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ORIGINAL ARTICLE

A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis

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Abstract The signs and symptoms of ankylosing spondylitis (AS) respond inadequately to nonsteroidal antiinflammatory drugs, corticosteroids, and disease modifying antirheumatic drugs in quite a number of patients. Tumor necrosis factor inhibitors have demonstrated to be of value in reducing AS disease activity in clinical trials. The efficacy and safety of both etanercept and infliximab in patients with ankylosing spondylitis were compared in a 2-year open label randomised study. Our results are consistent with a significant more rapid clinical improvement in the infliximab treated group. Treatment with both etanercept and infliximab at the end of the study was effective, safe, and well tolerated.

Keywords Ankylosing spondylitis · Etanercept · Infliximab

Introduction

Ankylosing spondylitis (AS) is a debilitating disease predominantly affecting the spine characterized by axial skeletal ankylosis [1]. Therapeutic options for AS, such as non-steroidal anti-inflammatory drugs (NSAIDs), offer temporary pain relief with little if any clinical benefit on spinal mobility, and disease modifying antirheumatic drugs (DMARDs) do not appear to affect the spinal involvement of AS [2].

Tumor necrosis factor is a proinflammatory cytokine that appears to have a key role in the pathogenesis of AS inflammation [3]. Etanercept is a fully human recombinant protein, comprising two molecules of soluble TNF receptor p75 and the crystallisable fragment component of immunoglobulin G1, which specifically binds to and neutralizes TNF-alpha. Several clinical studies have shown that etanercept reduces disease activity in patients with spondyloarthropathies, including reactive arthritis and AS [4–8]. Similar results have been reported with infliximab, a chimeric monoclonal antibody against TNF [9–15]. The aim of the present work was to compare the efficacy and safety of both etanercept and infliximab in patients with ankylosing spondylitis in a two-year open label randomised study.

Patients and methods

Fifty consecutive patients that fulfilled the modified New York criteria for the diagnosis of AS [16] were enrolled in the study. Patients had to be non responder to oral non-steroidal anti-inflammatory drugs and naïve for DMARDs or other TNF blocking agents. Patients with complete ankylosis (fusion) of the spine were excluded. Approval from an independent ethics committee was obtained, and all patients provided written informed consent to participate. Patients were randomised to receive alternatively etanercept or infliximab with a ratio of 1:1. Efficacy and safety evaluations were performed at weeks 2, 4, 8, and 12 and then every 3 months until 2 years. Criteria for inclusion were: active disease for at least 3 months, a BASDAI >4 and a VAS for spinal pain score >4.

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Patients received etanercept at a 50 mg dose delivered subcutaneously weekly or infliximab at 5 mg/kg at week 0, 2, 6 and every 6 weeks for a period of 102 weeks. The clinical response to etanercept or infliximab was evaluated on the basis of response criteria recommended by the ASAS Working Group [17]. An ASAS 20 and 40 responder was defined as a patient who showed at least 20 or 40% improvement from baseline and had an absolute improvement from baseline of at least 1 unit (on a scale of 0–10) in at least 3 of the following 4 assessment domains: patient's global assessment, spinal pain, function according to the Bath Ankylosing Spondylitis Functional Index (BASFI), and morning stiffness (the average of the last 2 questions of the BASDAI).

Disease activity was assessed bay the Bath Ankylosing Spondylitis Activity Index (BASDAI). Functional impairment was assessed by the ten item Bath Ankylosing Spondylitis Functional Index (BASFI). The BASMI is an aggregate score (ranging from 0 to 10) of patient mobility assessments, including tragus-to-wall lumbar flexion (Schober test), cervical rotation, lumbar side flexion, and intermalleolar distance [18, 19]. Chest expansion is the difference between the circumference of the chest in maximal inspiration and that in maximal expiration.

Patients were monitored for adverse events and abnormal laboratory test results over the course of the study. Vital signs were monitored, and standard hematology, serum chemistry, and urine analysis tests were evaluated.

Statistics

To compare mean differences between time points (week 0 vs. week 12, week 54 and week 104), a unpaired *t*-test was applied. In the case of skewed distributions [CRP and erythrocyte sedimentation rate (ESR)], the corresponding non-parametric test (Wilcoxon test) was used. McNemar test was applied in the case of proportions.

