CONCISE REPORT

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

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

Methods

The study was designed as an open, single centre, pilot trial involving patients aged 18–65 years with SLE and severe, 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 urine analysis).

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), 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

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

**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 our 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 AM and MTX 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>
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<tbody>
<tr>
<td><strong>Patient No</strong></td>
<td><strong>Age (years)</strong></td>
</tr>
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</tr>
<tr>
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*Normal value for ANA titre <1/160.*

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Anti-dsDNA Abs, complement factors C3/C4, CRP, VAS, number of swollen and tender joints at t0, t4, and t12 (weeks)</th>
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<tbody>
<tr>
<td><strong>Patient No</strong></td>
<td><strong>anti-dsDNA Abs (U/ml)†</strong></td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>3</td>
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<tr>
<td>3</td>
<td>18</td>
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</table>

*No 12 week (t12) data available, patient flared after 6 weeks although responding initially; †normal value <7 U/ml; ‡normal value C3 900–1800 mg/l; C4 100–400 mg/l; ¶normal value <5 mg/l.
Despite the fact that patients with RA have now been treated sufficiently for more than 10 years with TNFα blockers, only single reports of patients with connective tissue diseases treated with biological agents have been published. The observation of newly developed antinuclear antibodies (ANA) and anti-dsDNA Abs, as well as cases of drug induced lupus has so far hampered the evaluation of TNFα blocking in connective tissue diseases. With anakinra a promising new approach in cytokine targeted treatment was recently admitted for the treatment of active RA, but its use in the treatment of SLE has not yet been described.

This study presents the first administration of anakinra in four patients with treatment refractory lupus arthritis. Although the number of patients is small and their characteristics are heterogeneous, we showed that anakinra is well tolerated and apparently safe and that certain clinical and serological improvements were achieved, bearing in mind that surrogate markers for monitoring treatment responses in SLE are not yet available and validated in detail.

In all four patients enrolled in the study, we found a decrease in the clinical measures tender joint count and ECLAM® after four weeks (t4); this is similar to comparable RA studies. After 12 weeks, however, the clinical activity measures tended to increase again (fig 1, table 2). So far our preliminary results do not allow a detailed explanation for that observation. During the follow up period, patient 1 remained in remission after discontinuation of anakinra, patient 3 was still receiving anakinra, and two patients were switched to a different treatment because of lack of efficacy: patient 4 after 6 weeks and patient 3 after 32 weeks. In clinical practice, dropout rates in RA are comparable to those of our study cohort, with <50% of patients continuing to receive anakinra after 6 months. Again parallel to reports from RA studies, we observed a decrease in CRP at t4 in all patients (t0: mean (SD) 54 (40) mg/l; t4: mean (SD) 16.3 (12.7) mg/l; p = 0.06). When raised at t0, anti-dsDNA Abs decreased over the study period (patients 1 and 3). Complements C3/C4 improved slightly in patients 1 and 3, while not altering significantly in the other two (table 2). In contrast with RA, we introduced anakinra as a monotherapy in the standard dosage (100 mg subcutaneously/daily), not added to MTX but to concomitant drugs such as AM (in all patients) and to AZA (in patient 2).

The safety of anakinra in patients with RA has been established in large scale trials and studies of long term use; the most commonly reported adverse event in the present study was an injection site reaction in patients 1 and 3. The occurrence of pneumonia in one of our patients (patient 2) 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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This study was presented as a poster at the Annual European Congress of Rheumatology EULAR 2004 in Berlin, Germany, 9–12 June 2004

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Accepted 22 August 2004
Published Online First 2 September 2004

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