Efficacy of Anakinra in Active Ankylosing Spondylitis: A Clinical and Magnetic Resonance Imaging Study

Ai Lyn Tan, Helena Marzo-Ortega, Philip O’Connor, Alexander Fraser, Paul Emery, and Dennis G McGonagle

DISCLAIMER
The initial version of ARD Online First articles are papers in manuscript form that have been accepted and published in ARD Online but they have not been copy edited and not yet appeared in a printed issue of the journal. Copy editing may lead to differences between the Online First version and the final version including in the title; there may also be differences in the quality of the graphics. Edited, typeset versions of the articles may be published as they become available before final print publication.

Should you wish to comment on this article please do so via our eLetter facility on ARD Online (http://ard.bmjjournals.com/cgi/eletter-submit/ard.2004.020800v1).

DATE OF PUBLICATION
ARD Online First articles are citable and establish publication priority. The publication date of an Online First article appears at the top of this page followed by the article's unique Digital Object Identifier (DOI). These articles are considered published and metadata has been deposited with PubMed/Medline.

HOW TO CITE THIS ARTICLE

*Replace with date shown at the top of this page - remove brackets and asterisk

Online First articles are posted weekly at http://ard.bmjjournals.com/onlinefirst.shtml
Efficacy of Anakinra in Active Ankylosing Spondylitis
A Clinical and Magnetic Resonance Imaging Study

Ai Lyn Tan, Helena Marzo-Ortega, Philip O’Connor, Alexander Fraser, Paul Emery, Dennis McGonagle

Ai Lyn Tan MRCP, Research Fellow (1 & 3)
Helena Marzo-Ortega MRCP, Research Fellow (1)
Philip O’Connor FRCR, Consultant in Musculoskeletal Radiology (2)
Alexander Fraser MRCPI, Consultant Rheumatologist (1)
Paul Emery MA MD FRCP, arc Professor of Rheumatology (1)
Dennis McGonagle PhD FRCPI, Professor of Investigative Rheumatology (1 & 3)

(1) Academic Unit of Musculoskeletal Disease, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, United Kingdom
(2) Department of Radiology, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, United Kingdom
(3) Calderdale Royal Hospital, Salterhebble, Halifax HX3 0PW, United Kingdom

Address for correspondence: Professor Dennis McGonagle.
E-mail: d.g.mcgonagle@leeds.ac.uk
Phone: 0044-113-3923956
Fax: 0044-113-3922896
**Objective.** To determine the efficacy of anakinra, an interleukin-1 receptor antagonist in active ankylosing spondylitis (AS) and to use magnetic resonance imaging (MRI) to investigate the effect of anakinra therapy on spinal enthesitis/osteitis.

**Methods.** A 3-month open-label study of anakinra (100mg subcutaneous injection daily) was carried out in 9 patients with active AS who had back pain and an elevated acute phase response, and had failed to respond to at least 1 non steroidal anti-inflammatory drug. Clinical assessment included the Bath AS Functional Index (BASFI), Bath AS Disease Activity Index (BASDAI) and AS Quality of Life (ASQoL) pre and post therapy. Fat suppressed MRI of the spine and sacro-iliac joints were performed using a 1.5T scanner at baseline and at 3 months to determine the effect of therapy on spinal enthesitis/osteitis.

**Results.** There was a statistically significant improvement in the BASFI (median baseline=5.88, 3-month=3.63, \(p=0.021\)), BASDAI (median baseline=5.63, 3-month=3.48, \(p=0.028\)), ASQoL (median baseline=12, 3-month=8, \(p=0.011\)) and laboratory parameters reflecting inflammation with the C-reactive protein (median baseline=31mg/L, 3-month=17mg/L, \(p=0.036\)) and erythrocyte sedimentation rate (median baseline=19mm/hr, 3-month=15mm/hr, \(p=0.008\)) also showing significant improvement. Six patients (67%) achieved the Assessments in AS (ASAS) Working Group criteria of 20% improvement. Of the 38 regions of MRI determined enthesitis/osteitis demonstrated at baseline, 61% either improved or regressed completely.

**Conclusions.** This open label pilot study suggests that anakinra is effective in controlling the clinical manifestations of AS. The clinical response was reflected by an improvement in MRI determined spinal enthesitis/osteitis.