Results

A total of 50 patients were enrolled in the study; 25 were assigned to receive etanercept and 25 were assigned to infliximab. The average age of patients was 32.2 ± 8 years. 39 patients were male (79%) and the duration of symptoms was 15.6 ± 8.7 years. The treatment groups had similar baseline disease activity scores and demographic characteristics (Table 1). No patients discontinued therapies. Although the difference was not statistically significant, more infliximab patients than etanercept patients responded at the ASAS 20 level as early as week 2 but sustained differences were not evident up to week 12. After 12 weeks, 19 of 25 patients (75%) in the infliximab group were ASAS 20 responders compared with 15 of 25 patients (60%) in the etanercept group (Fig. 1). On the 12th week, 55% of patient treated with infliximab and 43% of patients treated with etanercept were at the ASAS 40 level (Fig. 1). At week 12 more infliximab than etanercept treated patients achieved a significantly reduction of BASDAI (4.8 vs. 5.9; $p < 0.005$ and 3.5 vs. 5.6; $p < 0.005$) (Fig. 2), and of BASFI (3.5 vs. 5; $p < 0.005$) (Fig. 3). Acute phase reactants, BASMI, SP and HAQ significantly decreased in both group of patients from baseline during the observation period without differences between the two groups (not shown). Treatments were generally well tolerated and adverse events were mostly mild to moderate (Table 2). There were no discontinuations for safety reasons. In particular, there was no

Table 1 Baseline characteristics of patients

Baseline characteristics	Treatment groups		*p*
	Infliximab ($n = 25$)	Etanercept ($n = 25$)	
Age (mean ± SD)	31.9 ± 9.2	32.6 ± 6.8	NS
Sex, M/F	19/6	20/5	NS
Duration of AS, years (mean ± SD)	15.4 ± 10.6	15.7 ± 6.5	NS
HLA-B27 positive (%)	23 (92)	24 (96)	NS
BASDAI score, 0–10 (mean ± SD)	6.5 ± 1.2	6.6 ± 1.1	NS
BASFI score, 0–10 (mean ± SD)	6.1 ± 0.9	6.5 ± 1.1	NS
BASMI score, 0–10 (mean ± SD)	3.7 ± 1.6	3.9 ± 1.7	NS
Chest expansion, cm (mean ± SD)	2.9 ± 0.8	3.1 ± 0.9	NS
Spinal Pain, 0–10 (mean ± SD)	6.0 ± 1.5	6.3 ± 1.2	NS
Patient's global assessment, 0–10 VAS	6.4 ± 1.4	6.7 ± 1.4	NS
CRP level, mg/l (mean ± SD)	25 ± 12.1	22.9 ± 10.5	NS
ESR mm/1 h (mean ± SD)	32.1 ± 14.6	29.6 ± 13.7	NS
HAQ (mean ± SD)	1.5 ± 0.5	1.4 ± 0.5	NS

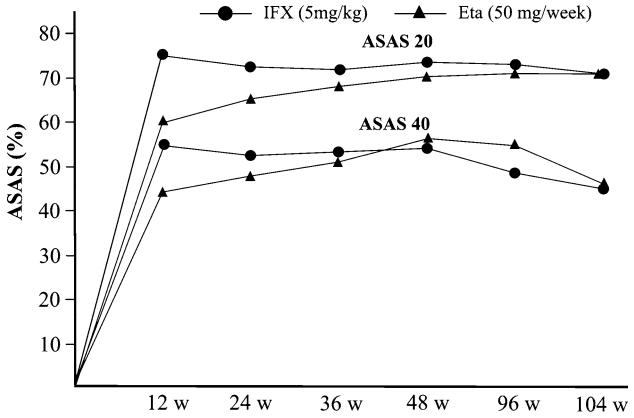

Fig. 1 ASAS 20 and ASAS 40 response during a 2-year follow up. *Circles* indicate patients treated with infliximab. *Triangles* indicate patients treated with etanercept. Although morte infliximab treated patients reacted an ASAS 20–40 response at the 12th week, the difference was not statistically significant

