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Original Article

Promising effect of infliximab on the extent of involvement in ulcerative colitis

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Abstract

BACKGROUND: Ulcerative colitis (UC) is a disabling disease with increasing incidence in Iran. In spite of combined medical therapy, some patients eventually undergo total colectomy. Infliximab has proved itself as a rescue therapy and even as an early aggressive therapy for severe extensive UC. Meantime, there are concerns about its complications. The aim of this study was to evaluate the efficacy of infliximab in Iranian refractory UC patients.

METHODS: This multi centric case-series study included 29 UC patients receiving two to three of the drugs prednisolone, AZT/6MP and 5ASA but yet having flare-ups. At first, the extent of colon involvement was determined by colonoscopy; then the drug was administered at baseline, 2nd week and 6th week and colonoscopy repeated afterwards. Clinical and laboratory data were also recorded.

RESULTS: In first endoscopy 18 patients (62%) out of 29 suffered from pancolitis and none had normal results. In second examination (done on 19 patients), one was normal and only 8 of 18 (27.6%) had pancolitis. Considering missing cases, at least in 33.3% of patients the drug has reduced the extreme extent of colon involvement. Also a wilcoxon signed ranks test revealed significant reduction of the disease extension after this treatment ($p = 0.008$). There were only one leucopenic and one hypotensive reactions in short term. The drug showed effectiveness in the term of disease modifying, too.

CONCLUSIONS: These data show the usefulness of the drug in refractory UC. Longer follow ups and controlled trials are needed.

KEYWORDS: Infliximab, Colitis, Ulcerative, Colon.

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Inflammatory bowel diseases (IBD) affect patients in the prime of their lives.[1] Many contributing factors such as genetic, racial, environmental, behavioral, bacterial, viral, immunological and neuropsychological factors are accused.[2] It is suggested that genetic factors may predispose patients to an abnormal immune response to environmental and microbial antigens [3] and the immune response persists with lack of tolerance to nonpathogenic enteric bacteria.[4]

Ulcerative colitis (UC) is a type of IBD confined to the large intestine and has an annual incidence rate of 2-7 per 100,000 in the United

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States.[5] In best circumstances, 66% of patients will achieve clinical remission with medical therapy, and 80% of treatment-compliant patients maintain remission.[5] Up to 15% of UC patients will have severe colitis and are less likely to respond to first-line conventional therapy.[6] About 30-40% of patients will not respond to corticosteroid therapy and will need urgent colectomy.[7] Medical treatment failure in UC is reported in different countries such as Newzealand,[8] USA (concomitantly introducing intravenous cyclosporine for the disease),[9] UK,[10] Sweden,[11] France [12] and Scotland.[13]

The incidence and prevalence rate of IBD in Iran is not clear. However there is some other information. In 1985, a review of 112 Iranian UC patients diagnosed between 1973 and 1982 was published. The authors yielded significant differences with other countries including the mild course of the disease, the absence of skin manifestations, and the rarity of colorectal cancer and Crohn's disease (CD) in Iranian patients.[14] In 2000 the increasing rate of CD in Iran was announced.[15] In 2005 a study reported some features of 457 Iranian IBD cases [401 UC, 47 CD and 9 indeterminate colitis (IC)] and revealed almost the same picture of other developing countries. Also it was not as rare as previously thought, and it seemed as if gradual adoption of a Western lifestyle may be associated with the continuing rise in IBD.[16] In 2009 epidemiologic characteristics of 500 Iranian IBD patients from tertiary care referral centers of Tehran was reported. Among the cases, 41.4% were diagnosed as CD and 58.6% as UC and none as IC patients. The researchers concluded that though the course of IBD is milder among Iranian patients, the total number of IBD patients reported in their study is an alarm and maybe improved sanitation and hygiene is important in the pathogenesis of IBD.[17] Some genetic predisposing factors are studied in Iran; there has been a significant difference in both allele and genotype frequency at position -800G > A of transforming growth factor-β1 gene promoter between UC patients and normal subjects,[18] the R702W mutation of CARD15/NOD2 gene is shown to be associated with Crohn's disease [19] and a probable association of the Fok I polymorphism in vitamin D receptor gene and Crohn's disease susceptibility is indicated.[20] No association was found between class one HLA antigens and UC in a study in Iran.[21] A review on the relapse rate in 163 Iranian UC patients showed that during the initial attack, UC was controlled by 5-ASA agents in 42 patients and others received corticosteroids. Of them, 53 ones (32.5% of total) received azathioprine because of corticosteroid dependence. Seven patients never achieved complete remission. The extent of the disease in the colon was an important prognostic factor. Patients with distal colitis showed lesser tendency to relapse.[22]