**Key words:** Anakinra, ankylosing spondylitis, interleukin-1, magnetic resonance imaging
The spondyloarthopathies (SpA) are a heterogeneous group of diseases including ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, enteropathic arthritis and undifferentiated spondyloarthopathy. Collectively these arthritides are characterized by enthesitis/osteitis accounting for the axial disease manifestations in addition to synovitis that accounts for some of the peripheral disease manifestations [1]. Until recently the treatment options for AS and SpA were limited with drugs including sulphasalazine and methotrexate showing little efficacy in comparison to that seen in rheumatoid arthritis (RA).

In both RA and SpA the introduction of tumour necrosis factor-α (TNF-α) blocking agents has heralded an exciting new era in the therapeutic of these diseases with TNF blockade showing good efficacy in both RA and SpA [2-6]. Infliximab has been approved in the European Union for AS, and etanercept has been granted the Food and Drug Administration approval in the USA for the treatment of psoriatic arthritis. Like TNF the pro-inflammatory cytokine, interleukin-1 (IL-1), is also pivotal in the inflammatory cascade [7]. Upregulation of IL-1 has been reported in AS in the peripheral tissues, and IL-1 polymorphisms are associated with AS [8-11]. Interleukin-1 blockade in experimental arthritis has been shown to ameliorate joint damage [12]. A prominent feature of AS and SpA is diffuse osteitis in the spine and peripheral sites [13] and this is likely to be associated with osteoclastic activation that contributes to joint damage at these sites. Interleukin-1 plays a prominent role in osteoclastic mediated bone damage [14]. Therefore IL-1 antagonism may be of central importance to controlling the osteitis associated with AS and SpA.

Magnetic resonance imaging (MRI) represents an exciting development in the diagnosis and monitoring of therapy in AS and SpA and can monitor axial enthesitis/osteitis that cannot be assessed by clinical means or radiography. MRI has been used to show that the majority of pathologic changes in the spine and bone either regress completely or improve following biologic blockade with etanercept or infliximab [2, 15].

Since IL-1 plays a crucial role in the inflammatory cascade and has been shown to be upregulated in AS, the aim of this study was to assess the effect of anakinra, an IL-1 receptor antagonist, in the therapy of AS in a proof-of-concept clinical and imaging study. MRI was used to specifically assess the response of enthesitis and osteitis in the axial skeleton to anakinra.

**Patients and Methods**

**Patients and study protocol**

The study is a single-centre, 3-month open-label pilot proof-of-concept trial approved by the local ethics committee. Nine patients with AS according to the New York Modified Criteria [16] were recruited for the study with all patients giving written informed consent beforehand. All patients had active disease as defined by visual analogue scale (VAS) (0-100mm scale) for both nocturnal and total back pain of greater than 30 and acute inflammatory response (C-reactive protein (CRP) greater than 10mg/L), and had failed to respond to at least 1 non steroidal anti-inflammatory drug (NSAID). All patients had been on stable doses of NSAIDs at baseline, with patients failing between 1 and 6 NSAIDs (mean 3 NSAIDs). None of the patients were on corticosteroids, and no patients received any corticosteroids during the study. Disease modifying anti-rheumatic drugs were discontinued 4 weeks prior to commencing the study. Two patients discontinued
methotrexate, and 2 sulphasalazine. Exclusion criteria included psoriasis, inflammatory bowel disease, previous anti-TNF therapy, pregnancy and known significant concurrent medical disease. Patients were treated with a 3-month course of daily subcutaneous injection of 100mg of anakinra. The efficacy of therapy with anakinra was evaluated based on clinical and MRI assessment at the end of the treatment period at week 12.

**Clinical assessment**
Patients were followed up at 2, 8 and 12 weeks after commencing anakinra therapy. Patients attended one further follow-up post cessation of anakinra therapy 2-7 weeks later to assess their response on stopping anakinra. Clinical outcome parameters were collected on each occasion which included VAS scores for patient global assessment of disease activity (PGA), nocturnal back pain (NBP), total back pain (TBP), Bath AS Functional Index (BASFI) [17], and Bath AS Disease Activity Index (BASDAI) [18]. The quality-of-life was assessed based on the AS Quality of Life questionnaire (ASQoL) [19]. Functional assessments including the Schober test for lumbar flexion, lumbar side flexion and chest expansion were performed on each visit by the same observer (ALT), who also assessed enthesitis using the Maastricht AS Enthesitis Score [20]. All patients also had their tender and swollen joint counts (TJC, SJC) documented at each visit.

Routine laboratory tests including a full blood count, urea and electrolyte levels, liver function tests, CRP and erythrocyte sedimentation rate (ESR) were performed at each visit. HLA-B27 type, rheumatoid factor and antinuclear antibody (ANA) positivity were assessed at baseline, with ANA repeated at week 12.

