A Double-blind, Placebo-controlled Trial of Low Dose Infliximab in Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** The tumor necrosis factor-α (TNF-α) inhibitor infliximab (IFX) has been proven effective for the treatment of ankylosing spondylitis (AS). The primary objective of this double-blind, placebo-controlled study was to assess the safety and efficacy of low-dose (3 mg/kg q8w) IFX therapy in AS.

Methods. In the 12-week double-blind phase of the study, patients (N = 76) were randomized to infusions of placebo or IFX (3 mg/kg) at Weeks 0, 2, and 6. The primary endpoint was 20% improvement in ASsessments in Ankylosing Spondylitis criteria (ASAS20) at 12 weeks. In the open-label extension phase, all patients received scheduled IFX infusions (q 8 weeks) up to 46 weeks. Patients who did not meet target response criteria (i.e., BASDAI score did not improve by at least 50% and was > 3) at Weeks 22 or 38 had a dose increase to IFX 5 mg/kg.

Results. At 12 weeks, 53.8% of IFX-treated patients achieved ASAS20, compared with 30.6% of placebo-treated patients (p = 0.042). IFX-treated patients showed significant improvement in measures of disease activity, spinal mobility, and quality of life over the course of the study. During the extension phase, 68% of patients in the IFX group did not meet the clinical target and had an increase in the dose of IFX to 5 mg/kg by 38 weeks. In general, IFX was safe and well tolerated. Ten patients withdrew from the study for various reasons, with only 2 (2.6%) attributed to adverse events.

Conclusion. IFX 3 mg/kg was effective in reducing the signs and symptoms of active AS, and was generally safe and well tolerated. Dose escalation to 5 mg/kg every 8 weeks was warranted in most patients to achieve the target clinical response of the study. (J Rheumatol First Release March 15 2010; doi:10.3899/jrheum.091042)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS INFLIXIMAB DOUBLE-BLIND
ANTI-TUMOR NECROSIS FACTOR-α THERAPY CLINICAL TRIAL

Ankylosing spondylitis (AS), the prototypic disease in the group of chronic inflammatory disorders known as spondyloarthritis (SpA), affects 0.1% to 1.1% of the general population[1,2]. The disease manifests predominantly in the second or third decade of life[1], yet is often not diagnosed until after a long period of symptoms. Biopsy of the sacroiliac (SI) joints of patients with AS has demonstrated infiltrating T cells and macrophages in the synovium, as well as high levels of the proinflammatory cytokine tumor necrosis factor-α (TNF-α)[3]. Infliximab (IFX) is a chimeric monoclonal IgG1 antibody that is capable of binding both soluble and membrane-bound TNF-α to inhibit its inflammatory activity. Early trials of IFX in AS established the efficacy of an induction regimen of infusions of IFX 5 mg/kg at Weeks 0, 2, and 6[4,5], followed by scheduled infusions every 6 weeks thereafter[6,7]. Indeed, such a continuous treatment strategy has recently been found to be superior to an on-demand infusion schedule, with a greater percentage of patients in the continuous treatment group achieving partial remission after 1 year compared with patients in the on-demand treatment group (27% vs 7%; p < 0.0001)[8].

Lower doses of IFX are efficacious in the treatment of RA, raising the possibility that the same could be true for the management of AS[9]. In an open-label study of lower-dose IFX (3 mg/kg every 8 wks) in patients with AS, 58.8% of patients demonstrated ≥ 50% improvement in Bath AS Disease Activity Index (BASDAI) scores at 14 weeks, along with a significant reduction in Bath AS Functionality Index (BASFI) and Bath AS Global Index (BASGI) scores[10]. Complete remission of joint disease was seen in 45.5% of patients at 14 weeks. Followup indicated that efficacy was sustained over 3 years, with 33% of patients remaining in remission at 24 months, and only 5 of the 34 patients requiring a change in the IFX dosing regimen to either 3 mg/kg every 6 weeks, or 5 mg/kg every 8 weeks[11].

With these observations, there was a need to evaluate the

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Supported by Schering-Plough Canada Inc., Kirkland, Quebec. Prof. Maksymowych is a Scientist of the Alberta Heritage Foundation for Medical Research.

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Accepted for publication December 16, 2009.

efficacy and safety of low-dose (3 mg/kg) IFX in the treatment of AS in a controlled study. The primary objective of our study was to assess the reduction in the signs and symptoms of AS at 12 weeks and 1 year after an induction regimen of 3 mg/kg IFX, followed by maintenance infusions every 8 weeks, with the option for patients with an inadequate response to increase dose to 5 mg/kg IFX.