As one can see, about one third of patients need third line therapy in their first attack. On the other hand the quality of life of the patients is not so favorable. It is shown that the prevalence of irritable bowel syndrome-like symptoms in UC patients in remission is about three times higher than in controls, and these patients have impaired health related quality of life in comparison with that of UC patients in the active phase.[23] In addition, low bone density (LBD) in Iranian UC and CD patients is in accordance with Western societies and corticosteroid use is one of the predicting factors for LBD.[24] Iranian gastroenterologists frequently encounter patients who don't respond to conventional treatments as expected and suffer from the disabling course of the disease and drug complications.

In 2006, FDA approved infliximab for use in patients who have moderately to severely active UC with an inadequate response to conventional agents.[25] Infliximab is a 149,100-d chimeric monoclonal antibody directed against tumor necrosis factor α. The variable domain is murine derived and is linked to a human IgG1 constant region.[4] The early studies indicated that infliximab shows promise for the treatment of active UC, and the most recent studies confirm its superiority over placebo in clinical response, clinical remission, mucosal healing, reduction of dose, and discontinuation of corticosteroid.[4] It could be a rescue therapy for se-

vere UC cases even with its probable adverse events [7] and long term safety issues.[26] There was no published evidence of its use in our country. It seemed reasonable to offer this therapeutic choice to the eligible patients and follow the results.

Methods

Our study was an open label, multi centric, prospective case series study. It was approved both scientifically and ethically by the Isfahan University of Medical Sciences and done in some gastroenterology clinics in Iran during 2008 and 2009 on definitely diagnosed UC patients. The diagnosis of UC was established according to the clinical, radiological, pathological and laboratory examinations. The contributing medical centers consisted of Al-Zahra hospital (Isfahan University of Medical Sciences, Isfahan), Imam Khomeini hospital (Tehran University of Medical Sciences, Tehran), Baqiyatallah hospital (Baqiyatallah University of Medical Sciences, Tehran) and two private clinics in Tehran. The patients were from two cities and they could be a good representative sample of such patients.

We enrolled patients who were suffering from severe ulcerative colitis in this study. Disease severity was evaluated by Mayo scoring index.[27] According to this scale, remission is defined when patient's score is ≤ 2 and severe ulcerative colitis is defined when the score is ≥ 10. All patients received standard therapy [two to 3 of these drug lines: prednisolone, azathioprine/6-mercaptopurine (AZT/6-MP) and 5-aminosalicylates (5-ASA)] but showed poor response and were considered refractory to treatment. When patients' Mayo score was 10 or more and any of the later mentioned indications of infliximab use was present, this new therapeutic choice and its considerations was discussed with them. If the patient agreed to try the drug and signed the consent form, the drug was administered.

Indications of infliximab use were as steroid-dependent colitis (unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids without recurrent active disease, or to have a relapse within 3 months of stopping steroids), steroid unresponsiveness or steroid-refractory colitis (active disease despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks), multiple relapses in spite of complete therapy (≥ 2 relapses per year) and fulminant colitis (acute severe colitis in a toxic patient).[28]

We excluded patients who had hypersensitivity to the drug or to a murine protein, severe congestive heart failure (functional classes 3 and 4), active infection, current or recent malignancy, latent or active tuberculosis and demyelinating disorders.[4,29]

A colonoscopy examination (Olympus CV 165, Japan) was done in all patients before starting the treatment and the extent of colon involvement was recorded. A checklist form containing demographic and disease related data, defecation rate (number), severity of rectal bleeding (4 grades), abdominal pain, anorexia, nausea and vomiting, fecal urgency and fever (yes/no), heart rate (normal/abnormal), drug regimen (name), last year flare-ups (number), qualitative CRP (4 grades), values of hemoglobin, ESR, serum albumin and stool smear RBC count and side effects of the drug was completed for each patient at baseline and right after each dose of the drug. The relevant physicians filled this form through interview with the patients, clinical examination and laboratory data observation.

