Efficacy of infliximab in refractory ankylosing spondylitis: results of a six-month open-label study

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Abstract

Objective. To evaluate the efficacy and safety of a loading regimen of the anti-tumour necrosis factor α (TNF-α) antibody infliximab in predominantly axial severe ankylosing spondylitis (AS).

Methods. We enrolled in this study 50 patients (76% males, 87% HLA-B27$^+$, median age 35 yr, median disease duration 13 yr) with active AS [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) $\geqslant 30/100$ and serum C-reactive protein concentration $\geqslant 15$ mg/l] despite treatment with a non-steroidal anti-inflammatory drug, and without peripheral arthritis, uveitis or active inflammatory bowel disease. Other disease-modifying anti-rheumatic drugs were discontinued $\geqslant 3$ months before inclusion and were not allowed during the study. Patients received three infusions of infliximab (5 mg/kg) at weeks 0, 2 and 6 and were monitored clinically and biologically until week 24.

Results. Forty-eight patients completed the treatment. In intention-to-treat analysis, all parameters were significantly improved at week 2 and generally reached maximal improvement at week 8. The proportion of responders, defined by a reduction of $\geqslant 20\%$ in the global assessment of pain (GAP) or by the AS Assessment Study Group (ASAS 20%) criteria, and the proportion of patients reaching partial remission were 98, 94 and 70% respectively. Relapse, defined as $\geqslant 50\%$ loss of maximal GAP improvement, occurred in 73% of completers, with a median delay of 14 weeks after the third infusion. No serious adverse event related to the treatment was observed.

Conclusions. This study confirms, in a large group of severely affected AS patients, the remarkable efficacy of infliximab. Relapse usually occurred after discontinuation of the drug, but almost one-third of completers were still free of relapse 4 months after the last infusion.

Ankylosing spondylitis (AS) is a disease which benefits from few therapeutic options other than symptomatic treatment dominated by the non-steroidal anti-inflammatory drugs (NSAIDs), and patients with the most severe forms of the disease are difficult to manage [1]. Among the conventional disease-modifying drugs that are commonly used for the treatment of chronic inflammatory arthritides, such as rheumatoid arthritis (RA), significant efficacy has been demonstrated in AS only for sulphasalazine [2]. However, the efficacy of this

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drug is very inconstant, especially in the most typical forms of the disease, which involve predominantly the axial skeleton [3].

Tumour necrosis factor α (TNF-α) is one of the most critical mediators in the pathogenesis of chronic inflammation. In recent years, therapeutic strategies aimed at blocking TNF-α have shown significant efficacy in the treatment of RA, psoriatic arthritis and Crohn's disease [4–6]. *In situ*, detection of TNF-α mRNA and protein in the sacroiliac joint of patients affected with AS [7] has provided a rationale for several studies in AS, using anti-TNF-α agents such as thalidomide, which is thought to decrease TNF-α mRNA production [8], or, more recently, the biological agents infliximab and etanercept [9, 10]. These early observational studies, conducted on limited numbers of patients, have shown very promising results [11].

The present open-label study was designed to investigate the efficacy of a loading regimen of infliximab in a large group of patients affected with axial AS that was refractory to conventional therapy and had no concomitant extra-articular manifestation, such as peripheral arthritis, uveitis or active inflammatory bowel disease (IBD). Particular attention was devoted to the duration of efficacy.

Patients and methods

Patients

Adult patients (>18 yr old) fulfilling the modified New York criteria for the diagnosis of AS [12] were recruited for the study via 10 rheumatology departments in France. The patients were required to have predominantly the axial form of AS, without active peripheral arthritis, uveitis or IBD at the time of inclusion. The criteria for inclusion were the presence of severely active disease, as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) $\geqslant 30/100$ [13] and a serum C-reactive protein (CRP) level $\geqslant 15$ mg/l. Although it was not mandatory for inclusion in the study, full radiographs of the spine were recommended at baseline. The extent of fusion was scored semiquantitatively on a 0–3 scale.

Disease-modifying anti-rheumatic drugs, such as sulphasalazine, methotrexate, hydroxychloroquine, intramuscular gold, thiol compounds, cyclosporin and intravenous bisphosphonate, had to have been discontinued for at least 3 months before inclusion. In addition, patients were required not to have received intra-articular injection of corticosteroid, parenteral injection of $\geqslant 30$ mg prednisolone or a daily intake of >10 mg prednisone within the last month, and to have been on a stable dose of NSAID for at least 1 month.

A negative pregnancy test result was required for non-menopausal female patients, and contraception during the study period and for 6 months after the last infusion of infliximab was recommended to all patients of childbearing potential.