MATERIALS AND METHODS

Study design. This Phase IIIb, randomized, multicenter, double-blind, placebo-controlled study was conducted at 8 investigational centers in Canada. The study protocol was reviewed and approved by the appropriate institutional review board or independent ethics committee at each site. Patients were randomly assigned in a 1:1 ratio to receive infusions of either placebo or IFX 3 mg/kg at Weeks 0, 2, and 6, with evaluation for primary and secondary endpoints at Week 12. In the subsequent open-label phase of the study, which lasted 46 weeks with followup for efficacy and safety assessments through 52 weeks, the IFX group continued infusions as scheduled, at Week 14 and every 8 weeks thereafter. During this phase, the placebo group crossed over to receive infusions of IFX 3 mg/kg at Weeks 14, 16, and 22, and every 8 weeks thereafter. All patients could receive dose-escalation of IFX to 5 mg/kg at Weeks 22 or 38 if the patient had an absolute BASDAI score > 3 and and a relative decrease of < 50% in BASDAI from baseline.

Patient population. To be eligible for the study, patients were required to be ≥ 18 years of age at the time of screening, previously diagnosed with AS according to the modified New York criteria[12] and have active disease (BASDAI score ≥ 4) at baseline and at screening. In those patients taking nonsteroidal antiinflammatory drugs (NSAID), disease-modifying antirheumatic drugs (DMARD), analgesics, or corticosteroids, the dose must have been stable for at least 14 days (30 days for DMARD) prior to the first infusion of study drug. Patients were excluded from the study if they had a history of chronic/recurrent infectious disease, including tuberculosis, hepatitis B, or HIV, and/or a diagnosis of malignancy or lymphoproliferative disease currently or within the past 5 years.

Efficacy and safety assessments. The primary endpoint of our study was the proportion of patients achieving a 20% improvement in ASsessment in AS (ASAS) International Working Group criteria (ASAS20) after 12 weeks of treatment. An ASAS20 responder must demonstrate improvement of ≥ 20% from baseline (or absolute improvement of at least 1 unit on a numerical rating scale of 0–10) on at least 3 of the following 4 domains: patient's global assessment, spinal pain, function according to BASFI, and inflammation (the average of the last 2 questions of the BASDAI concerning morning stiffness), as well as absence of deterioration from baseline of ≥ 20% or 1 unit in the remaining domain.

Secondary endpoints at Weeks 12 and 50 included the proportion of patients achieving 40%, 50%, and 70% improvement in ASAS criteria (ASAS40, ASAS50, and ASAS70, respectively), and the change from baseline in BASDAI, BASFI, and BASGI. The number of patients achieving a 50% improvement in baseline BASDAI (BASDAI 50) was also recorded. Spinal mobility was assessed using the Bath AS Mobility Index (BASMI) at Weeks 12 and 50. The ASAS 5/6 is defined as a 20% improvement in at least 5 of 6 domains including the 4 core domains of the ASAS20 as well as C-reactive protein (CRP) and spinal mobility.

Erythrocyte sedimentation rate (ESR) and CRP were recorded at screening and at Weeks 12, 30, and 50. The Medical Outcomes Study Short Form-36 (SF-36) health survey questionnaire was administered at Weeks 12 and 50 to assess the effect of treatment on quality of life. The number of patients requiring dose increase and the time of dose increase was recorded.

Safety assessments included incidence and severity of adverse events (AE), and an evaluation of the relationship of AE to the study drug as assessed by the individual investigator.

Statistical methods. Sample size requirements for the study were based on the assumption that 55% of the IFX-treated patients and 20% of the placebo-treated patients would achieve the primary study endpoint. In order to detect this difference as statistically significant at an alpha level of 5.0% with 90% power, 40 patients per group were required.

Descriptive statistics including the mean, standard deviation, median, and range for continuous scale variables, and frequency distributions for categorical scale variables were reported for patient demographics and baseline characteristics. Between-group differences with respect to demographics and baseline characteristics were assessed for statistical significance with the independent samples Student t test for continuous variables and the chi-square statistic for continuous scale variables.

The between-group difference with respect to the proportion of patients achieving the primary study endpoint of ASAS20 at 12 weeks of treatment was assessed with the chi-square statistic. Multivariate logistic regression was used to produce adjusted estimates for the between-group differences with respect to the rate of achieving the primary efficacy endpoint. Similarly, between-group differences with respect to all dichotomous secondary outcomes (ASAS40, ASAS50, ASAS70, BASDAI 50%, and ASAS 5/6) at 12 and 50 weeks of treatment were assessed with the chi-square statistic. Between-group differences with respect to the mean change from baseline in the BASDAI, BASFI, and BASGI at 12, 22, and 50 weeks of treatment were assessed with the Student t test for independent samples.

A post-hoc analysis was carried out to identify baseline characteristics in patients most likely to achieve the clinical target with low-dose IFX. In this analysis, patients in the IFX group were stratified by their dosing status at the first dose-escalation timepoint (Week 22).