Infliximab (Remicade ®, Schering-Plough, NJ, USA) was diluted in normal saline and infused intravenously over a period of at least 2 hours using an in-line low-protein-binding filter (pore size ≤ 1.2 micrometer) at the baseline, 2nd week and 6th week with the dose of 5 mg/kg for body weight. Any side effects of drug infusion was recorded and treated.

A second colonoscopy examination was planned at 12th-14th week. It is not a routine part of the treatment protocol and due to its cost and annoying procedure the patients were not under obligation to do this. If that colonoscopy was done the results were recorded. The therapeutic plan continued according to the physician's decision but the research project

had no longer follow-ups.

Gathered data were analyzed by descriptive statistics, Chi-square and Wilcoxon statistical tests (for qualitative data) and paired T-test (for quantitative data) using SPSS software version 13 (SPSS Inc., Chicago, IL). P values less than 0.05 were considered statistically significant.

Results

Twenty nine patients entered the study. Fifteen were female and fourteen were male. Mean age of them was 35.97 ± 10.49 years. Mean age at diagnosis was 28.63 ± 10.52 years. Patients' mean body weight was 62.09 ± 12.18 kilograms (Table 1).

Drug regimen consisting of all three drug lines (prednisolone, AZT/6-MP and 5-ASA) was seen in 21 patients, and two of three drugs were used in eight patients. The mean of last year's disease flare-ups frequency was 2.91 ± 1.88 (Table 1).

Indication for infliximab administration was steroid dependency in 37.9% of the cases, multiple relapses in 31%, steroid unresponsiveness in 6.9% and fulminant colitis in 3.4%; 20.6% had more than one indication (Table 1).

Table 1. Demographic and disease characteristics of the patients at baseline

Parameters	All patients	Patients underwent the 2nd colonoscopy
No.	29	19
Age	35.97 (10.49)	38.32 (10.10)
Sex (%):		
Female	15 (51.7)	9 (47.4)
Male	14 (48.3)	10 (52.6)
Weight (kg)	62.09 (12.18)	63.06 (11.16)
Age at diagnosis	28.63 (10.52)	31.05 (10.56)
Job (%):		
Housewife	12 (41.4)	7 (36.8)
Student	7 (24.1)	4 (21.4)
Freelance worker	3 (10.3)	1 (5.3)
Army member	4 (13.8)	4 (21.4)
Clerk	1 (3.4)	1 (5.3)
Unknown	2 (6.9)	2 (10.5)
Drug regimen (%):		
All 3 drugs	21 (2.4)	16 (84.2)
Two of three	8 (27.6)	3 (15.8)
Last year flare-ups	2.91 (1.88)	2.56 (1.15)
Causes of flare-ups (%):		
Insufficient drug doses	8 (27.6)	5 (26.3)
Drugs discontinuance	7 (24.13)	6 (31.6)
Incomplete treatment	4 (13.8)	1 (5.3)
Infection	1 (3.4)	1 (5.3)
Emotional	1 (3.4)	0
No results	8 (27.6)	6 (31.6)
Indication for infliximab administration (%):		
Steroid dependency	11 (37.9)	11 (57.9)
Multiple relapses	9 (31)	3 (15.8)
Steroid unresponsiveness	2 (6.9)	2 (10.5)
Fulminant colitis	1 (3.4)	0
More than one	6 (20.6)	3 (15.8)

Data are shown as means (± standard deviation) or numbers (percent).
AZT: azathioprine; 6MP: 6 Mercaptopurine; 5ASA: 5 Aminosalisylic Acid

In the first endoscopic examination 18 patients (62%) suffered from pancolitis and none had normal results. In second examination (done on 19 patients), one patient's colon was normal and 8 (27.6%) had pancolitis. Of the 18 baseline pancolitis cases, 14 patients participated in the second colonoscopy. Eight of them (44.4%) still showed pancolitis and 6 ones (33.3%) showed lesser degrees of involvement (Table 2). Thus at least in 33.3% of the pancolitis cases the drug has reduced the extreme extent of colon involvement. This reduction is seen in most other degrees of colon involvement, too (Table 2, Figures 1 and 2). Also a wilcoxon signed ranks test revealed significant reduction of the disease extension with this treatment (p = 0.008).

