearance of the fistula in 3 cases. Patients with luminal crohn's disease 4 out of 6 improved clinically and in 2 cases there was no change in symptomatology. The arthritis and skin lesion resolved with improvement in bowel disease.

Conclusion: Infliximab treatment is associated with remarkable clinical improvement in patients of crohn's disease with minimal adverse effects but further assessment of its long-term efficacy and safety needs to be determined.

Key words: Crohn's disease. Infliximab.

INTRODUCTION

Crohn's disease (CD) is a chronic nonspecific transmural inflammatory bowel disorder involving any part of the GI tract. Crohn's, Ginzberg and Oppenheimer localized it to the Ileum in the original description in 1932.[1] It is commonly grouped together with Ulcerative Colitis as inflammatory bowel disease (IBD). It is advisable to distinguish between these two conditions because of certain differences in their management. Crohn's disease usually involves the terminal Ileum and the adjacent large bowel (ileocolitis). In 20% of the cases the colon alone is affected (Crohn's colitis). Ulcerative colitis affects only the Colon or occasionally the adjacent terminal Ileum. Unlike ulcerative colitis, which involves the mucosa only, Crohn's disease is a transmural inflammatory process that can result in mucosal ulceration, stricturing, abscess and fistula formation. The endoscopic findings of CD include ulcers, coarse irregularity of the mucosa (cobblestone appearance) and skip lesions with areas of intervening normal bowel. Noncaseating granulomas on intestinal biopsy may be found in up to 50 percent of patients with Crohn's disease.[2] Positive antibodies to the yeast, S cerevisiae (ASCA) and negative antineutrophil cytoplasmic antibodies with perinuclear staining (pANCA) are fairly sensitive (50%) and highly specific (97%) for Crohn's disease.[3] In10% of the cases, it may be difficult to distinguish Crohn's disease from ulcerative colitis.

The medical management of CD has been challenging in view of less than satisfactory response to the conventional agents. Drugs traditionally used to manage CD are aminosalicylates,antimicrobials, immunomodulatory agents and glucocorticoids. Infliximab (Remicade) is a tumor necrosis factor-alpha (TNF-alpha) antibody and has been introduced since October 1998 for the treatment of active, moderate to severe Crohn's disease.[4] Infliximab is most useful in patients with refractory, moderate to severe Crohn's disease. The drug is used intravenously as a single dose of 5mg/kg body weight for uncomplicated Crohn's disease. Retreatment with infliximab every 8 weeks is recommended for some patients (having fistula, Sinuses) to maintain remission or to manage flare up of the disease.[5] Remission occurs in one third of patient with moderate to severe disease and over two third improves with this form of treatment. Maximal response is seen within two weeks in most patients, which gradually diminishes over 3 months. Limited experience suggests that remission is maintained over long term. Antinuclear and human antichimeric antibodies may develop leading to a risk of infusion related hypersensitivity reaction and sometimes lupus like syndrome.[3]

The purpose of our study was to determine the efficacy of Infliximab in patients having moderate to severe Crohn's disease.

MATERIAL AND METHODS

The study was conducted in Al Hammadi Hospital as open label trial lasting for a period of one year. The Hospital is a tertiary care facility situated in Riyadh Saudi Arabia.

Inclusion criteria: Patients with confirmed Cohn's disease of the bowel who were not responsive to standard treatment were included in the study.

Exclusion criteria: Patients with mild symptomatic disease limited to the bowel and controlled on conventional treatment (aminosalicylates) were excluded from the study. These patients had very infrequent bowel symptoms and no systemic manifestation of the disease. Other exclusions were active tuberculosis and pregnancy.

A total of 10 cases were included in the study. 6 out of 10 patients were previously diagnosed in other hospitals. Patient coming from these referring hospitals had been on standard treatment of Crohn's disease i.e. tapering doses of steroids, 5 Amino salicylic acid, Immunosuppressive drugs (Azathioprin 2mg per kg) for quite some time.