Safety and tolerability were assessed by the incidence of treatment-emergent adverse events. All adverse events were coded using the MedDRA dictionary of terms (version 9.0).

There were no imputations or replacement of missing values. All analyses were conducted on the intent to treat (ITT) population, defined as all enrolled patients that received at least one infusion of IFX. Statistical significance was established at $p < 0.05$. All statistical analyses were conducted with SPSS version 12.0 and SAS version 8.0.

RESULTS

Patient demographics and baseline characteristics. Of the 99 patients enrolled at screening, 23 were screen failures. The remaining 76 patients were randomized to receive infusions of placebo (n = 37) or IFX 3 mg/kg (n = 39). Thirty-four of 37 patients (92%) in the placebo group and 32 of 39 patients (86%) in the IFX group completed the study. A total of 10 patients withdrew from the study for the following reasons: 1 because of protocol violation, 2 withdrew consent, 2 were lost to followup, 3 due to lack of efficacy, 1 as the result of an AE, and 1 for a serious adverse event (SAE) (Figure 1).

The treatment groups were well matched with regard to patient demographics and baseline characteristics and represented a typical cohort recruited to recent phase III trials of anti-TNF agents in AS (Table 1). Compared with patients in the placebo group, patients in the IFX group had lower values of ESR (mean 28.24 mm/h vs 18.58 mm/h, respectively; p = 0.010) and CRP (mean 22.84 mg/l vs 12.90 mg/l; p = 0.012) at screening. Sixty-two patients were tested for HLA-B27 and 55 of them were positive (88.7%).

Efficacy assessment. During the placebo-controlled phase of the study, 53.8% of patients in the IFX group achieved the primary endpoint of ASAS20 at 12 weeks, compared with