Patients were also evaluated according to the Assessments in AS (ASAS) Working Group criteria of 20% improvement at week 12 [21]. This is defined as at least 20% improvement and an absolute improvement of at least 10 units on a scale of 0-100 in at least 3 of the following domains: patient global assessment, pain, function (BASFI), and inflammation (mean of the last 2 scores in the BASDAI concerning morning stiffness intensity and duration), with absence of deterioration in the potential remaining domain, where deterioration is defined as a change for the worse of at least 20% and net worsening of at least 10 units. ASAS 50% and 70%, defined as 50% and 70 % improvement as before but not requiring an absolute change of 10 units in the domains, were also assessed in all the patients at week 12.

**Radiography**
All the patients had x-rays of the chest, lumbar spine and sacro-iliac joints (SIJ) performed at baseline.

**MRI**
Scans were performed at baseline and at week 12 using a 1.5T Gyroscan ACS NT (Philips, Best, The Netherlands) MRI scanner. T1-weighted turbo spin-echo (TSE) and short tau inversion recovery (STIR) TSE fat-suppressed sagittal sequences of the lumbar spine were obtained. For the SIJ T1-weighted TSE and STIR TSE fat-suppressed coronal oblique sequences were obtained.

The MRI parameters were as follows: T1-weighted TSE for the spine- repetition time (TR) 666msec, time to echo (TE) 14msec, matrix 384/512, field of view (FOV) 375mm, slice thickness 4.0mm, slice gap 0.4mm, number of signals averaged (NSA) 3, and acquisition time 4 minutes 18 seconds; T1 oblique of SIJ- TR 892msec, TE 14msec, matrix 384/512, FOV 320mm, slice thickness 4.0mm, slice gap 0.4mm, NSA 3, and
acquisition time 5 minutes 44 seconds. The STIR TSE acquisition parameters were TR 2500msec, TE 10msec, matrix 382/512, FOV 375msec (spine) and 320msec (SIJ), slice thickness 4.0msec, slice gap 0.8msec, NSA 2, and acquisition time 4 minutes 35 seconds.

**MRI scoring**
A number of areas were systematically analyzed per joint as previously described [2]. In the SIJs, 4 quadrants were assessed: right upper, left upper, right lower and left lower. Each quadrant was subdivided into ilial and sacral aspects. Spinal lesions were classified as present within vertebral bodies, facetal joints and spinous processes or paraspinal soft tissues. MRI enthesitis was defined on STIR TSE images as bone oedema (high or intermediate marrow signal) and/or soft tissue oedema (high signal in the extracapsular connective tissues) adjacent to entheses. All features were recorded as present or absent at baseline, and the total number of lesions per area scanned (SIJ and spine) was counted. The pre and post anakinra MRI scans were scored together but the assessors were masked to the order of the scans. Paired scoring was performed by 2 experienced scorers for every lesion using a semi quantitative scale (resolution, improvement, no improvement, deterioration) with consensus in equivocal cases.

**Statistical analysis**
Variables are presented as the median, unless stated otherwise. Wilcoxon’s matched pairs signed rank test was used to measure the significance of the change from baseline. P values less than 0.05 were considered statistically significant.

**Results**
All the patients were male with a mean age of 45 years old (31-58 years old), with mean disease duration of 18.6 years (3-33 years), all were sero-negative for rheumatoid factor, all had radiographic bilateral sacroiliitis and 7 of the 8 available HLA-B27 results were positive. All the patients have active axial disease (mean VAS (0-100mm) NBP=67.8 (40-91), TBP=64.8 (44-91)). Only one patient had chronic synovitis of both wrists which persisted throughout the study.

**Clinical outcomes**
All nine patients completed the 12-week study. The most significant side effects experienced were injection site reactions in all 9 patients and initial transient mild headaches in 5 patients. The injection site reaction occurred between commencement of therapy and 16 days later, and resolved completely by 6 weeks in all patients. No other adverse reactions were observed. Two patients tested weak positive for ANA at 1/40 but were negative following therapy, whilst one other was weak positive at 1/40 following therapy.