The remaining 4 patients presented to us with intermittent lower abdominal pain and altered bowel habits. They were diagnosed in our unit after thorough investigation. All cases had base line investigation including full blood count ESR, C reactive protein, blood chemistry, and liver function tests including serum albumin and clotting profile. Stool microscopy and cultures were done to rule out infectious colitis. HIV serology was requested in two males with history of deviant sexual behavior. Chest X ray were obtained to rule out pulmonary tuberculosis. Abdominal sonography was requested in all the patients to look for complications of the disease. Barium follow through studies were performed in all patients and CT abdomen with contrast was done in 8 out of 10 cases. Pan colonoscpy and where possible terminal iliem/colonic biopsy was taken for histopathology Repeat colonoscopy was done where appropriate (3 cases) to assess the response of the colonic disease to treatment. Serology for PANCA and ASCA was done in two patients in whom it was difficult to confirm the diagnosis on histopathology.

Patients presenting to our hospital for the first time were initially put on conventional treatment. These patients were started on oral prednisolone 60mg per day and had a short course of oral ciprofloxacin. Immunosuppressive medications were introduced while the dose of oral steroids was gradually reduced. One of our patients with Crohn's colitis also received cyclosporin and total parenteral nutrition in view of the severity and refractoriness of the disease. These patients did not respond satisfactorily to the conventional treatment and were recruited for infliximab trial. The drug was given as i/v infusion (5mg/kg-body weight). 4 patient with fistulising Crohn's disease and one patient with having extensive colonic involvement received a 2nd and 2 amongst the former also had a 3rd dose .

Physicians were asked to complete a Proforma that in addition to the history included information regarding disease site, severity other medical and surgical treatments and global clinical assessment of disease outcome as complete, partial and no response. The hospital ethics committee approved the study design and informed consent was taken from each patient. These patients were followed up for a period of 4 to 6 months (average 5 months) and assessed for the disease activity or any adverse effects of the study drug.

RESULTS

The total numbers of patients included in the study were 10. 7 patients were male (70%), majority in their twenties and thirties. 3 out of 10 were female.

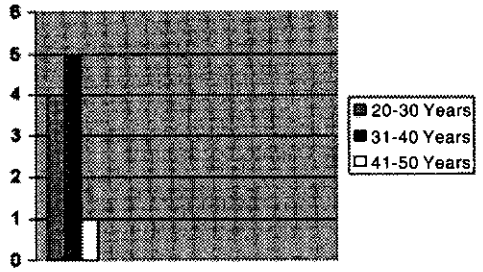
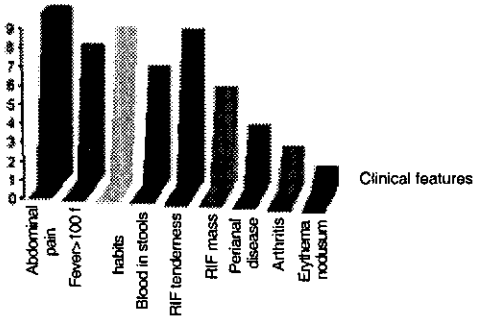


Figure showing age distribution of patients.

Most patients had lower abdominal pain, altered bowel in the form of loose stool sometimes mixed with blood and low-grade fever. Right iliac fossa mass and tenderness was another commonest finding. Three patients had extra intestinal manifestation of the disease.

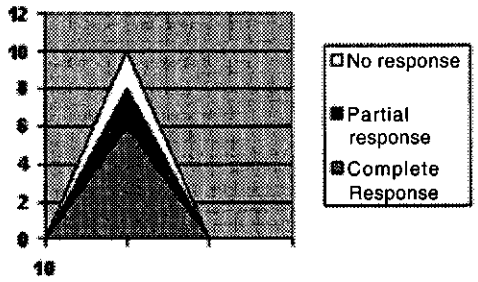
Figure 2 showing clinical features of Crohn's disease.