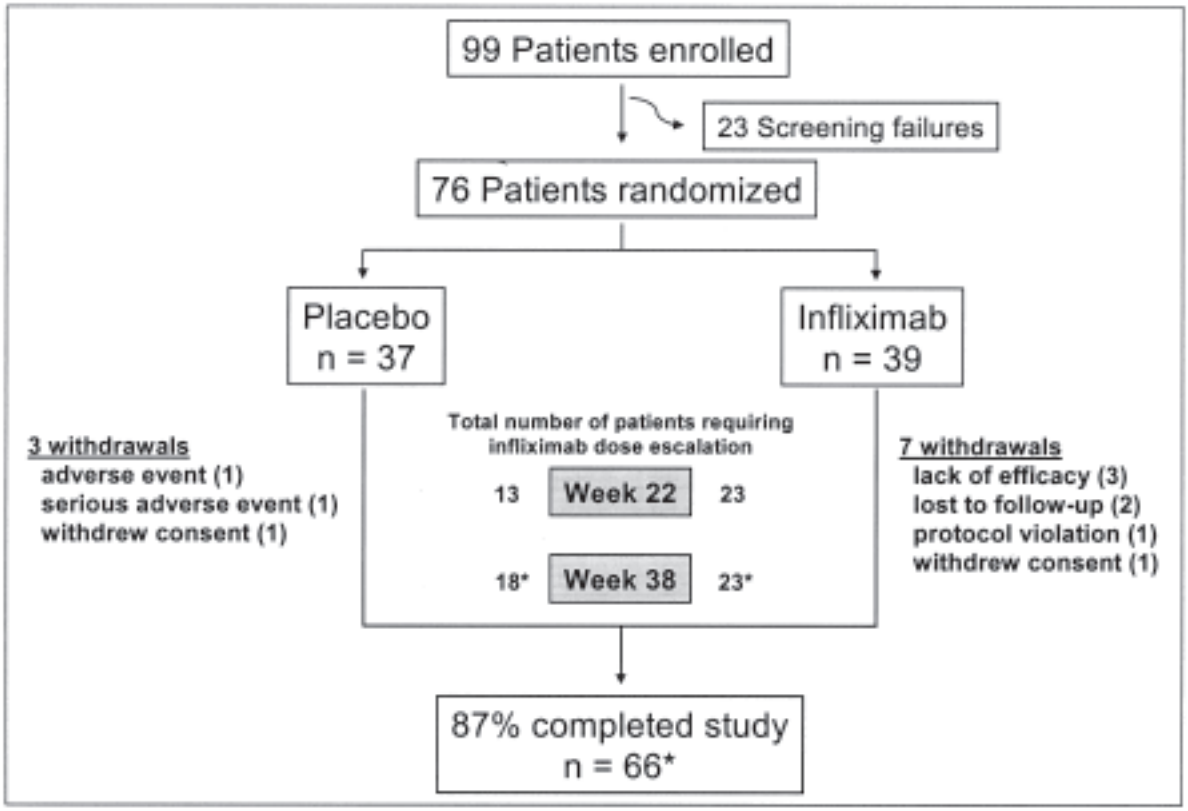

Figure 1. Patient disposition. Of 99 patients enrolled at screening examination, 23 were screen failures. The remaining 76 patients were randomized to the IFX group (n = 39; 51.3%) or the placebo group (n = 37; 48.7%). Of these 76 patients, 75 (98.7%) finished the 18-week assessment, 66 completed the study at Week 46, and 10 withdrew. After 22 weeks, an increase in IFX dose from 3 mg/kg to 5 mg/kg was required in 13 patients who had originally received placebo and 23 patients who had originally received IFX; dose optimization was required at Week 38 in an additional 6 patients from the placebo group and 3 from the IFX group. *Number accounts for patients who withdrew after Week 22 evaluation.

Table 1. Patient demographic data and baseline characteristics.

Characteristics	Placebo, n = 37	Infliximab, n = 39
Age, yrs, mean (SD), median (minimum-maximum)	39.3 (9.0) 39 (24–60)	42.9 (10.4) 44 (21–65)
Male, n (%)	29 (78)	32 (82)
Caucasian, n (%)	33 (89)	34 (87)
Time since first manifestation of AS symptoms, yrs, mean (SD), median (minimum-maximum)	18.6 (9.8) 16.7 (0.3–37.2)	18.7 (11.3) 15.2 (2.3–45.3)
AS disease duration, yrs, mean (SD), median (minimum-maximum)	11.1 (10.3) 7.2 (0.2–37.2)	11.7 (10.6) 8.4 (0.2–37.4)
ESR, mm/h, mean (SD)	28.24 (17.95)	18.58 (13.39)
CRP, mg/l, mean (SD)	22.84 (20.53)	12.90 (11.64)
HLA-B27-positive, n (%)	27 (73)	28 (72)
Extraarticular manifestations, n (%)		
IBD complications	4 (11)	3 (8)
Uveitis	13 (35)	13 (33)
Psoriasis	2 (5)	3 (8)

AS: ankylosing spondylitis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HLA-B27: human leukocyte antigen B27; IBD: irritable bowel disease.

30.6% of patients in the placebo group (p = 0.042) (Figure 2). Additionally, a greater proportion of IFX-treated patients achieved ASAS40 (46.2% vs 8.3% of placebo-treated patients; p < 0.001), ASAS50 (41.0% vs 5.6%; p < 0.001),

