

Concise Report

Effectiveness of reducing infliximab dose interval in non-responder patients with refractory spondyloarthropathies. An open extension of a multicentre study

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Objective. To evaluate the therapeutic effectiveness of reducing the infliximab dose interval to 6 weeks in spondyloarthropathy patients not responding to 5 mg/kg every 8 weeks.

Methods. After 30 weeks of infliximab therapy, 25 patients were classified as responders [Bath Ankylosing Spondylitis Activity Index (BASDAI) <4 cm or ESR <30 mm/h and CRP <5 mg/l, $n=15$; group A] or non-responders (patients who did not achieve the response established for group A; $n=10$; group B). Responders continued on 5 mg/kg every 8 weeks and non-responders decreased the dose interval to 6 weeks. BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), ESR, CRP and ankylosing spondylitis assessment (ASAS) criteria were used to assess response.

Results. At 62 weeks, 11 of 15 patients (73.3%, 95% confidence interval = 44.9–92.2%) from group A and three of 10 patients (30%, 95% confidence interval = 6.7–65.2) from group B were responders ($P=0.049$). Eighty per cent (eight of 10 patients from group A) and 22.2% (two of 9 patients from group B) achieved 50% BASDAI improvement ($P=0.023$), and nine of 11 patients (81.8%) and four of 10 (40%) from groups A and B, respectively, reached ASAS20 at 62 weeks ($P=0.08$).

Conclusion. Patients on infliximab 5 mg/kg every 8 weeks with persistent disease activity may benefit from reducing the dose interval to 6 weeks.

KEY WORDS: Ankylosing spondylitis, Spondyloarthropathies, Infliximab, Anti-tumour necrosis factor- α .

The spondyloarthropathies (SpAs) are a heterogeneous group of inflammatory interrelated diseases involving peripheral joints and the spine and sharing similar clinical, epidemiological, radiological and immunogenetic features. Ankylosing spondylitis (AS) is the prototype disease of this group; other entities include reactive arthritis (ReA), arthritis and spondylitis associated with psoriasis (PsA) or inflammatory bowel disease (IBD), and undifferentiated SpA (uSpA). Although SpAs have traditionally been considered to have a more favourable prognosis than rheumatoid arthritis (RA), we now know that patients with SpA not only experience pain and disability similar to that found in RA, but also have reduced quality of life and increased mortality [1–2]. A limited number of alternative therapeutic approaches, other than physiotherapy, have been made available for these patients [3]. Serum tumour necrosis factor- α (TNF- α) levels are increased in spondylitis patients compared with non-inflammatory back pain patients [4]. Although there is now accumulating evidence that anti-TNF therapy is highly effective in SpA, especially in AS and PsA [5, 10], around 20% of patients do not

respond (non-responders) or have a limited response (poor responders) [6]. Infliximab is a chimeric anti-TNF- α monoclonal IgG1 antibody that neutralizes the soluble and membrane-bound cytokine [7]. Infliximab dose regimens of 3–5 mg/kg at dose intervals between 6 and 12 weeks have been used in SpA patients [8–11]. The optimal dose regimen necessary to suppress disease activity in SpA has not been fully defined. We addressed this issue by evaluating the therapeutic effectiveness of a reduction in the dose interval of infliximab to 6 weeks in SpA patients not responding to the classic regimen of 5 mg/kg every 8 weeks.

Patients and methods

This study is an extension of our 38-week open-label, multicentre, prospective study in 40 patients with active and refractory SpA [12]. After the administration of intravenous infusions of infliximab at 5 mg/kg body weight at weeks 0, 2, 6, 14, 22 and 30, 25 patients agreed to continue in the study and were

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Submitted 1 July 2005; revised version accepted 19 July 2005.

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classified in two groups according to the therapeutic effectiveness obtained at week 38. Group A (responders) consisted of 15 patients with Bath Ankylosing Spondylitis Activity Index (BASDAI) <4 cm or ESR <30 mm/h and CRP <5 mg/l. Group B were non-responders and consisted of 10 patients who did not achieve the response specified for group A. Patients in group A maintained the initial therapeutic regimen of 5 mg/kg every 8 weeks and group B patients had their infliximab dose regimen modified to receive 5 mg/kg every 6 weeks.

