**CONCISE REPORT**

Interleukin 13 in synovial fluid and serum of patients with psoriatic arthritis

A Spadaro, T Rinaldi, V Riccieri, G Valesini, E Taccari

**OBJECTIVES:** To compare the pattern of interleukin (IL) 13 production in synovial fluid (SF) and serum of patients with psoriatic arthritis (PsA) with that in patients with rheumatoid arthritis (RA) and osteoarthritis (OA), investigating its relation to the proinflammatory cytokine IL12.

**METHODS:** SF and serum IL13 levels were determined in 35 patients with PsA, 36 with RA, and 15 with OA. The main clinical and laboratory variables, including number of painful and/or swollen joints, Ritchie index, morning stiffness, erythrocyte sedimentation rate, level of C reactive protein, level of rheumatoid factor, and SF analysis, were also evaluated.

**RESULTS:** SF IL13 levels were significantly higher in patients with PsA (p<0.02) or RA (p<0.012) than in patients with OA, with no significant difference between the former two. SF IL12 levels were significantly higher in patients with PsA (p<0.023) than in those with OA. Serum IL13 (p<0.0001) and IL12 (p<0.02) levels were lower in patients with PsA than in those affected by RA. Only patients with PsA had higher IL13 levels in SF than in serum (p<0.002). The IL13 SF/serum ratio was higher in the PsA group than in the group with RA (p<0.005) or OA (p<0.026). SF IL13 levels correlated with serum IL13 levels (p<0.0001) in RA and with SF IL12 levels (p<0.03) in PsA.

**CONCLUSIONS:** In PsA, there appears to be localised production of IL13, in balance with IL12, in the inflamed joints. The distinct IL13 secretion profiles in PsA, RA, and OA may be related to the clinical pictures, reflecting the different pathogenic mechanisms involved in inflammatory and degenerative joint diseases.

**RESULTS**

Table 1 shows the main data for all the patients and controls, and figure 1 shows SF and serum IL13 levels. SF IL13 levels were significantly higher in patients with PsA (p<0.02) or RA (p<0.012) than in patients with OA, with no significant difference between the former two groups. SF IL12 levels were significantly higher in patients with PsA (p<0.023) than in those with OA.

Serum IL13 (p<0.0001) and IL12 (p<0.02) levels were significantly lower in patients with PsA than in those affected by RA. We did not find any relevant difference in serum IL13 or IL12 levels among patients with PsA or OA or healthy subjects. Serum IL13 (p<0.017) and IL12 (p<0.05) levels were significantly higher in patients with RA than in healthy subjects. Comparison of SF and serum cytokine levels in the PsA, RA, and OA groups showed that only patients with PsA had higher IL13 levels in SF than in serum (p<0.002). The SF/serum ratio was higher in the PsA group (1.8/1–5.3) than in the RA

**PATIENTS AND METHODS**

We studied 35 patients with PsA, diagnosed by the presence of psoriasis and seronegative peripheral arthritis, with a knee

**Abbreviations:** PsA, psoriatic arthritis; RA, rheumatoid arthritis; OA, osteoarthritis; IL, interleukin; SF, synovial fluid.
(1/0.7–1.5; p<0.005) or OA (1/1–1.3; p<0.026) groups. Figure 2 shows mean (SD) SF/serum ratios in patients with PsA, RA, or OA. SF IL13 levels correlated with serum IL13 levels (r=0.651; p<0.0001) in RA and with SF IL12 levels (r=0.390; p<0.03) in PsA.

We did not find any correlation between SF or serum cytokine levels and the SF characteristics analysed, the main clinical and laboratory measures of disease activity, or treatment in the different patient groups. Patients with RA who had SF or serum IL13 levels >100 pg/ml showed a higher, but not significantly so, prevalence of rheumatoid factor than those with lower levels (88% vs 52% and 83% vs 57% respectively).

**DISCUSSION**

T cells and derived cytokines have a major role in the induction and maintenance of synovial inflammation. IL13, an anti-inflammatory cytokine secreted by activated T cells, may be a key modulator of inflammation in autoimmune diseases. It inhibits proinflammatory cytokines (such as IL12), chemokines, and haemopoietic growth factor production, upregulates production of IL1 receptor agonist by monocytes/macrophages, and suppresses cytotoxic functions of monocytes/macrophages and cytokine mediated fibroblast growth. The anti-inflammatory properties of IL13 in vitro may have been supported by its presence at a low level in SF and peripheral blood samples of patients affected by RA, OA, and other diseases, including five patients with PsA. However, we found higher SF IL13 levels in patients with PsA than in controls.

### Table 1 Basic, clinical, and laboratory data for patients with psoriatic arthritis (PsA), rheumatoid arthritis (RA), and osteoarthritis (OA) and controls