Table 2. Results of colonoscopy examinations. Data are shown as numbers (percent)

Before Drug		**Changed to (after drug)**	
Finding	Frequency	Finding	Frequency
Pancolitis	18 (62)	Proctitis	1 (5.6)
-	-	Proctosigmoiditis	4 (22.2)
-	-	Left-sided colitis	1 (5.6)
-	-	Pancolitis	8 (44.4)
-	-	Missing	4 (22.2)
Left-sided colitis	7 (24.1)	-	-
-	-	Normal	1 (14.3)
-	-	Proctitis	1 (14.3)
-	-	Proctosigmoiditis	1 (14.3)
-	-	Left-sided colitis	1 (14.3)
-	-	Missing	3 (42.9)
Proctosigmoiditis	3 (10.3)	-	-
-	-	Missing	3 (100)
Proctosis	1 (3.4)	-	-
-	-	Proctosigmoiditis	1 (100)
Total number = 29		Total number = 29	

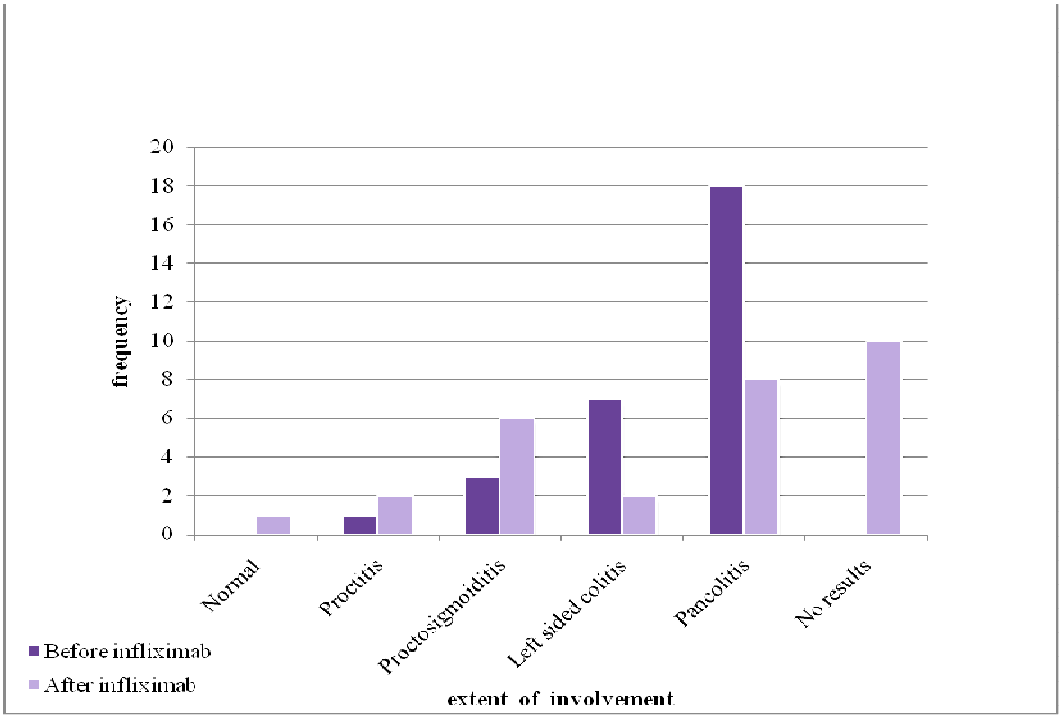

Figure 1. Frequency of colonoscopy findings in all patients

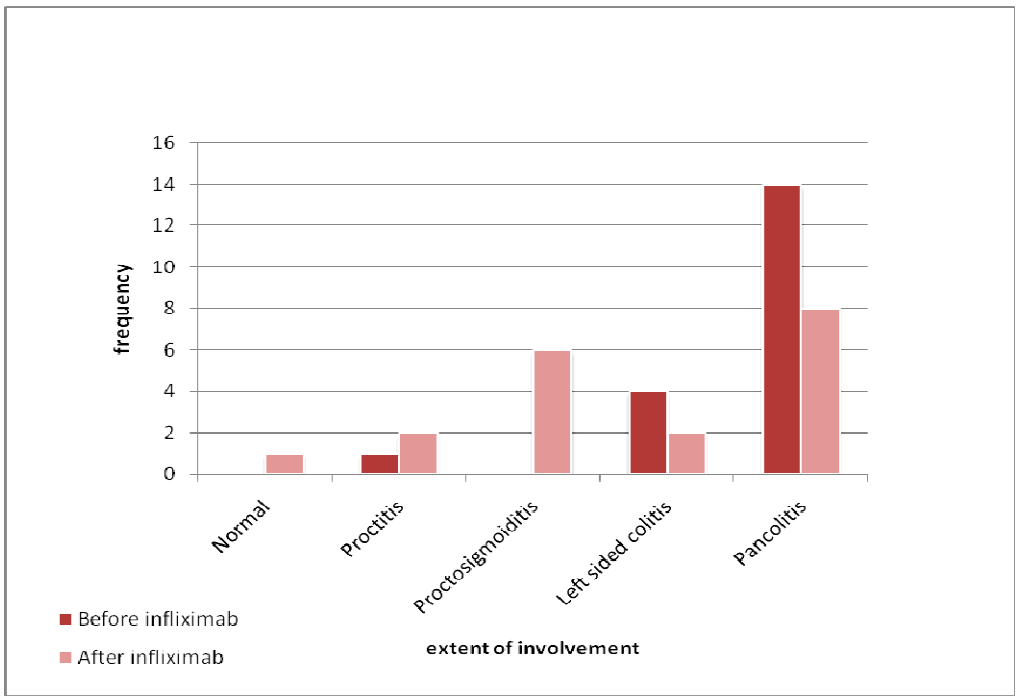

Figure 2. Frequency of colonoscopy findings in patients with second endoscopy done

Disease modifying effect of the drug was assessed too. Clinical modification rate was defined as reduction in both defecation rate and rectal bleeding severity and no abdominal colicky pain. Eight patients (27.5%) after first dose and 12 patients (41.3%) after second dose matched these criteria. After third dose (6^{th} week), 17 of 24 patients whom their relevant data was completely recorded (70% (58.6% of all) enrolled patients) reached this goal.

Hemoglobin value and stool smear RBC count were considered as paraclinical modification indicators. There are 14 missing cases in this regard in the evaluation after the third dose. From 15 remainders, thirteen patients [86.6% (44.8% of all)] showed increased hemoglobin level which was significant ($p = 0.001$). Seven patients [46.6% (24.1% of all)] showed reduction of stool smear RBC to less than 4 per high power field. It is significant too ($p = 0.017$).

Systemic and topical steroid use was reduced significantly after third dose of infliximab ($p = 0.039$ and $p = 0.018$ respectively). At least 13 of 28 systemic steroid users (46.4%) and 6 of 10 topical steroid users (60%) could be weaned off these drugs. Other results are summarized in table 3.