Exclusion criteria included pregnancy, breastfeeding, vaccination with a live organism during the last month, present infection or any episode of serious infection within the last 3 months, active malignancy within the previous 5 yr, alcohol or drug addiction, severe chronic concomitant disease, and administration of an investigational drug within the last 3 months or of any known anti-TNF-α treatment (such as thalidomide or infliximab) in the past.

Concurrent drugs

Patients were required to continue their NSAID at a stable dose throughout the study. No intra-articular or parenteral injections of steroids were allowed during the trial. Physical therapy was allowed if it had been initiated more than 2 weeks before screening.

Study design

This prospective, multicentre, open-label, 6-month observational study was conducted in accordance with the Declaration of Helsinki (1964) and its revision (1975), and was approved by the Institutional Review Board of the Cochin Hospital (Paris, France). Patients entered the study after reading and signing an informed consent form.

Drug administration

In this observational study, patients were scheduled to receive a loading regimen of infliximab consisting of three infusions of infliximab at weeks 0, 2 and 6, and to be followed up thereafter. For each infusion, infliximab was administered intravenously at a dose of 5 mg/kg in 250 ml NaCl 0.9% over a 2-h period.

Evaluation of efficacy

Patient status was assessed once every 2 weeks from week 0 to week 8 and once every 4 weeks thereafter. The end point of the follow-up period was set to week 24 or to the occurrence of relapse at any intermediate visit between week 8 and week 24, whichever came first.

The following clinical variables were evaluated at each visit: patient global assessment of pain (GAP) on a 100 mm visual analogue scale (VAS); patient global assessment of disease activity (100 mm VAS); BASDAI; Bath Ankylosing Spondylitis Disease Functional Index (BASFI [14]); physician global assessment of disease activity (100 mm VAS); fatigue, using a 13-item composite scale adapted from the fourth version of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system [15]; weight; the Schober test; the fingers-to-floor test; the occiput-to-wall test; chest expansion; Westergren's erythrocyte sedimentation rate (ESR) in the first hour; and serum CRP level.

The main outcome variable for efficacy was patient GAP. Accordingly, a patient was defined as a responder if a reduction of GAP greater than 20% was achieved at any time-point during the follow-up period. For the patients who qualified as responders, relapse was defined as a loss of $\geqslant 50$% of maximal efficacy.

Although not included in the original design, criteria of response and of partial remission, as defined by the AS Assessment Study Group (ASAS [16]) were included in the analysis of efficacy. A response to treatment according to ASAS criteria requires improvement of ⩾20% and a net improvement of ⩾10 units on a scale of 0–100 in three of the following four domains: (i) patient global assessment of disease activity; (ii) pain (in the present study, GAP); (iii) function (in the present study, BASFI); and (iv) inflammation (in the present study, the mean of the two morning stiffness-related BASDAI VAS scores); and the absence of deterioration by ⩾20% and by ⩾10 units in the fourth domain. These criteria of response are referred to in the present study as 'ASAS 20%'. Similar combined criteria were also used with thresholds of improvement of ⩾50% and ⩾70% to define ASAS 50% and ASAS 70% levels of response respectively.

Evaluation of safety

Patients were monitored for adverse reactions and vital parameters (blood pressure, pulse, and temperature) during each infusion, and for 1 h afterwards. At each visit, patients were asked about side-effects and we recorded the peripheral blood white cell count, haemoglobin level and platelet count.

Statistical analysis

Treatment efficacy was evaluated from week 0 to week 8 by analysis of each outcome variable in all patients enrolled in the study (intention-to-treat analysis), applying a 'last observation carried forward' analysis. The significance of the change from baseline was measured with the Wilcoxon signed ranks test. An intention-to-treat analysis of the kinetics of the response was conducted for the main outcome variable (GAP) and for the ASAS responses and partial remission criteria during the entire study period. The maintenance of response was also analysed for these variables. A negative correlation between the extent of spinal fusion on baseline radiographs and the maximal level of improvement of GAP was tested by using the one-tailed Spearman's test.

Relapse, defined as a loss of 50% of maximal improvement of GAP, was only analysed in completers. Delay to relapse corresponded to the time elapsed between maximal improvement of GAP and the visit when relapse had occurred. A correlation (either positive or negative) between the maximal level of improvement of GAP and the delay to relapse was tested with the two-tailed Spearman's test.

A *P* value less than 0.05 was considered as significant.