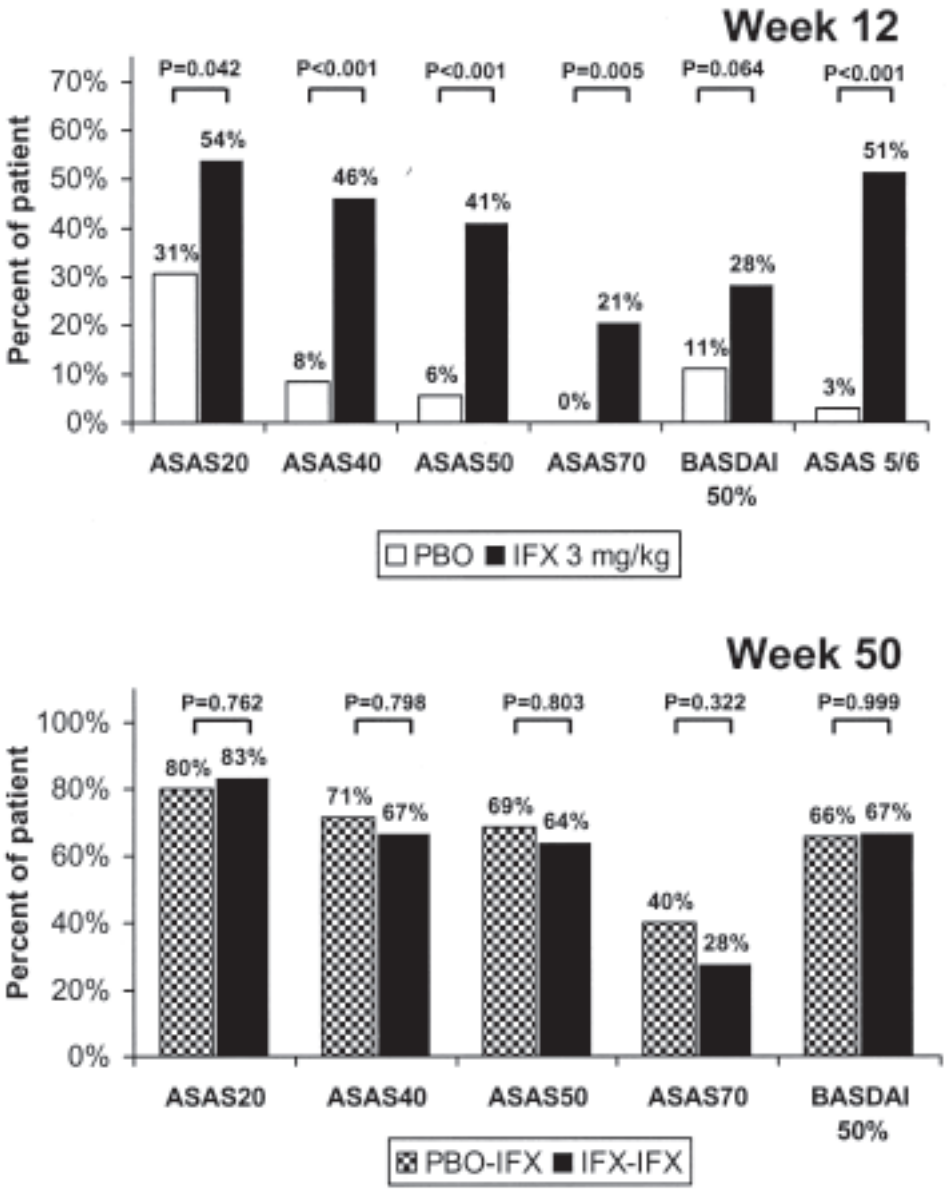

Figure 2. Clinical response at Weeks 12 and 50. At Week 12, a greater proportion of patients receiving IFX 3 mg/kg achieved 20%, 40%, 50%, and 70% improvement in ASAS scores compared to placebo (PBO). Results were similar with respect to 50% improvement in BASDAI scores and demonstration of at least 20% improvement in 5 of the 6 ASAS domains. Starting at Week 12, all patients received open-label IFX (3 mg/kg or 5 mg/kg if they required dose optimization by Week 22 or 38). By Week 50, a similar proportion of patients achieved 20%, 40%, 50% and 70% improvement in ASAS scores, a 50% improvement in BASDAI scores, and at least 20% improvement in 5 of the 6 ASAS domains. These data include patients who continued the original 3 mg/kg dose and patients who were optimized to 5 mg/kg.

and ASAS70 (20.5% vs 0%; p = 0.005). An ASAS 5/6 response was observed in 51.3% patients receiving IFX, compared with 2.8% of patients receiving placebo (p < 0.001) (Figure 2). Patients receiving IFX also demonstrated significantly greater mean change in BASDAI from baseline to 12 weeks compared with patients in the placebo group (–2.1 vs –0.7; p = 0.003) (Figure 3). 28.2% of IFX-treated patients showed 50% improvement in their BASDAI scores (BASDAI 50%) during the first phase of the study compared with 11.1% in the placebo group, but this did not reach statistical significance (p = 0.064) (Figure 2). At 12 weeks, patients receiving IFX reported significant reductions from baseline values for mean BASFI and BASGI compared with patients receiving placebo (–1.8 vs –0.4; p = 0.004, and –2.3 vs –0.2; p < 0.001, respectively) (Figure 3).