In the course of the study two short term drug reactions (one leucopenic and one hypotensive) were recorded.

Discussion

We designed this study to find out the efficacy of inflixmab in Iranian patients who are suffering from Ulcerative Colitis refractory to conventional treatment. As mentioned in results an improvement in disease activity was seen soon after infusion of the drug. Clinical improvement was in accordance with endoscopic and laboratory positive changes. More than thirty three percent of the patients achieved definite colonoscopic improvement. This is in agreement with a recent meta-analysis who suggests that infliximab is effective in patients with moderate to severe ulcerative colitis whose disease is resistant to conventional therapy using corticosteroids and/or immunosuppressive agents.[30] The Active Ulcerative Colitis Trials 1 and 2 (ACT1 and ACT2, respectively)

Table 3. Review of statistical results comparing parameters before and after drug use

Parameters	Number of patients with complete data (baseline and after 3rd dose)	P value
Extent of colon involvement	19	0.008
Defecation rate	24	0.000
Rectal bleeding severity	24	0.000
Abdominal pain	24	0.005
Fever	24	0.194*
Anorexia	24	0.041
Nausea and vomiting	24	0.000
Pulset rate	21	0.001
Fecal urgency	20	0.074*
Serum albumin	6	0.167*
Hemoglobin	15	0.014
Stool smear RBC	14	0.003
ESR	15	0.001
CRP	27	0.026
Systemic steroid use	19	0.039
Topical steroid use	18	0.018
5-ASA use	23	0.000
AZT/6MP use	23	0.007

Data are shown as numbers.
AZT: Azathioprine; 6MP: 6 Mercaptopurine; 5ASA: 5 Aminosalisylic Acid; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; RBC: Red Blood Cell
Total number of enrolled patients was 29.
* Not significant

evaluated the efficacy of infliximab for induction and maintenance therapy in adults with UC. In overall, 61-69% of patients receiving infliximab (5-10 mg/kg) had a clinical response at 8th week, as compared with 29-37 percent of those who received placebo.[31] Our clinical response rate at 6th week was about 60% too and it is achieved in a therapeutic setting.