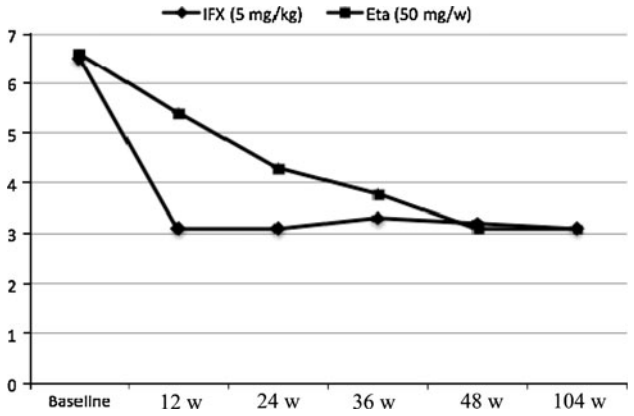

Fig. 2 BASDAI levels in patients treated with infliximab or etanercept, at 12th week a significant decrease of BASDAI was obtained in patients treated with infliximab ($p < 0.005$)

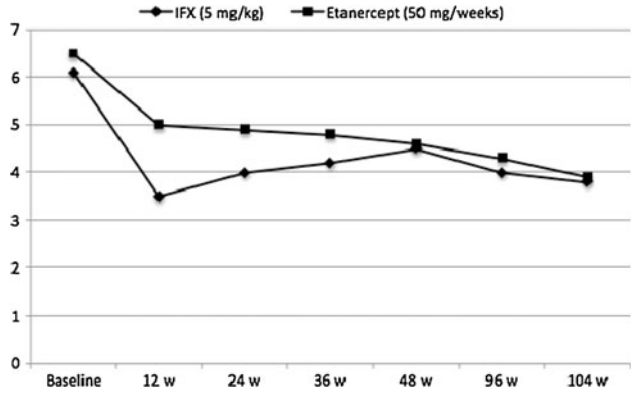

Fig. 3 BASFI levels in patients treated with infliximab or etanercept, at 12th week a significant decrease of BASFI was obtained in patients treated with infliximab ($p < 0.005$)

Table 2 No (%) of adverse events (AE) through week 104

AE	Infliximab *n* (%)	Etanercept *n* (%)	*p*
Injection site reactions	1 (4)	5 (25)	<0.005
Infusion reactions			
Headache	8 (32)	7 (28)	NS
Diarrhea	2 (8)	1 (4)	NS
Tachycardia	12 (48)	8 (32)	NS
Hypertension	4 (16)	2 (8)	NS
Abdominal pain	1 (4)	1 (4)	NS
Uveitis	1 (4)	2 (8)	NS
Optic neuritis	1 (4)	1 (4)	NS
Arthralgia	4 (16)	3 (12)	NS
Vertigo	1 (4)	2 (8)	NS
Severe infections	2 (8)	1 (4)	NS

cases of opportunistic infections, tuberculosis, congestive heart disease, demyelinating disorders, lupus-like syndromes, and malignancy.

Discussion

TNF blocking agents are internationally considered to represent a major progress in the treatment of AS. Comparative studies with etanercept and infliximab treatments were not yet published, however. A 50 mg dose of etanercept delivered subcutaneously weekly and 6 weeks infusion of infliximab (5 mg/kg) produced rapid, significant, and sustained improvement in multiple clinical and laboratory measures of AS. Although no significant differences were observed at the end of the study, our results are consistent with a significant more rapid clinical improvement in the infliximab treated group. At week 12 in fact more infliximab than etanercept treated patients achieved a significantly reduction of BASDAI and BASFI, and there were also more responders in the infliximab group at the ASAS 20 and ASAS 40 level.

In general, improvements with both therapies were observed at 2 weeks and were sustained up to the end of observation. The potential interest of our study was also that patients enrolled in our study were outpatients that have to be considered at community levels.

CRP levels and ESR values significantly decreased and spinal mobility, as measured by Schober's test, significantly improved in patients undergoing both treatments. The results of this randomised study suggest that treatment with both etanercept and infliximab is effective, safe, and well tolerated in patients with AS. Patients with AS, in fact, were treated continuously and we did not observed any reduction in efficacy with both treatments.

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