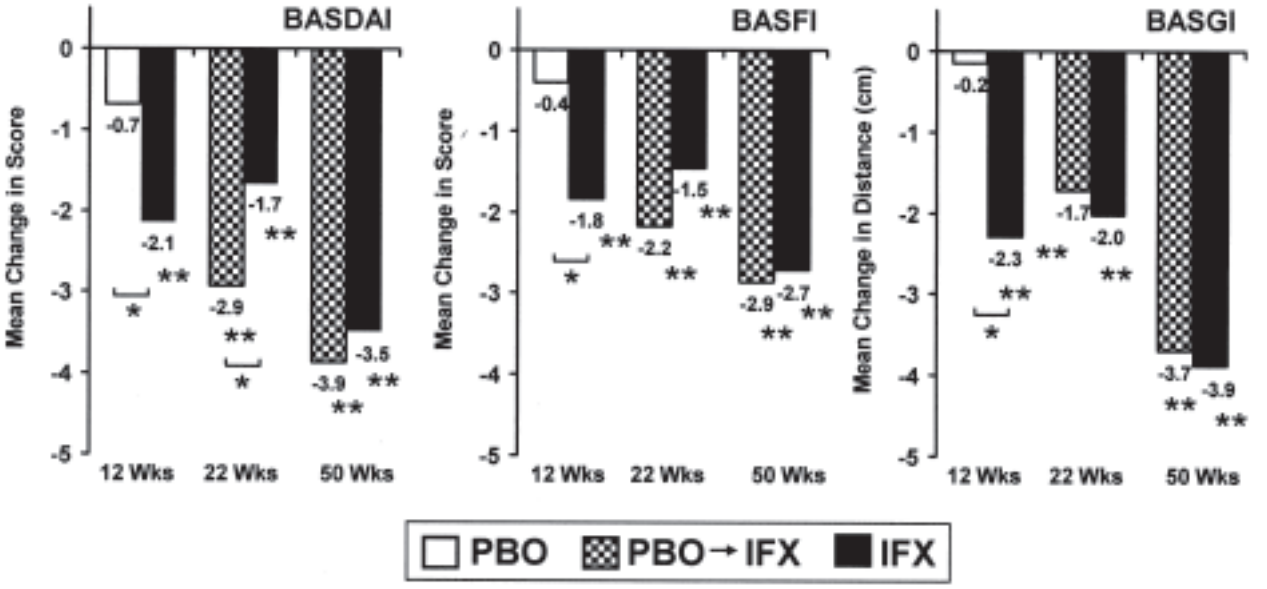

Figure 3. Change in BASDAI, BASFI, and BASGI scores over baseline values. At 12 weeks, patients in the IFX group (IFX) reported significant reductions in BASDAI, BASFI, and BASGI scores compared to placebo (PBO). Similar improvements in BASDI, BASFI, and BASGI were seen at Weeks 22 and 50 in patients receiving IFX from the beginning of the study as well as patients who crossed over from placebo to IFX after Week 12. These data include patients who continued the original 3 mg/kg dose and patients who were optimized to 5 mg/kg. *$p < 0.05$; **$p < 0.001$.

There was no difference at baseline in spinal mobility scores for placebo and IFX treatment groups as measured by BASMI (4.1 vs 4.3; $p = 0.630$). The mean change (± SD) in BASMI from baseline to 12 weeks was –0.45 (± 1.03) in IFX-treated patients, compared with 0.24 (± 0.60) in placebo-treated patients ($p = 0.001$).

Patients in the IFX group demonstrated significant reductions in measures of acute-phase reactants at Week 12. The mean change in ESR from screening to Week 12 was –10.66 (± 12.5) mm/h in IFX-treated patients, compared to 1.59 (± 12.42) mm/h in placebo-treated patients ($p = 0.001$). The mean change in CRP concentrations was –6.75 mg/l (± 16.31) in IFX-treated patients, versus 2.18 (± 14.88) mg/l in placebo-treated patients ($p = 0.019$).

At baseline, the only significant difference between groups with regard to patients' health-related quality of life was in the mental health portion of the SF-36 questionnaire (mean score in the IFX group was 58 and in the placebo group 67; $p = 0.028$). After 12 weeks, IFX-treated patients reported significant changes from baseline in all SF-36 survey domains, while placebo-treated patients showed significant improvement only in physical functioning. The change in scores observed in the IFX group were significantly greater ($p < 0.05$) than that observed in the placebo group for a number of domains, including role physical, bodily pain, vitality, social functioning, and mental health.

During the open-label phase of the study, dose escalation was conducted for patients not meeting the prespecified criteria (BASDAI improvement > 50% or BASDAI < 3) at Weeks 22 and 38. At Week 22, in 23/37 patients (62.2%) who received IFX 3 mg/kg at the beginning of the trial, the protocol required dose escalation to 5 mg/kg. This number of patients for which dose escalation by the protocol criteria rose to 23/34 (67.6%) at Week 38 (3 patients receiving 5 mg/kg dropped out between Weeks 22 and 38). Comparatively, 13/35 patients (37.1%) originally assigned to placebo had a dose escalation to IFX 5 mg/kg at Week 22, which corresponded to 6 weeks of IFX treatment. At the Week 38 dose evaluation visit, corresponding to 22 weeks of IFX treatment, an additional 6 patients (18/33 or 54.5% of this group) had their dose titrated to 5 mg/kg. Overall, 61.2% of patients (41/67) treated with IFX 3 mg/kg received dose escalation to 5 mg/kg at the Week 38 analysis.

At the end of the 12-week placebo-controlled phase of the study, patients in the placebo group crossed over to receive IFX infusions. By the study end at Week 50, there were no significant differences between treatment groups with respect to ASAS or BASDAI response (Figure 2), and all patients demonstrated significant improvements in BASFI and BASGI scores compared to baseline values (Figure 3). Indeed, there were no statistically significant differences in all endpoints within the 2 treatment groups. Both treatment groups also reported significant improvements in all domains of the SF-36, both physical and mental domains, by the end of the study.

