CONCISE REPORT

Open label trial of anakinra in active ankylosing spondylitis over 24 weeks

H Haibel, M Rudwaleit, J Listing, J Sieper

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Objective: To examine the therapeutic effect of the interleukin 1 (IL1) receptor antagonist anakinra in ankylosing spondylitis in an open label trial.

Methods: Anakinra (100 mg) was given subcutaneously daily over 24 weeks to 20 NSAID refractory patients with ankylosing spondylitis. Thirteen completed the study. Clinical outcome assessments included disease activity, function, metrology, patients' and physicians' global assessment, peripheral joint assessment, quality of life, and C reactive protein. Dynamic magnetic resonance imaging (MRI) of sacroiliac joints or spine, using gadolinium DTPA as contrast agent, was done before treatment in 15/20 patients, and in 10 patients at study end. The primary end point was the Bath ankylosing spondylitis disease activity index (BASDAI) and ASAS (assessments in ankylosing spondylitis) short term response after six months.

Results: Using an intention to treat analysis, an ASAS 20% response (ASAS 20) was achieved in five patients, ASAS 40 in four, and ASAS 70 in two after 24 weeks. There was no change in mean C reactive protein (22.3 *v* 33.1 mg/l) or in MRI score. The drug was well tolerated. Injection site reaction was the commonest adverse event.

Conclusions: In this open study, anakinra improved spinal symptoms in only a small subgroup of patients with active ankylosing spondylitis.

Ankylosing spondylitis is a rather frequent inflammatory rheumatic disease[1] and the prototype of the spondyloarthritides. Currently, the established treatment consists of non-steroidal anti-inflammatory drugs (NSAID) and physical therapy. Except for sulfasalazine, which seems to be effective in peripheral joint involvement,[2] no established disease modifying antirheumatic drug (DMARD) treatment is available. The tumour necrosis factor α (TNFα) blocking agents infliximab and etanercept were recently shown to be highly effective in active ankylosing spondylitis resistant to NSAIDs.[3 5]

Like TNFα, interleukin 1 (IL1) is a proinflammatory cytokine which causes chronic inflammation and joint destruction by activating macrophages and osteoclasts and inducing fibroblast proliferation. It has been found to be upregulated in the spondyloarthritides.[6] Suppression of IL1 is an important strategy for decreasing inflammation and bone resorption.[7] Anakinra is the first recombinant human IL1 receptor antagonist and has been shown to be effective in the treatment of rheumatoid arthritis.[8 9]

Our aim in this study was to investigate the potential therapeutic effects of anakinra in patients with active NSAID refractory ankylosing spondylitis.

METHODS

In this open study we examined 20 patients (for characteristics see table 1) who fulfilled the 1984 modified New York criteria for ankylosing spondylitis and who did not respond sufficiently to NSAID treatment, defined as failure or intolerance to maximum dose of at least one NSAID. To be eligible, patients had to have active disease defined as a Bath ankylosing spondylitis disease activity index (BASDAI)[10] of 4 or more. DMARDs and steroids at a dose of more than 7.5 mg/day were not permitted and had to be discontinued at least one month before the start of treatment. Previous treatment with TNFα blocking agents was allowed but had to be stopped at least three months before the start of the study.

Local ethics committee approval was obtained.

Exclusion criteria were pregnancy, history of uncontrolled concomitant diseases, or clinical and laboratory investigations with abnormal or clinically relevant changes.

Anakinra 100 mg was given subcutaneously every day for 24 weeks. Clinical outcome assessments were made every month. They included BASDAI, Bath ankylosing spondylitis functional index (BASFI),[11] Bath ankylosing spondylitis metrology index (BASMI),[12] and patients' and physicians' global assessment (numerical rating scales). Primary outcome indices were an improvement according to the ASAS (assessments in ankylosing spondylitis) criteria[13] and a BASDAI improvement after six months. Laboratory outcome assessments included the erythrocyte sedimentation rate (ESR) and C reactive protein. NSAID doses could be reduced but had to be recorded.

