CONCISE REPORT

Preliminary results of safety and efficacy of the interleukin 1 receptor antagonist anakinra in patients with severe lupus arthritis

B Ostendorf, C Iking-Konert, K Kurz, G Jung, O Sander, M Schneider

Background: Joint involvement occurs in most patients with systemic lupus erythematosus (SLE), and severe lupus arthritis is often refractory to conventional treatments. Anakinra is used in the treatment of rheumatoid arthritis, but its therapeutic potential has not been proved in patients with SLE.

Objective: To determine the safety/tolerability and efficacy of anakinra in patients with SLE with leading joint involvement.

Methods: In patients with SLE with active polyarthritis and no other uncontrolled systemic/organ manifestations, 100 mg/day anakinra was self administered subcutaneously for 3 months. Disease activity was assessed by VAS, number of swollen/tender joints, ECLAM score, and serological and immunological measures.

Results: Four patients with SLE were studied; anakinra was safe in all four patients and no drug related serious adverse events occurred. A subjective benefit was seen in all patients and a trend towards better activity measures after 4 weeks. After an initial response, one patient left the study because of an arthritic flare after 6 weeks.

Conclusion: In this study anakinra was apparently safe and well tolerated and led to clinical and serological improvement. Anakinra might be an interesting alternative in individual patients with lupus arthritis not responding to conventional treatments.

RESULTS

Four patients with SLE (two male, two female) with an average age of 38 years (range 32–46) were recruited by the Centre for Rheumatology/University of Duesseldorf. All patients had non-erosive polyarthritis (three patients with deforming JA, one patient with symmetrical finger polyarthritis, all with normal conventional radiography) refractory to previous treatment, including NSAIDs, antimalarial drugs (AM), corticosteroids (CORT), methotrexate (MTX), cyclophosphamide (CYC), and azathioprine (AZA). These patients presented no other major organ involvement for at least 6 months before entering the study. Table 1 shows the characteristics of the patients.

Case 1

A 33 year old man, diagnosed with SLE in March 2000, was initially treated with CORT, AM, and NSAIDs for leading arthritis, with 5-mesalazine for colitis (December 2000), and finally with CYC pulse therapy for lupus nephritis (March 2001–December 2002; WHO type III). Because of treatment refractory and deforming JA he was enrolled in the study in September 2003. At session t4 (see table 2) he responded clinically with a reduction in swollen and painful joints and serologically with a slight decrease in acute phase parameters (CRP) and anti-dsDNA Abs and with an increase in treatment refractory polyarthritis/JA (≥6 swollen joints or >3 swollen joints and tendovaginitis in at least two locations and ≥6 tender joints) and no other uncontrolled major organ involvement, diagnosed according to the American College of Rheumatology criteria for the classification of SLE. SLE was otherwise to be controlled by a stable dose of corticosteroids (CORT < 15 mg/day) and/or concomitant antirheumatic/immunosuppressive drugs (unchanged for 6 months before study entry); treatment of pain with non-steroidal anti-inflammatory drugs (NSAIDs) and/or other drugs was to be administered in a stable dose 4 weeks before and throughout the study. Anakinra (100 mg) was self administered subcutaneously daily over the 3 month study period. Safety and efficacy were assessed before the study and after 4 and 12 weeks by clinical (European Consensus Lupus Activity Measurement (ECLAM)), total joint count of swollen and tender joints, visual analogue scale (VAS) and laboratory measures (for example, anti-dsDNA antibodies (Abs), C3/C4, blood count, C reactive protein (CRP), and uric acid levels).

Abbreviations: Abs, antibodies; AM, antimalarial drugs; ANA, antinuclear antibodies; AZA, azathioprine; CORT, corticosteroids; CRP, C reactive protein; CYC, cyclophosphamide; ECLAM, European Consensus Lupus Activity Measurement; IL, interleukin; JA, Jaccoud’s arthropathy; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor; VAS, visual analogue scale
Anakinra in lupus arthritis

There was a clinical response with a reduction in swollen and painful joints and a serological response with a slight reduction in CRP. We noted a mild skin reaction at the injection site (after 1 month, lasting for 2 weeks), myalgia (after the seventh injection, lasting for about 5 months; improved under NSAIDs), and an upper respiratory tract infection in September 2003, treated with oral antibiotics. After 8 months’ treatment, she had a renewed arthritic flare and anakinra was discontinued as the disease was insufficiently controlled.