Because of the significant proportion of patients that received dose escalation to 5 mg/kg, a post-hoc analysis was carried out to identify baseline characteristics the patient most likely to achieve the clinical target with low-dose IFX. Patients in the IFX group were stratified by their dosing sta-

tus at the first dose-escalation timepoint [Week 22 among patient demographics and baseline characteristics, only baseline CRP was significantly higher in patients who escalated to 5 mg/kg compared to those who remained at 3 mg/kg (15.8 ± 12.6 vs 7.2 ± 6.4 mg/l; $p < 0.05$)]. Indeed, multivariate logistic regression analysis showed that baseline CRP was associated with dose-escalation status, with an odds ratio of 1.163 (95% CI 1.013–1.334, $p = 0.034$). Thus, higher CRP level was a predictor of failure to achieve a 50% reduction in BASDAI and a BASDAI < 3 with the 3 mg/kg dosing.

Safety assessment. A total of 338 AE were reported in 69 of 76 patients (90.8% of total study population; Table 2). The incidence of AE was similar in placebo to IFX-treated and IFX to IFX-treated patients (89% and 92%, respectively), with the majority being mild (54 patients) or moderate (50 patients) in intensity (319/338, 94%). Severe AE were reported in 14 patients (18.4% of total study population); hospitalization was required in 7 patients (9.2%), one patient (1.3%) discontinued the study due to AE and an additional one (1.3%) due to an SAE. Overall, 80.3% of AE were classified according to the assessment of the treating physician as unlikely to be related to the study medication. The most common complaint in both treatment groups was nasopharyngitis. Nasopharyngitis, upper respiratory tract infection, pruritus, and urticaria were reported in 7.7% of patients in the IFX to IFX treatment group, while patients in the placebo to IFX group most often experienced nasopharyngitis (13.5%), nausea, dizziness, headache, infusion site reaction, pyrexia, and urticaria (5.4%; Table 2).

Since patients in the placebo group were crossed-over to IFX at 12 weeks, a post-hoc analysis was carried out to evaluate AE classified as definitely, probably, or possibly related to the study drug, before and after Week 12. There was a total of 94 such events recorded, of which 24 occurred before Week 12. The AE that occurred more than once in the placebo group were nasopharyngitis (3 events) and nausea (2 events). In the IFX group, there were 3 reports of upper respiratory tract infection.

Eight patients experienced SAE, 3 in the IFX group and 5 in the placebo to IFX group. Only one SAE occurred in the first 12 weeks in an IFX-group patient (arthralgia). Two SAE, an infusion-related reaction in one patient and acute cholecystitis in another, were classified as possibly or probably related to the study medication. Other SAE included cholelithiasis, decreased hemoglobin and abdominal pain, gastrointestinal hemorrhage, an aortic aneurysm, and an AS flare, all classified as unlikely to be related to study treatments.

Table 2. Non-serious adverse events reported during double-blind and/or open label phase of study in at least 5% of patients.

Adverse Event, n (% of patients)	Placebo to IFX*	IFX to IFX
Total	157 (89.2)	181 (92.3)
Mild	87 (70.3)	106 (71.6)
Moderate	59 (59.5)	67 (71.8)
Severe	11 (21.6)	8 (15.4)
Nasopharyngitis	5 (13.5)	3 (7.7)
Upper respiratory tract infection	1 (2.7)	3 (7.7)
Pruritus	1 (2.7)	3 (7.7)
Nausea	2 (5.4)	1 (2.6)
Dizziness	2 (5.4)	1 (2.6)
Headache	2 (5.4)	1 (2.6)
Infusion site reaction	2 (5.4)	0 (0)
Pyrexia	2 (5.4)	0 (0)
Urticaria	2 (5.4)	2 (5.1)
Infusion site urticaria	0 (0)	2 (5.1)

* Cross-over group (placebo to infliximab); IFX-IFX: infliximab-only group.

DISCUSSION

Extensive clinical experience indicates that conventional treatments prove inadequate for a substantial number of patients with AS. NSAID are superior to placebo in numerous trials in AS, but often are not found to be sufficient to control ongoing pain, stiffness, and fatigue. DMARD such as sulfasalazine and methotrexate lack demonstrated efficacy in controlling spinal inflammation in AS. For patients in whom NSAID provide inadequate disease control, anti-TNF agents have been a major advance in the therapeutics of AS. Studies have clearly demonstrated the efficacy of IFX in AS when given at a dose of 5 mg/kg at Weeks 0, 2, and 6 and every 6 weeks afterwards[4-7]. However, this regimen uses a higher dose than in rheumatoid arthritis (5 vs 3 mg/kg, respectively) and a shorter treatment interval (every 6 weeks vs every 8 weeks). Our study was initiated to determine if a lower initial dose and longer treatment interval with IFX, which would come with a smaller health-economic burden, are efficacious in treatment of this disease.