Patients were seen for clinical evaluation before each infusion, group A patients at weeks 38, 46, 54 and 62 and group B patients at weeks 38, 44, 50, 56 and 62. The following variables were then evaluated: BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI) and biological inflammatory parameters (ESR and CRP).

The primary end-point was the improvement at week 62 of the same criteria used for classification: BASDAI <4 cm or ESR <30 mm/h and CRP <5 mg/l. We also evaluated the improvement of at least 50% of the initial BASDAI [13] after 38 weeks (start of the extension phase) and after 62 weeks of treatment. Ankylosing spondylitis assessment 20% (ASAS 20) [14] was also assessed.

The principles of the Declaration of Helsinki were followed. The Research Standards Committee of our centre and all other participating hospitals approved this project. All patients gave their informed consent after the nature of the study had been fully explained to them.

Statistical analysis

The primary outcomes were analysed by intention-to-treat; proportions were compared using Fisher's exact test or the McNemar test when appropriate. Patients who withdrew were regarded as non-responders. For other secondary end-points, the statistical significance of the change from baseline (intragroup analysis) was measured using the Friedman test; *post hoc* multiple comparisons were performed with the Wilcoxon signed rank test. Comparison of the groups dosed at 6- and 8-week intervals (intergroup analysis) was performed using the Mann-Whitney test. To include the three patients who withdrew, the last observation carried forward method was applied.

Results

Patients

Twenty-five patients, 15 from group A (nine AS, two PsA, two IBD and two uSpA) and 10 (nine AS, one uSpA) from group B, were eligible to participate in the study. Three patients from group B did not complete the study due to prostatitis (week 46), dyspnoea (week 54) and lack of efficacy and change of therapy (week 54). The proportion of males was 67% in group A and 80% in group B. The mean age was lower in responders (38 ± 11 vs 44 ± 9 yr). The mean disease duration was also different in both groups: 13 ± 6 yr in responders vs 21 ± 10 yr in non-responders.

Four patients in group A at 38 weeks and two at 62 weeks and none in group B with BASDAI >4 had ESR <30 and CRP <5 mg/l. In group A there were seven patients at week 38 with BASDAI <4, ESR <30 and CRP <5 mg/l; four of them maintained these values and three more reached them in week 62, as did one patient from group B.

Efficacy

At 62 weeks, 11 of 15 [73.3%, 95% confidence interval (CI)=44.9–92.2%] patients from group A maintained the response criteria [BASDAI <4 cm or ESR <30 mm/h and CRP <5 mg/l], as did three of 10 (30%, 95% CI=6.7–65.2%) patients from group B ($P=0.049$) (Fig. 1A). In Table 1 we show the

changes in BASDAI, ESR and CRP of these three patients in group B.

At the beginning of this extension phase (38 weeks), 10 patients in group A and none in group B reached BASDAI 50 response with respect to the baseline (start of study). After 62 weeks of infliximab therapy, eight of 10 group A patients (80%, 95% CI=44.4–97.5%) and two of nine group B patients (22.2%, 95% CI=2.8–60.0%) achieved a BASDAI 50 response ($P=0.023$) (Fig. 1B). Nine of 11 patients (81.8%, 95% CI=48.2–97.7%) and four of 10 (40%, 95% CI=12.2–73.8%) from groups A and B, respectively, reached ASAS 20 at 62 weeks ($P=0.08$) (Fig. 1C).