Case 4
A 45 year old man diagnosed in April 2002 as having SLE with severe polyarthritis initially responded to MTX. Because of lupus pneumonitis, he was switched to intravenous CYC pulse therapy, resulting in an improvement. In November 2002 he developed septic endocarditis, necessitating mitral valve replacement. In January 2003 his arthritis relapsed. As CORT and AM (started in March 2003) failed to control the condition, he was enrolled in our study in July 2003. After 10 injections of anakinra (100 mg/day), he responded clinically with a reduction in swollen and painful joints and serologically with a decrease in CRP (106 to 4 mg/l). No side effects were seen. Nevertheless, after 6 weeks the patient developed active arthritis again and the treatment was discontinued in October 2003 as the disease was insufficiently controlled.

DISCUSSION
Although AM9 and MTX10 are well studied and commonly used in patients with SLE with joint involvement, the control of lupus arthritis is still a core problem.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients’ characteristics</th>
</tr>
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<tr>
<td>Patient</td>
<td>Age (years)</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
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</table>

*Normal value for ANA titre <1/160.

Table 2  Anti-dsDNA Abs, complement factors C3/C4, CRP, VAS, number of swollen and tender joints at t0, t4, and t12 (weeks)

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Anti-dsDNA Abs (U/ml)</th>
<th>C3/C4 (mg/dl)</th>
<th>CRP (mg/ml)</th>
<th>VAS</th>
<th>Number of tender joints</th>
<th>Number of swollen joints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I0</td>
<td>I4</td>
<td>I12</td>
<td>I0</td>
<td>I4</td>
<td>I12</td>
</tr>
<tr>
<td>1</td>
<td>124</td>
<td>115</td>
<td>59</td>
<td>800/150</td>
<td>1030/130</td>
<td>990/140</td>
</tr>
<tr>
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<td>3</td>
<td>3</td>
<td>3</td>
<td>1050/220</td>
<td>1000/190</td>
<td>1040/170</td>
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<td>3</td>
<td>18</td>
<td>22</td>
<td>13</td>
<td>990/210</td>
<td>1080/190</td>
<td>1060/230</td>
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<tr>
<td>4</td>
<td>130</td>
<td>140</td>
<td>*</td>
<td>1630/180</td>
<td>1480/190</td>
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</tr>
</tbody>
</table>

*No 12 week (t12) data available, patient flared after 6 weeks although responding initially; tnormal value <7 U/ml; tnormal value C3 900–1800 mg/l, C4 100–400 mg/l; tnormal value <5 mg/l.

No further signs of infection have occurred.

Case 2
A 41 year old woman, with SLE diagnosed in December 1998, was initially treated for arthritis with CORT, NSAIDs, and MTX (since December 1998) then, as she did not respond with AZA and AM, anakinra (100 mg/day) was introduced in August 2003 because of persisting polyarthritis. After three injections she developed pneumonia during concomitant treatment with 100 mg AZA/day; this led to admission to hospital and antibiotic treatment. Because of the initially good clinical response, anakinra was restarted at a reduced dose (100 mg every other day) 4 weeks after recovery from the infection, again with a positive impact on the painful and swollen joints.

The patient is still receiving 100 mg anakinra every other day during the follow up period. No further signs of infection have occurred.

Case 3
A 33 year old woman, with SLE diagnosed in April 1990, was initially treated for arthritis with AM, CORT, and NSAIDs. Because of progression of joint deformity and functional loss, MTX was added in March 2003. Despite a good response, MTX was discontinued after 2 months because of side effects, resulting in a relapse of arthritis. Therefore the patient was enrolled in the study in July 2003. After 14 injections of anakinra (100 mg/day) there was a clinical response with a reduction in swollen and painful joints and a serological response with a slight reduction in CRP. We noted a mild skin reaction at the injection site (after 1 month, lasting for 2 weeks), myalgia (after the seventh injection, lasting for about 5 months; improved under NSAIDs), and an upper respiratory tract infection in September 2003, treated with oral antibiotics. After 8 months’ treatment, she had a renewed arthritic flare and anakinra was discontinued as the disease was insufficiently controlled.

DISCUSSION
Although AM9 and MTX10 are well studied and commonly used in patients with SLE with joint involvement, the control of lupus arthritis is still a core problem.
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was probably due to the concomitant immunosuppression with AZA. Nevertheless, she was re-exposed because of the good clinical effect and showed no further signs of infection. Throughout the study and the follow up period, there were no signs of SLE flares in other organ systems—for example, skin or kidneys.

Our preliminary results suggest that anakinra might be an interesting therapeutic alternative for individual patients with SLE and active joint involvement or JA not responding to conventional treatment. Efficacy and tolerability were comparable to data achieved in patients with RA. Tender joint count, ECLAM, and CRP may be measures for assessing the therapeutic response in studies of patients with SLE and arthritis (fig 1). Further controlled clinical investigations of the long term effects of IL1 blockade, particularly its safety, need to be evaluated in a larger cohort of patients with SLE and polyarthritis.

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