In the retrospective study of Lees et al on a total of 39 patients with acute severe ulcerative colitis, 66% responded to infliximab, and 2 serious reactions including one death was seen. Their response was defined as need to colectomy and had 90 days follow up.[7] We didn't focus on this endpoint but there were few cases who escaped colectomy at least at short term.

Su et al in a retrospective review reported a total of 27 patients with active UC who received infliximab. Twelve patients (44%) achieved remission in a median of 4 days and 22% had partial response. There were relapses and 95% of these relapses were successfully treated with repeated infusions. Steroid-refractory patients were less likely to respond to infliximab therapy than steroid-responsive patients. They have reported a death attributable to the drug.[32] In Gornet et al published series of 30 patients, a 75% response rate (defined as a decrease of the clinical signs and no need for additional medical treatment or surgery) was found at the 7th day which lessened to 50% after a month. Long-term results were less favorable, with frequent relapses, and about one-third of the patients required a colectomy.[33] We yielded lower prompt clinical response than these reports. Our patients were UC cases refractory to standard therapies but their cases consisted of steroid-responsive or indeterminate colitis too. May be it is the cause. Moreover their longer time results are worst. Our study revealed the opposite. It is probably due to more doses of the drug we used.

Chey et al in a case series study on 16 refractory UC patients have shown 88% dramatic clinical, endoscopic, and histological responses after first dose of infliximab. This study showed steroid-sparing effect of the drug

too.[34,35] Kaser et al in their open label study on 6 severe steroid-refractory ulcerative colitis cases have shown 100% response to infliximab in short-term (7 days).[36] In another study which was done by Actis et al on 8 steroid-refractory UC patients 50% response rate is reported. They had used single initial dose of 5 mg/kg for body weight.[37] Kohn et al in a series study on 13 severe refractory UC patients have reported 77% response after 2 days. Their prescription was single dose infusion of 5 mg/kg for body weight of infliximab.[38] Our finding is more similar to Actis et al results than others. It seems that genetic or racial factors influences on the response of this drug.

Bermejo et al presented seven cases of ulcerative colitis (6 with chronic active disease despite immunosuppressive therapy, and one with acute steroid-refractory ulcerative colitis) treated with infliximab 5 mg/kg of body weight. Five out of six patients (83.3%) with corticosteroid-dependent disease could be successfully weaned off these drugs.[39] At least 60% of our patients receiving topical steroids and 46% of patients receiving systemic steroids could discontinue them.

There are also controlled studies with different response rates. Sands et al in a pilot, controlled study, included 11 patients (8 infliximab and 3 placebo). Their therapeutic schemes was single dose of 5, 10 or 20 mg/kg of body weight of infliximab and their results showed 50% treatment success in infliximab group at the 2nd week.[40] A randomized controlled trial that was done by Ochsenkuhn et al on 13 acute moderate or severe UC patients showed good and similar results at weeks 3 and 13 in both infliximab and prednisolone groups (5/6 and 6/7 successful therapies in each group, respectively).[41]

Conclusions

We focused mostly on the effect of drug on the extent of colon involvement. It is rarely reported and we observed good results in this regard. It may be considered as an efficacy indicator. Also our clinical response is near the ACT1 & 2 clinical trials even though our criteria may not be the same. In our study two short term adverse drug reactions was recorded. As mentioned before there are other studies which have produced different results but neither has been done in our population. However this study has its own limitations such as short duration, uncontrolled design and missing data. Longer follow ups and controlled studies are needed in order to assess long term efficacy and safety of the drug. Issues such as cost/efficiency and cost/benefit must be assessed too.

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Conflict of Interests

One of the authors (MA) is indirectly affiliated to Schering-Plough pharmaceutical company. But no financial or other kind of support has been offered to her or any other author from this company.

Authors' Contributions

PA carried out the design and coordinated the study in multiple centers and participated in manuscript preparation. PM provided assistance in the design of the study, coordination of the study and manuscript preparation. ZF prepared and finalized the manuscript and did statistics. Other authors (NED, HA, HK, FD, AK, MA and HT) did patients' follow ups, gathered the data and helped in preparing the manuscript. All authors have read and approved the content of the manuscript.

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