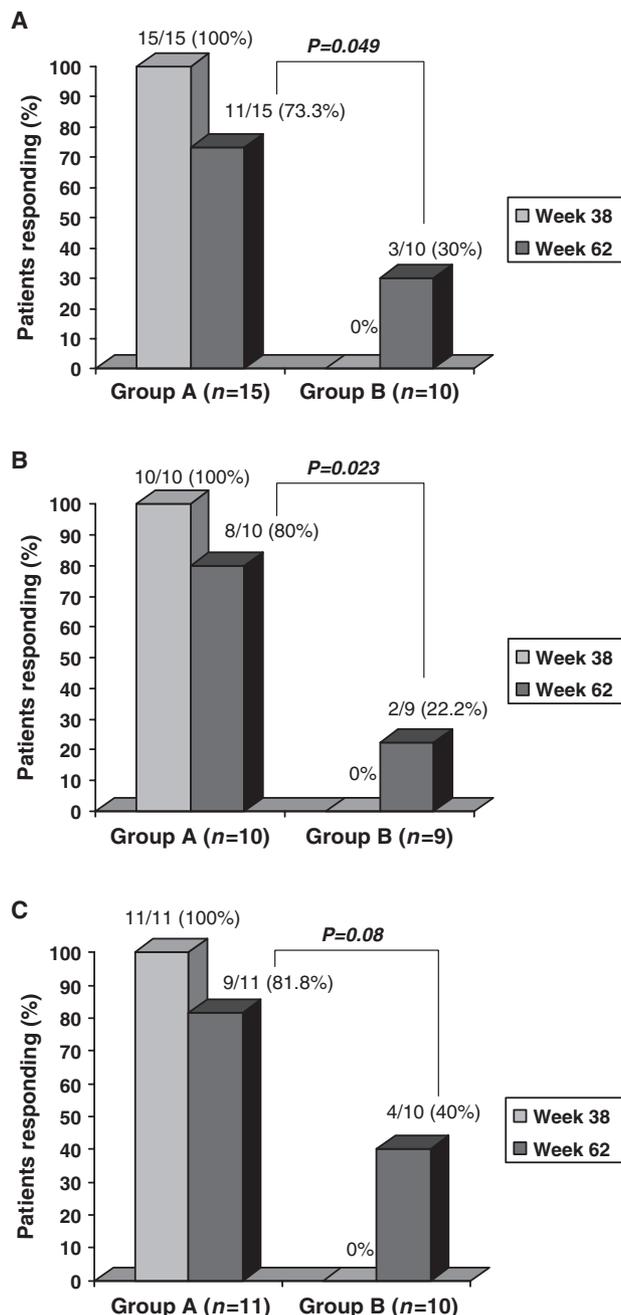


FIG. 1. Patients responding. Number of patients every 6 weeks = 10. Number of patients every 8 weeks = 15. (A) BASDAI <4 cm or ESR <30 mm/h and CRP <5 mg/l. (B) BASDAI 50. (C) ASAS 20 Analysis by intention-to-treat, patients who withdrew were regarded as non-responders. *P* values (between groups) were calculated by Fisher's exact test. No statistically significant differences were found within groups (McNemar test).

The results of the secondary outcomes analysis (BASFI, BASDAI, ESR, CRP and metrological variables) are shown in Table 2. Outcome measurements did not differ at baseline (start of the study), except for the occiput-to-wall distance, which was higher in non-responders (7.0 vs 0.5 cm). At week 38 (start of extension phase), mean BASDAI, BASFI, ESR and CRP group B measurements were statistically significantly higher than group A results. No difference was seen in metrological variables at this time, including occiput-to-wall distance. At the end of the study, after non-responders had been switched to dosing at 6-week intervals, the differences between measurements were reduced. Nevertheless, non-responders always

exhibited higher BASDAI, BASFI, ESR and CRP values than responders.

Discussion

Therapy with infliximab is highly effective in SpA patients [5]; nevertheless, it is also known that an 8-week dosing interval does not always allow adequate control of disease inflammatory activity [6]. There is a subgroup of SpA patients who exhibit a poor response or do not respond at all to infliximab. In our previous study [12], 26 and 47% of the patients did not achieved BASDAI20 and 50 responses, respectively.

This extension phase was conducted to explore whether a reduction of infliximab dosing interval could improve the therapeutic effectiveness in non-responders. Most baseline disease outcomes (BASDAI, BASFI, ESR, CRP, chest expansion, Schober modified, fingers-to-floor) were similar in responder and non-responder patients; only occiput-to-wall mean values were significantly different. The mean age and disease duration were lower in group A than in group B patients.

Responder patients continued on the 8-week dosing interval, and were able to maintain the benefit obtained during the first phase of the study. Patients with persistent active disease while

TABLE 1. Changes in BASDAI, ESR and CRP in the three patients in group B who became responders

Patient	BASDAI (cm VAS)		ESR (mm/h)		CRP (mg/l)	
	Week 38	Week 62	Week 38	Week 62	Week 38	Week 62
1	6.6	2.3	38	13	27.9	16.9
2	4.0	2.7	24	42	12.2	19.1
3	5.8	0.3	29	9	12.0	2.8