All outcome measures monitored improved in the patients (Table 1). The Schober test (mean baseline=2.06cm, 3-month=2.44cm, p=0.176), lumbar side flexion (mean baseline=7.14cm, 3-month=9.69cm, p=0.085), chest expansion (mean baseline=2.89cm, 3-month=3.44cm, p=0.44) and MASES (mean baseline=1.22, 3-month=0.44, p=0.129) all improved following anakinra therapy. Six of the nine patients (67%) responded according to the ASAS Working Group criteria of 20% improvement, and 3 patients (33%) achieved ASAS 50% and ASAS 70% (Figure 1). Significant improvements in the BASFI (p=0.021), BASDAI (p=0.028), ASQoL (p=0.011) and the VAS score for NBP
(p=0.038) were noted. The laboratory assessment of inflammation as determined by CRP and ESR also showed significant improvement (CRP, p=0.036; ESR, p=0.008).

All 9 patients developed a symptomatic flare between 1 and 2 weeks after they received their last injection of anakinra. All parameters measured between 2 to 7 weeks after the last dose of anakinra deteriorated, and this was statistically significant in the ESR (p=0.012), early morning stiffness (p=0.012), VAS scores for PGA and TBP (p=0.011 and 0.021 respectively), BASFI (p=0.028), BASDAI (p=0.019) and ASQoL (p=0.011).

**Table 1**
Summary of patient demographics and clinical and functional assessments at baseline, week 12 following therapy and week 14-19 (2-7 weeks post cessation of therapy)*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 12</th>
<th>Week 14-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range) years</td>
<td>45 (31-58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, %</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Disease duration, mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range) years</td>
<td>18 (3-33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B27 positive, %</td>
<td></td>
<td>87.5%</td>
<td></td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>31 (14-65)</td>
<td>17 (6-47) †</td>
<td>24 (14-45)</td>
</tr>
<tr>
<td>ESR, mm/hr</td>
<td>19 (13-66)</td>
<td>15 (5-58) †</td>
<td>22 (8-98) †</td>
</tr>
<tr>
<td>EMS, minutes</td>
<td>60 (15-120)</td>
<td>20 (5-120)</td>
<td>60 (20-180) †</td>
</tr>
<tr>
<td>VAS scores (0-100mm scale)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night back pain</td>
<td>75 (40-91)</td>
<td>35 (8-94) †</td>
<td>59 (24-94)</td>
</tr>
<tr>
<td>Total back pain</td>
<td>64 (44-91)</td>
<td>41 (5-85)</td>
<td>63 (40-95) †</td>
</tr>
<tr>
<td>Patient’s global assessment</td>
<td>67 (42-91)</td>
<td>41 (3-80)</td>
<td>74 (28-96) †</td>
</tr>
<tr>
<td>BASFI score (0-10)</td>
<td>5.88 (2.81-7.49)</td>
<td>3.63 (0.63-8.24) †</td>
<td>6.13 (3.52-8.74) †</td>
</tr>
<tr>
<td>BASDAI score (0-10)</td>
<td>5.63 (3.83-7.8)</td>
<td>3.48 (0.48-7.68) †</td>
<td>6.55 (2.82-8.27) †</td>
</tr>
<tr>
<td>ASQoL score (0-18)</td>
<td>12 (5-16)</td>
<td>8 (0-15) †</td>
<td>12 (5-17) †</td>
</tr>
</tbody>
</table>

* Except where indicated otherwise, values are the median (range).

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; EMS = early morning stiffness; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; VAS = visual analogue scale; BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASQoL = Ankylosing Spondylitis Quality of Life questionnaire.

† Significant values (p<0.05) by Wilcoxon’s matched pairs signed rank test.

**MRI results**
Eight patients completed the MRI of the lumbar spine and SIJs at baseline and at week 12 with the ninth patient being unable to tolerate repeat scanning. Eight patients had a total of 38 MRI-detectable enthesal lesions (7 SIJ lesions in 2 patients, 31 lumbar spine lesions in 8 patients). Overall 23 MRI-detected enthesal lesions (61%) either resolved completely (n=7) or improved (n=16).
In the case of the SIJs, 3 patients (mean disease duration 21.3 years) had bilaterally ankylosed SIJs. Of the 2 patients with active satieties (subchondral oedema), 1 patient had 6 lesions and the other had one lesion. All 6 lesions improved in the first patient who had the shortest disease duration of the 9 patients, while the 1 lesion in the other patient remained unchanged.

In the case of the spine, 8 patients had a total of 31 active lesions in the spine (Table 2). Vertebral body lesions included Romanus lesions (n=15), end-plate oedema (n=3), facet joint oedema (n=8) and spinous process oedema (n=5). Seventeen lesions (55%) improved following therapy. Seven of these lesions (23%) resolved completely, while the other 10 lesions (32%) improved. Eleven lesions remained unchanged, and 3 of the lesions deteriorated. At week 12 post therapy, 4 new lesions were noted in 2 patients both of whom demonstrated a corresponding deterioration in the VAS for night back pain.