Results

Patients

The 50 screened patients were all considered eligible for the study and allowed to receive infliximab. Of these, 48 received three infusions as scheduled; one received only one infusion and was withdrawn from the study because of a serious adverse event unrelated to infliximab (gastric ulcer perforation related to NSAID intake); and one missed the third infusion at week 6. This last patient was the only patient who was lost to follow-up during the study period. The proportion of males was 76%. The median age was 35 yr (range 21–54 yr). The median disease duration was 13 yr (range 2–32 yr). Median time from diagnosis was 10 yr (range 1–28 yr). HLA-B27 was present in 40 of 46 tested patients (87%). The frequency of AS-related manifestations in the medical history was as follows: peripheral arthritis, 53%; talar pain, 50%; dactylitis, 20%; psoriasis, 36%; uveitis, 30%; IBD, 6% (IBD was in remission in all three patients). Radiographs of the spine were performed at baseline in 38 patients, showing no fusion in 15 (39%), mild to moderate fusion in 14 (37%) and advanced ossification (bamboo spine) in 9 (24%).

Efficacy

Baseline characteristics of the 50 patients, and their subsequent evolution until week 8 is shown in Table 1. Intention-to-treat analysis exhibited improvement of all outcome measures compared with baseline, reaching statistical significance as early as 2 weeks after the first infusion of infliximab. Maximal average improvement was reached at week 8 for all parameters, except for ESR and CRP, for both of which maximal improvement was observed at week 4. However, the delay to reach maximal improvement was highly variable from patient to patient, as shown in Fig. 1 for GAP. In the subgroup of patients for whom baseline radiographs of the spine were available, there was no statistically significant negative correlation between the extent of fusion of the spine and the maximal level of GAP improvement (correlation test).

Cumulative proportions of patients reaching a 20, 50 or 70% improvement in GAP, of patients reaching the ASAS 20, 50 and 70% response criteria and of patients reaching a partial remission state at any time point during follow-up are shown in Table 2. Altogether, 98% of the patients (100% of completers) achieved 20% improvement in GAP, 94% of the patients (96% of completers) were responders according to the ASAS 20% criterion and 70% of the patients (72% of completers) reached partial remission.

Among 10 patients with psoriasis present at inclusion, eight reported improvement of their lesions upon infliximab treatment.

Relapse

Maintenance of the level of response concerning GAP improvement, the ASAS criteria and partial remission was subjected to intention-to-treat analysis, which showed progressive loss of beneficial effect after discontinuation of infliximab. Of 48 completers (who were all responders), 35 (73%) experienced frank relapse, defined by a loss of at least 50% of their maximal GAP improvement, within 19 weeks after the last infusion,

TABLE 1. Clinical and biological course of AS during treatment of 50 patients with infliximab (intent-to-treat analysis from week 0 to week 8)

Outcome measure	Week 0	Week 2 (week 2 minus week 0)	Week 4 (week 4 minus week 0)	Week 6 (week 6 minus week 0)	Week 8 (week 8 minus week 0)
Global assessment of pain (0–100)	67 ± 3.1	$34 \pm 3.6 (-49\%)^c$	$21 \pm 3 (-69\%)^c$	$21 \pm 3.4 (-67\%)^c$	$18 \pm 3.1 (-72\%)^c$
Disease activity by patient (0–100)	70 ± 2.9	$40 \pm 3.6 (-44\%)^c$	$26 \pm 3.2 (-63\%)^c$	$22 \pm 3.5 (-69\%)^c$	$19 \pm 3.1 (-71\%)^c$
Disease activity by physician (0–100)	66 ± 2.1	$32 \pm 3 (-52\%)^c$	$20 \pm 2.5 (-71\%)^c$	$20 \pm 2.9 (-71\%)^c$	$18 \pm 2.9 (-73\%)^c$
BASDAI (0–100)	58 ± 2.2	$30 \pm 3 (-50\%)^c$	$20 \pm 2.4 (-68\%)^c$	$18 \pm 2.5 (-71\%)^c$	$17 \pm 2.3 (-72\%)^c$
BASFI (0–100)	61 ± 3	$35 \pm 3.6 (-45\%)^c$	$24 \pm 3 (-63\%)^c$	$22 \pm 3.2 (-68\%)^c$	$19 \pm 3 (-69\%)^c$
FACIT fatigue (0–100)	27 ± 1.1	$17 \pm 1.3 (-33\%)^c$	$15 \pm 1.2 (-42\%)^c$	$14 \pm 1.1 (-43\%)^c$	$14 \pm 1.1 (-44\%)^c$
ESR (mm/1st h)	52 ± 3.9	$17 \pm 2.4 (-67\%)^c$	$13 \pm 2.1 (-73\%)^c$	$14 \pm 2.8 (-72\%)^c$	$14 \pm 2.8 (-72\%)^c$
CRP (mg/l)^d	49 ± 4.3	$7 \pm 1.3 (-76\%)^c$	$6 \pm 0.8 (-82\%)^c$	$8 \pm 2.1 (-80\%)^c$	$7 \pm 1.6 (-76\%)^c$
Weight (kg)	67.7 ± 2.2	$68.3 \pm 2.2 (+1\%)^a$	$68.8 \pm 2.2 (+1.7\%)^c$	$69.1 \pm 2.2 (+2.2\%)^c$	$69.4 \pm 2.2 (+2.7\%)^c$
Schober test (cm)	2.2 ± 0.3	$2.6 \pm 0.3 (+18\%)^c$	$2.8 \pm 0.3 (+27\%)^c$	$2.5 \pm 0.3 (+18\%)^c$	$2.9 \pm 0.3 (+32\%)^c$
Finger to floor (cm)	30 ± 2.2	$24 \pm 2 (-22\%)^c$	$21 \pm 1.8 (-26\%)^c$	$19 \pm 2.1 (-37\%)^c$	$19 \pm 2 (-40\%)^c$
Occiput to wall (cm)	7.6 ± 0.9	$5.8 \pm 0.7 (-16\%)^b$	$6.1 \pm 0.8 (-12\%)^c$	$6.4 \pm 1 (-11\%)^b$	$5.6 \pm 0.7 (-16\%)^c$
Chest expansion (cm)	3.6 ± 0.2	$4.4 \pm 0.3 (+35\%)^b$	$4.5 \pm 0.3 (+36\%)^c$	$4.4 \pm 0.3 (+34\%)^b$	$4.2 \pm 0.4 (+37\%)^a$