TABLE 2. Comparison of secondary outcomes

	Baseline	Week 38 (Start of extension phase)	Week 62 (End of extension phase)	<i>P</i> (Intragroup)
BASDAI (cm VAS)				
Group A	6.9 (5.5–9.3)	2.5 (0.4–6.2) ^a	2.0 (0.3–8.2) ^a	<0.001
Group B	6.7 (5.5–9.0)	5.8 (4–9)	5.9 (0.3–8.0)	0.27
<i>P</i>	0.58	0.001	0.11	
BASFI (cm VAS)				
Group A	6.4 (4.2–8.3)	3.1 (0.9–6.5) ^a	3.2 (0.2–7.9) ^a	0.023
Group B	7.6 (3.3–9.9)	7.4 (5.7–9.5)	7.2 (0.2–9.8)	0.67
<i>P</i>	0.19	<0.001	0.021	
ESR (mm/h)				
Group A	40.0 (6–108)	13.0 (2–31) ^a	13.0 (1–50) ^a	<0.001
Group B	54.5 (18–127)	33.5 (13–99)	40.5 (9–104)	0.18
<i>P</i>	0.33	0.002	0.009	
CRP (mg/l)				
Group A	13.1 (0.5–67.7)	4.5 (0.6–23.5) ^a	4.5 (0.2–27.9) ^a	0.021
Group B	18.6 (7.6–44.4)	19.2 (9.2–53.3)	16.1 (2.8–51.5)	0.58
<i>P</i>	0.38	<0.001	0.030	
Metrological variables (cm)				
Chest expansion				
Group A	2.6 (0–5)	3.5 (0–5.8) ^a	3.2 (2–6) ^a	0.010
Group B	2.5 (0.6–4.0)	2.6 (1.0–4.8)	3.0 (0.8–4.3)	0.061
<i>P</i>	0.70	0.35	0.28	
Schober modified				
Group A	4.5 (1–12)	5.2 (2–12)	5.5 (2.2–20.0)	0.17
Group B	3.7 (0–7)	4.0 (2.0–7.5)	4.0 (2–8)	0.44
<i>P</i>	0.54	0.28	0.18	
Occiput to wall				
Group A	0.5 (0–14)	2.5 (0–13)	0 (0–13) ^b	0.023
Group B	7.0 (0–19)	6.0 (0–21)	5 (0–20)	0.17
<i>P</i>	0.026	0.13	0.048	
Fingers to floor				
Group A	26 (6–43)	27.0 (5–43)	21 (5–35) ^b	0.041
Group B	22 (10–64)	21.5 (6–41)	21 (5–37)	0.12
<i>P</i>	0.98	0.64	0.93	

Values are median (range).

Group A, 5 mg/kg infliximab every 8 weeks, *n* = 15; group B, 5 mg/kg infliximab every 6 weeks, *n* = 11.

P values were calculated with the Mann–Whitney test.

Intragroup *P* values were calculated using the Friedman test.

Post hoc multiple comparison tests were performed for the Wilcoxon test.

To include the three patients who withdrew, the last observation carried forward method was applied.

^aSignificant differences vs baseline.

^bSignificant differences vs week 38.

on infliximab, 5 mg/kg every 8 weeks (group B), achieved a significant improvement in their disease activity when their dosing interval was reduced to 6 weeks. This improvement was clearly seen just after the first infusion, and was maintained through the duration of the extension. Our results are in agreement with those observed in AS patients in whom the same dosing interval was used [15].

Clinical and biological parameters of disease activity and function improved from baseline in both patient groups. At week 62, 36.4% of group B patients reached a BASDAI 50 response, whereas at week 38 only 18.2% of them did so. Responders showed higher percentages of BASDAI 50 response: 66.7 and 60%, respectively.

Infliximab was also able to sustain the benefit in function achieved in group A patients and induced a modest, though clinically relevant, reduction in BASFI score in non-responders.

Patients with AS criteria improved in a manner similar to those with other SpA, confirming that the benefit of infliximab is not restricted to AS patients, but can also be seen in other SpA patients [5, 10].

No serious adverse events were observed in group A or B patients during the study.

Our results suggest that SpA patients with active disease despite infliximab, 5 mg/kg every 8 weeks, may benefit from reducing the dose interval to 6 weeks.

Acknowledgements

We thank Dr Elisa Muñoz for statistical assistance and help with the writing of the manuscript.

The authors have declared no conflicts of interest.

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