Out of 10 cases 6 had Luminal Crohn's disease (60%) and 4 had fistulising disease. Amongst the former 3 had disease restricted to the small gut 2 had iliocolitis and 1 patient had Crohn's colitis only. The commonest fistulas were between the bowel loops. Two patients had fistulas to the skin (perianal & abdominal).

Infliximab infusion was effective in 6 patients (60%) showing complete response in two to three weeks time. There was marked improvement in the form of decrease stool frequency, abdominal pain and improvement in general well being. There was resolution of arthritis and erythema nodusum in patient presenting with extra intestinal manifestation of the disease. There was resolution of abscesses on sonography and improvement in colonoscopic appearance of the mucosa in 3 patients with colonic involvement. All the 4 cases with fistulising disease responded to treatment (complete response). Two out of 6 patients with luminal Crohn's disease showed a complete response to infliximab infusion while 2 had a partial response in the form of less stool frequency and abdominal pain. The remission was maintained over a period of 3 to 6 months. 2 cases amongst the luminal Crohn's disease did not have any change in symptomatology. They continued to have abdominal pain, loose motions, low-grade fever and ill health. There was no significant reduction in their ESR.

Figure 3 showing response to infliximab.



Two patients have minor infusion related fever and chills, which responded to antihistamines and antipyretics. One patient had a new appearance of perianal abscess and another patient had exacerbation of facial acne possibly related to steroids intake.

DISCUSSION

Our findings show that treatment with Infliximab is effective in active moderate to severe and refractory cases of Crohn's disease. This is particularly true of steroid resistant and fistulizing disease. The efficacy of this drug has been established in multiple well-conducted trials.[6,7] Six out of our total number of ten patients showed complete response to infliximab. The response to treatment was fairly rapid i.e. in one to three weeks time and the remission was maintained in five out of these six patients who showed complete response. The fact has been supported by other studies.[8,12] One of our patients in the responsive group had Crohn's disease limited to the colon and did not improve with heavy doses of steroids and other conventional treatment. His response to the Infliximab infusion was quite dramatic (complete response). We gave him a 2nd dose of the infusion when he had symptomatic relapse with increased frequency of bloody stools. Repeat colonoscopy revealed improvement in mucosal oedema and inflammation. He had extensive involvement of the colon.

All the four patients with fistulising disease responded well to the drug. Infliximab is reported to more effective in with fistulising disease.[4,14] However there is endosongraphic evidence of persistence of fistula after infliximab treatment.[10] We were able to taper oral steroids to minimum in responsive patients with out recurrence or exacerbation of the disease. The fact is born out by one other study.[11] Seven out of ten patients who responded completely or partially to treatment were on azathioprine. The response is reportedly enhanced by concomitant administration of immunosuppressive drugs.[3,12]

Two out of six patients with luminal Crohn's disease showed no response to infliximab infusion. The failure rate of infliximab treatment has been reported from 20% to 40% in luminal Crohn's disease in prospective trials.[13,2] The drug is proved to be more effective in active fistulizing Crohn's disease.[14]

Our patients were remarkably free of major adverse reaction to the infusion except one patient who developed perianal abscess. This side effect has been reported in a well-conducted trial.[11] Another patient had exacerbation of his facial acne possibly related to heavy doses of steroids. The drug is known to cause infusion related hypersensitivity reaction, lupus like syndrome and reversible cholestatic liver disease.[3,15,16] Aseptic meningitis in a 53 year old has been reported who received the infusion for active rheumatoid arthritis.[17] Reactivation of tuberculosis may occur soon after initiation of therapy with Infliximab and patients should be screened for latent tuberculosis infection before starting treatment.[18]

CONCLUSION

The drug seems to be cost effective for this chronic debilitating disease for which there is no permanent cure at present. However the limiting factor is the high cost, which amounts to several thousands US dollars per infusion.

Furthermore this was an open trial with very small numbers of patients. It was not blinded or placebo controlled. Therefore no firm conclusion could be drawn from the study. There is need for large controlled trials to be conducted locally to establish its efficacy and safety profile in our patients.

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