Values are mean $\pm$ S.D. of the 50 AS patients in the study (last observation carried forward analysis) unless otherwise stated.
$^a P < 0.01$; $^b P < 0.001$; $^c P < 0.0001$.
^{d}Normal upper limit value of CRP varied between 3.6 and 12 mg/l according to the centre.
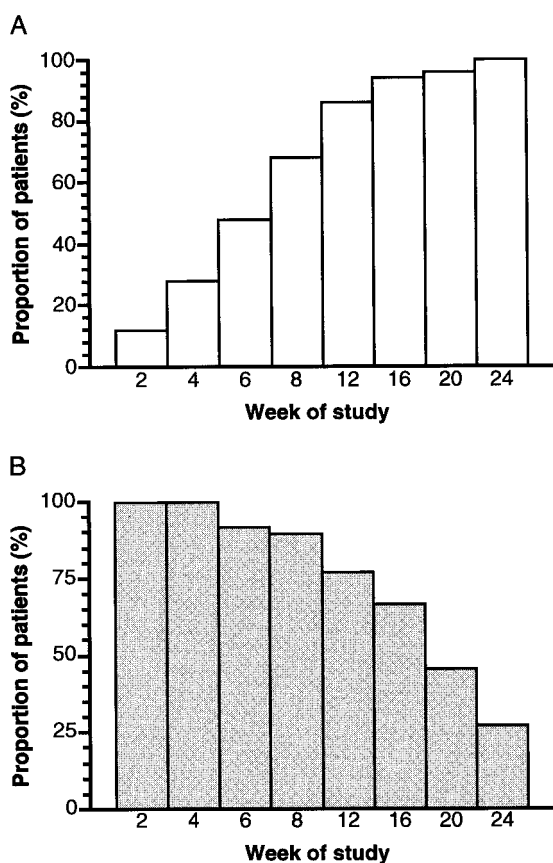
FIG. 1. (A) Time from onset of infliximab treatment to reach maximal improvement in global assessment of pain (cumulative proportion of patients in the intent-to-treat population). (B) Percentage of patients (completers only) remaining free of

TABLE 2. Level of response achieved according to time from onset of infliximab treatment (intention-to-treat analysis)

Level of improvement	Cumulative proportion of responders (%)					
	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16
Global pain (VAS)						
20%	82	96	98	–	–	–
50%	50	80	88	90	92	–
70%	34	62	72	76	80	82
ASAS criteria						
20%	70	94	–	–	–	–
50%	44	72	82	84	84	86
70%	22	54	68	72	74	76
Partial remission	22	44	52	64	66	70

patients who had relapse, the median delay between the last perfusion and relapse was 14 weeks (range 0–19 weeks). There was a small but statistically significant positive correlation between the level of maximal GAP improvement achieved and the delay to relapse (correlation test, $r^2 = 0.06$, $P < 0.05$). Peripheral arthritis occurred during relapse in five of the patients, all of whom had already experienced arthritis in the past.