**Table 2**
Summary of the scores for magnetic resonance imaging lesions before and after treatment with anakinra*

<table>
<thead>
<tr>
<th></th>
<th>SIJ</th>
<th>Spine</th>
<th>Total†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resolution</td>
<td>Improvement</td>
<td>Unchanged</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>7</td>
<td>0</td>
<td>6 (86)</td>
</tr>
<tr>
<td><strong>Week 12</strong></td>
<td>31</td>
<td>7 (23)</td>
<td>10 (32)</td>
</tr>
</tbody>
</table>

* Values are the number (%) of lesions.
† A total of 23 lesions (61%) either resolved completely or improved.

**Discussion**

This study assessed the clinical efficacy of anakinra in AS and specifically its effect on axial enthesitis and associated osteitis based on MRI evaluation. Improvement was observed in all clinical parameters, in particular the laboratory markers of inflammation, back pain, function (BASFI), disease activity (BASDAI) and quality of life (ASQoL). In addition, over half (61%) of the MRI-detectable lesions either resolved or improved following anakinra therapy. Therapy was well tolerated, although mild injection site reactions occurred initially in all patients. All 9 patients became symptomatic soon after treatment was discontinued.

Before biologic therapy such as the TNF-α blockers, there was no available proven effective therapy for AS. Our previously published MRI study in resistant SpA shows improvement of MRI determined axial enthesitis/osteitis following etanercept therapy [2], and this has been reflected in other randomized controlled trials with infliximab [22]. The efficacy of anakinra in causing regression of spinal enthesitis/osteitis is comparable with these two published studies. We have shown that etanercept was associated with an improvement of 86% of the SpA axial abnormalities on MRI [2]. In the study by Braun et
el, a 60% improvement in spinal enthesitis/osteitis on STIR sequence following infliximab therapy was reported compared to 21% deterioration in the placebo group [15]. Although the 61% improvement in spinal and SIJ enthesitis/osteitis suggests that anakinra is effective in treating AS, we noted that a few new regions of enthesitis/osteitis developed which we did not see in our previous study with etanercept in SpA suggesting that anakinra may be unable to completely suppress the development of MRI determined disease in all patients. Nevertheless, even in this small cohort anakinra produced a good and significant clinical efficacy that mirrored a fall in the inflammatory response and accompanied by a significant improvement in MRI determined axial inflammation, with disease flare upon cessation of therapy. Following completion of this study and associated disease flares we have recommenced anakinra in some patients and have noted clinical responses and normalisation of the acute phase response in these patients.

In conclusion, this study suggests that anakinra is effective in patients with resistant AS. These findings indicate that IL-1 plays a role in the pathogenesis of spinal enthesitis/osteitis in AS. Anakinra may have a role in patients with AS who have failed or cannot tolerate anti-TNF therapy but further randomized controlled trials are needed to formally demonstrate efficacy.

**Acknowledgements**

The authors would like to thank Sisters Claire Brown and Sally Smith for their help in coordinating this study and Dr Fabio Magrini for his help in setting up the study.

**Disclosure**

This study was supported by an Educational Grant from Amgen which paid for the supply of anakinra and MRI.
**Figure 1**
Response to treatment as measured by the Assessment of Ankylosing Spondylitis (ASAS) criteria for 20%, 50% and 70% improvement. By week 2, 67% (n=6) had achieved ASAS 20% improvement, which peaked at week 8 with 89% (n=8). At week 12, 67% (n=6) achieved ASAS 20% improvement, 33% (n=3) ASAS 50% improvement and 33% (n=3) ASAS 70% improvement.

**Figure 2**
Short tau inversion recovery (STIR) sagittal magnetic resonance image of the lumbar spine of a patient with ankylosing spondylitis **A**, before, and **B**, after treatment with anakinra, showing resolution of bone edema in the spinous process at the 2nd and 3rd lumbar vertebrae (asterisks). **C**, STIR coronal oblique sequence of the sacroiliac joints (SIJ) of a different patient showing oedema in both SIJs more extensive on the lower right and left quadrants (arrows). **D**, Follow-up scan after treatment with anakinra shows almost complete resolution of the edema at these sites, and improvement of the upper right and left quadrants of the SIJs (arrow heads).
References


Figure 1