Dynamic magnetic resonance imaging (MRI) of sacroiliac joints, spine, or both using gadolinium DTPA as a contrast agent was done before treatment and at study end. A modified scoring system for acute inflammation without scoring erosions, ranging from 0 to 3 and used for MRI readings for the spine, had a possible total score of between 0 and 72, as described recently.[14] The sacroiliac joints were evaluated for the right and left side for the iliac and sacral bone separately, using the following score: 0, normal; 1, less than 25% oedema of the bone surface; 2, 25 50%; 3, more than 50%; the total score ranged between 0 and 12.

Statistics

Statistics were done as an intention to treat analysis. The non-parametric Wilcoxon signed rank test was used to compare changes between baseline to post-treatment values. A probability (p) value of <0.05 was considered significant.

Abbreviations: ASAS, assessments in ankylosing spondylitis; BASDAI, Bath ankylosing spondylitis disease activity index; BASMI, Bath ankylosing spondylitis metrology index; DMARD, disease modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug; VAS, visual analogue scale

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Table 1 Patient characteristics

Number of patients	20
Male/female	14/6
Mean age (years (range))	39 (27 to 54)
Mean disease duration (years (range))	16 (3 to 31)
BASDAI (mean (range))	5.8 (4.3 to 7.6)
HLA-B27 positive (n)	20
Peripheral joint involvement (n)	5
History of uveitis (n)	5
Enthesitis (n)	5
Psoriasis (n)	1
IBD (n)	2
C reactive protein >10 mg/l (n)	16

BASDAI, Bath ankylosing spondylitis disease activity index; IBD, inflammatory bowel disease.

RESULTS

Thirteen of 20 patients completed the study period of six months. One patient failed screening and was excluded from further calculations. Using an intention to treat analysis on the 19 remaining patients, after 12 weeks both ASAS 20 (20% improvement) and ASAS 40 were achieved in two patients, but no patient achieved ASAS 70. After 24 weeks, ASAS 20 was achieved in five patients, ASAS 40 in four, and ASAS 70 in two (fig 1A). At week 24, the ASAS criteria for partial remission were achieved in one patient. The BASDAI response was similar and is shown in fig 1B.

There was a small and non-significant decrease in the absolute BASDAI over the six month study period (5.8 at baseline *v* 5.0 at week 12 ($p>0.05$), and 4.8 at week 24 ($p>0.05$)). No single components of the BASDAI improved significantly except the combined score for morning stiffness (questions 5 and 6 of the BASDAI: 6.5 at baseline *v* 5.0 at week 12, $p=0.037$; *v* 4.6 at week 24, $p=0.006$). No significant change was found in BASMI, BASFI, patients' and physicians' global assessment, or general pain during the observation period.

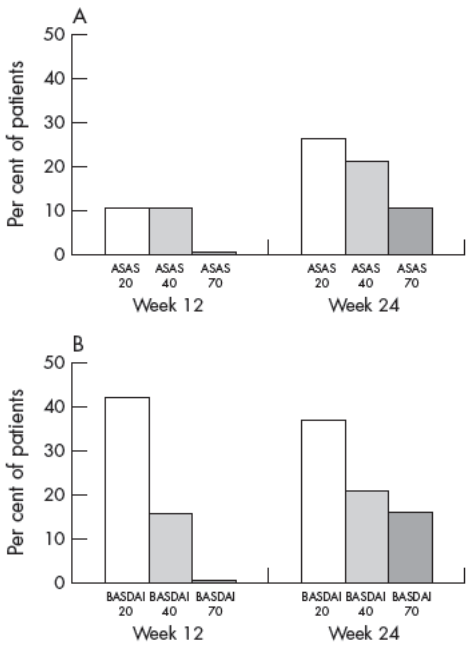

Figure 1 (A) Number of patients achieving ASAS (assessments in ankylosing spondylitis) 20% (ASAS 20), 40% (ASAS 40), or 70% (ASAS 70) response during treatment with anakinra after 12 and 24 weeks. (B) Bath ankylosing spondylitis activity index (BASDAI) during treatment with anakinra after 12 and 24 weeks.