Safety

The number of patients experiencing any adverse event was 40 (80%). Two of the events were considered serious but unrelated to the treatment (one case of gastric ulcer perforation requiring surgery and complicated by infection, and one case of lymphadenopathy, which preceded infliximab treatment, resolved spontaneously and remained unexplained). All other events were mild to moderate in intensity. Possible or proven infectious episodes were noticed in 25 patients (50%), most frequently affecting the upper airway (rhinitis 7, pharyngitis 5, sinusitis 3, bronchitis 2, otitis media 1).

among whom four who reached their maximum improvement before the third infusion of infliximab were already in relapse at week 6. In the group of

Discussion

Recently, several reports have consistently reported the efficacy of anti-TNF-α therapies in spondylarthropathy (SpA), including AS [8–10, 17]. Among anti-TNF-α agents, the chimeric monoclonal antibody infliximab has been the most extensively studied so far in this indication. Three open-label studies using infliximab have been reported previously [9, 17, 18]. In these three studies, a loading regimen consisting of three infusions of infliximab at weeks 0, 2 and 6 was used, just as in the present study. Altogether, 53 SpA patients have been treated in those three studies, among whom 42 had AS, several of them having peripheral arthritis. The duration of follow-up ranged from 12 to 14 weeks.

This report confirms the dramatic efficacy of a loading regimen of three infusions of infliximab in a larger group of homogeneous AS patients whose disease was considered to be severe and intractable with conventional treatments. Efficacy was evident for all parameters tested, including a FACIT fatigue scale and physical measures of spine and chest stiffness. In this study, an improvement in GAP of at least 20% was the main criterion used to define the response to treatment. According to this definition, 100% of completers were responders. Using the more stringent definition of short-term improvement published recently by the AS Assessment Group (ASAS 20% [16]), 96% of completers were still considered to be responders. We selected this ASAS definition of improvement because it allowed us to discriminate between an active product (NSAID) and placebo in active AS. Accordingly, the proportion of responders in the present study was far above what would be expected for a placebo (i.e. 25% [16]). In addition, 70% of the treated patients reached a partial remission state during the study period compared with 10% of the group of 605 AS patients (3% of the placebo-treated and 11% of the NSAID-treated patients) used for the development of ASAS criteria [16]. Although the present study was an open-label trial, its results are likely to be consistent with infliximab acting as a truly effective treatment. We observed a statistically significant increase in weight, which persisted after discontinuation of infliximab. Several explanations could account for this observation, including inhibition of TNF-α-mediated weight loss and potential recovery from occult bowel inflammation, which has been shown to be highly prevalent during the course of AS [19, 20].

In this study, the 6-month duration of follow-up allowed us to refine the kinetics of the response to infliximab and the rate and kinetics of relapse after discontinuation of the drug, in AS. Although almost the entire group of AS patients responded to infliximab, whatever the criteria used, the kinetics of this response was highly variable, some of the patients reaching their maximal level of improvement of GAP shortly after onset of infliximab but others only at the 6-month follow-up visit. However, a large majority of patients (86%) had reached their maximal improvement by week 12. Seventy-five per cent of the completers experienced clear relapse during the study period, implying that infliximab generally had a transient effect on disease evolution, and that repeated infusions are likely to be required to maintain the efficacy of the drug, just as in RA. However, a significant proportion of responders were still free of relapse after 6 months. Given such variability in the duration of efficacy with no straight-forward explanation at this stage, further investigations will be required to define the best treatment scheme with respect to the long-term management of such patients. It is noteworthy that no methotrexate was administered in combination with infliximab (as recommended in RA) in the present study or in other published studies of patients with AS. Such a difference can easily be explained by the lack of reported efficacy of methotrexate in AS, but it cannot be ruled out that, even in this case, the addition of methotrexate could improve the extent or duration of efficacy of infliximab.

The primary goal of this study was to study the efficacy of infliximab in typical severe AS. To achieve this goal, only AS patients with predominantly the axial form of disease at the time of inclusion were selected. It is noteworthy that a large proportion of these patients had experienced peripheral arthritis or dactylitis in the past. The unusually high proportion of cases of psoriasis may also reflect the particular severity of these cases, as psoriasis has been reported to be associated with the most severe forms of SpA [21].

There was a high proportion of patients experiencing an infectious event (50%), as in other studies in AS or RA [4, 9]. However, we observed no serious infection, such as tuberculosis or other opportunistic infections, which have recently been reported to occur at low but presumably increased frequency in patients treated with infliximab [22]. This was probably due to the relatively small number of patients included in this trial.

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