Our results demonstrate that there is rapid, significant improvement in the signs and symptoms of AS with low-dose (3 mg/kg) IFX. At 12 weeks, 53.8% of the patients receiving IFX 3 mg/kg attained the primary outcome measure (ASAS20), which was greater than that achieved by placebo-treated controls. In addition, patients receiving IFX 3 mg/kg more often achieved higher clinical target outcomes (ASAS40, ASAS50, and ASAS70) with greater frequency than the placebo-treated patients. In addition, patients in the IFX group showed significant improvements that were superior to placebo in BASDAI, BASFI, and BASGI, and in spinal mobility (BASMI). For health-related quality of life as defined by the SF-36, patients receiving IFX demonstrated greater changes at 12 weeks in the areas of bodily pain, role physical, vitality, social functioning, and mental health than placebo-treated patients ($p < 0.05$).

By study end, following cross-over of the placebo group to IFX, 81.7% of patients in the study achieved the primary endpoint of ASAS20, but, following the prespecified crite-

ria for dose increase, the majority of these patients were receiving 5 mg/kg every 8 weeks. Moreover, two-thirds of all patients were able to maintain 50% improvement in BASDAI scores. This is in keeping with the demonstrated efficacy of IFX at 5 mg/kg every 6 weeks in AS (ASSERT[7], etc.). In general, IFX was well tolerated in the majority of patients, with a similar incidence of AE in the placebo and IFX treatment groups. The majority of observed AE were mild/moderate, and did not interfere with treatment.

The rapidity of improvement reported here with low-dose IFX was similar to that observed in previous studies in which IFX was administered according to ASAS/EULAR guidelines (5 mg/kg at Weeks 0, 2, and 6 and every 6 weeks thereafter). In a small open-label observational study[6] of patients with AS who were refractory to conventional therapy, treatment with IFX 5 mg/kg led to significant improvement in measures of disease activity and global assessment of pain as early as Week 2, with 70% of patients achieving ASAS20 at that timepoint, a higher response rate than observed in our study. The Ankylosing Spondylitis Study for the Evaluation of Recombinant IFX Therapy (ASSERT) trial[7] using IFX at the 5 mg/kg dose described improvements in disease activity and function as early as 2 weeks after initiation of treatment that were maintained through Week 24, at which point 61.2% of patients in the IFX group had achieved ASAS20, compared with 19.2% of placebo-treated patients. Comparatively, in our study, 53.8% of patients achieved ASAS20 after 2 weeks of treatment with low-dose IFX, with this level of improvement maintained at 22 weeks.

In patients with AS refractory to traditional treatments, Jois, *et al*[13] conducted an open-label observation study using an induction regimen of IFX 3 mg/kg with maintenance infusions every 8 weeks thereafter. The percentages of these patients achieving ASAS20 and ASAS40 at 3 months (63.6% and 50%, respectively) and at 6 months (78.2% and 66.7%) were found to be comparable to studies using higher doses of IFX. Similarly, after 3 months of treatment with IFX 3 mg/kg in our study, ASAS20 and ASAS40 were achieved by 53.8% and 46.2% of patients, respectively; after 6 months, 64.7% and 52.9% of IFX-treated patients achieved these goals. In the study by Jois, *et al*[13], nearly two-thirds of patients receiving low-dose IFX maintained 50% improvement in BASDAI for up to 1 year.

In our study, 68% of patients in the IFX group required an increase in dose of IFX to 5 mg/kg by Week 38. A subanalysis of patients requiring dose-escalation at 22 weeks suggested that patients who required dose-optimization initially responded to the induction regimen of 3 mg/kg at 0, 2, and 6 weeks, but subsequently lost response. However, most of these patients regained clinical response once they were titrated to 5 mg/kg every 8 weeks. This was particularly evident with the acute-phase reactants, suggesting that CRP or ESR could be used as surrogate markers to determine which patient requires dose-escalation. Indeed, high CRP was the only baseline variable that was associated with subsequent dose-escalation. However, studies in patients with both RA[14] and AS[15] have found that higher CRP levels at baseline are correlated with greater symptom improvement following IFX treatment, although this measure correlated poorly with baseline disease activity. Conversely, a clinical outpatient evaluation in The Netherlands, France, and Belgium noted moderate to poor correlation between CRP levels and ESR and measures of AS disease activity (defined by BASDAI, physician-global, and patient-global)[16]. It is possible that this clinical outcome is related to trough serum levels of IFX, which would be highest after completion of the induction dosing regimen, but would likely decline in the following weeks during maintenance infusions (administered every 8 weeks).

Administration of the TNF-α inhibitor IFX at a dose of 3 mg/kg was found to be effective in reducing the signs and symptoms of active AS in some patients over 12 weeks, and was safe and well tolerated in the study population, with minimal discontinuations due to AE. In order to achieve a prespecified clinical target, most patients were escalated to 5 mg/kg dosing every 8 weeks. Clinical response was maintained until 1 year.

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