The mean C reactive protein decreased significantly after 12 weeks, from 22.3 to 14.9 mg/l ($p=0.016$) but this improvement was not sustained over 24 weeks (33.1 mg/l, $p>0.05$). In the five patients who suffered from peripheral arthritis before the start of the study, the number of swollen joints did not improve (mean number of swollen joints 1.2 before and after treatment).

In the four patients who achieved at least ASAS 40, the mean BASDAI decreased significantly from 6.2 at baseline to 2.1 after 24 weeks, and in two of these four patients the C reactive protein fell into the normal range. The onset of improvement ranged from eight to 20 weeks of treatment in these four patients. No improvement was seen in the only patient who was previously successfully treated with infliximab.

Fourteen of 15 available MRI investigations before treatment showed acute inflammatory changes of the spine or sacroiliac joints. In the 10 follow up MRI investigations at study end, no improvement in acute inflammatory lesions could be observed (spine: mean score 9 at baseline compared with 8 after 24 weeks, $p>0.05$; sacroiliac joints: mean score 2.4 at baseline compared with 2.5 at week 24, $p>0.05$).

Side effects

Anakinra was well tolerated. Injection site reactions, similar to these seen in rheumatoid arthritis, were the most common adverse events and appeared in 90% of patients. There were no serious infectious episodes or opportunistic infections.

Six patients stopped the treatment because of inefficacy and one patient because of injection site reactions.

DISCUSSION

This open label study with 20 NSAID refractory patients with ankylosing spondylitis treated with anakinra over 24 weeks showed a benefit in only a small number of patients. In those with a good response there was a slow but steady improvement over 24 weeks.

The ASAS short term improvement criteria were better than the expected placebo response in our placebo controlled trial with infliximab.[3] While in that trial the placebo response rate for ASAS 40 was 5.7%, in the present study with anakinra 21% of patients achieved ASAS 40 after 24 weeks of treatment. Similarly, the percentage of patients reaching 50% improvement in their initial BASDAI (16% after 12 weeks and 21% after 24 weeks) was higher than the expected placebo response (8.5%) seen in our recent trials with the TNFα blocking agents infliximab and etanercept.[3 4] However, compared with infliximab[3] and etanercept[4] where 61.8% and 61.6% of patients, respectively, achieved ASAS 40 anakinra was less effective.

When using an intention to treat analysis, there was no improvement for the group of patients as a whole when looked at mean BASDAI, BASMI, BASFI, general pain, patients' and physicians' global assessment, C reactive protein, or MRI scores. This contrasts with experiences from trials in rheumatoid arthritis, where a significant decrease in C reactive protein is observed soon after the introduction of anakinra, which lasts for at least 48 weeks.[8]

In the four patients who improved clinically, as measured by achieving ASAS 40 improvement after 24 weeks of treatment, no parallel change in acute inflammation was observed (as measured by MRI before treatment or after 24 weeks), but in two of these four patients the C reactive protein fell into the normal range. However, the observed improvement seemed to be real, as in one of the patients the disease flared only three days after anakinra was stopped, and three patients have now remained stable for at least three months after treatment was stopped, despite showing consistently high disease activity before the start of

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treatment. Compared with treatment studies with anakinra in rheumatoid arthritis, the number and pattern of adverse events did not differ.[8 9]

In conclusion, anakinra seemed to be effective in a small proportion of patients with active ankylosing spondylitis. The level of improvement was greater than the expected placebo response. In a very recent study[15] with a smaller group of patients (n = 9) with this disease who were treated with anakinra over three months, an ASAS 20 improvement was achieved in 67%, indicating a better response than seen in our study. Whether these effects are real can only be answered in a placebo controlled study.

Authors' affiliations
H Haibel, M Rudwaleit, J Sieper, Medical Department I, Rheumatology, Charité, Campus Benjamin Franklin Hospital, Berlin
J Listing, J Sieper, German Rheumatism Research Centre, Berlin

Correspondence to: Dr H Haibel, Medical Department I, Rheumatology, Charité, Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany; haibel@zedat.fu-berlin.de

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