<table>
<thead>
<tr>
<th></th>
<th>PsA (n=35)</th>
<th>RA (n=36)</th>
<th>OA (n=15)</th>
<th>Controls (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>45.9 (17–70)</td>
<td>54.6 (26–76)</td>
<td>58.3 (45–70)</td>
<td>48.3 (25–75)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>24/11</td>
<td>11/25</td>
<td>6/9</td>
<td>15/7</td>
</tr>
<tr>
<td>Disease duration (months)*</td>
<td>60 (3–336)</td>
<td>115 (5–588)</td>
<td>73.5 (3–192)</td>
<td>–</td>
</tr>
<tr>
<td>Disease onset [years]*</td>
<td>41 (17–67)</td>
<td>45 (18–72)</td>
<td>53 (36–70)</td>
<td>–</td>
</tr>
<tr>
<td>ESR (mm/1st h)†</td>
<td>29.2 (24.5)</td>
<td>35.8 (22.7)</td>
<td>11.8 (8.6)</td>
<td>7.7 (3.5)</td>
</tr>
<tr>
<td>CRP (mg/l)†</td>
<td>16 (14)</td>
<td>26 (25)</td>
<td>5.0 (3.0)</td>
<td>2.0 (1.0)</td>
</tr>
<tr>
<td>Rheumatoid factor†</td>
<td>0.9</td>
<td>61 (22)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DMARDs‡</td>
<td>49 (17)</td>
<td>69 (25)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Corticosteroids‡</td>
<td>26 (9)</td>
<td>69 (25)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Serum IL13 levels (pg/ml)§</td>
<td>2 (2–2)</td>
<td>10.2 (2–28.3)</td>
<td>2 (2–5.8)</td>
<td>2 (2–6.2)</td>
</tr>
<tr>
<td>Serum IL12 levels (pg/ml)§</td>
<td>2 (2–4.4)</td>
<td>4 (2–28.7)</td>
<td>4.8 (2–9.6)</td>
<td>2 (2–4.8)</td>
</tr>
<tr>
<td>SF IL13 levels (pg/ml)§</td>
<td>5.8 (2–14.8)</td>
<td>6.7 (2–75.5)</td>
<td>2 (2–3)</td>
<td>–</td>
</tr>
<tr>
<td>SF IL12 levels (pg/ml)§</td>
<td>4.2 (2–10)</td>
<td>2 (2–22.3)</td>
<td>2 (2–2)</td>
<td>–</td>
</tr>
<tr>
<td>SF low viscosity‡</td>
<td>74.3 (26)</td>
<td>83.3 (30)</td>
<td>13.3 (2)</td>
<td>–</td>
</tr>
<tr>
<td>SF mucin clot‡</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SF WBC (×10⁹/l)§</td>
<td>28.6 (10)</td>
<td>16.7 (6)</td>
<td>80 (12)</td>
<td>–</td>
</tr>
<tr>
<td>Good</td>
<td>60.0 (21)</td>
<td>61.1 (22)</td>
<td>20 (3)</td>
<td>–</td>
</tr>
<tr>
<td>Fair</td>
<td>11.4 (4)</td>
<td>22.2 (8)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Poor</td>
<td>71.6 (10)</td>
<td>8 (6–12.9)</td>
<td>2.175 (0.5–2.7)</td>
<td>–</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (range); †Values are expressed as mean (SD); ‡Values are expressed as % (n); §Values are expressed as median (25th–75th centile).

ESR = Erythrocyte sedimentation rate; CRP = C reactive protein; DMARDs = disease modifying antirheumatic drugs; SF = synovial fluid; IL = interleukin; WBC = white blood cells; PMN = polymorphonuclear.

Figure 1 Synovial fluid (SF) and serum levels of interleukin (IL) 13 in patients with psoriatic arthritis (PsA) (n=35), rheumatoid arthritis (RA) (n=36), or osteoarthritis (OA) (n=15) and healthy controls (n=22). Lines connect the corresponding samples (SF and serum) of each patient. *Significantly different from SF of patients with PsA (p<0.002); **significantly different from SF of patients with OA (p<0.02); ***significantly different from serum of patients with PsA (p<0.001); ****significantly different from serum of patients with OA (p<0.001); and controls (p<0.017).

Figure 2 Interleukin (IL) 13 SF/serum ratio (mean (SD)) in patients with psoriatic arthritis (PsA) (n=35), rheumatoid arthritis (RA) (n=36), or osteoarthritis (OA) (n=15).
those with OA, suggesting a role for this cytokine in joint inflammation.

These results agree with those of Isomaki et al,11 who showed that IL13 was present in 27 out of 28 SF samples from patients with RA, and IL13 mRNA was detectable in SF mononuclear cells, indicating that this cytokine is consistently present in rheumatoid joints.

The discrepancy between our results and those of Woods et al5 could be partly due to the different methods used to detect IL13 and to the clinical features of the patients. A relatively low percentage of our arthritic patients had been treated with disease modifying antirheumatic drugs because many of them were newly diagnosed. The discrepancies may also be explained by the fact that SF contains an IL13 inhibitor or that large amounts of IL13 could be absorbed by activated cells,2 but we have no results to support this hypothesis.

The relation between SF and serum IL13 levels has been poorly investigated in PsA.2 We found that only in patients with PsA were IL13 levels higher in SF than in serum, suggesting that the IL13 secretion profile is different in different types of arthritis. In fact, in RA, which has the characteristics of a systemic disease, IL13 levels are higher in both SF and serum, compared with in OA. Moreover, SF and serum IL13 levels in patients with RA correlated with each other, whereas this was not so in patients with PsA, who had a higher SF/serum ratio than patients with RA. These data, together with the evidence that serum IL13 levels were lower in patients with PsA than in patients with RA, suggest localised production of this cytokine in the inflamed joints of patients with PsA.

Another explanation for the difference in serum IL13 levels between patients with PsA and those with RA could be the larger total amount of synovial tissue in the latter, leading to larger amounts of IL13 leaking into the circulation.

Our results are not surprising as IL13 production depends on activated T helper lymphocytes,1 which are known to play a major role in PsA, as well as in RA.8,10 In PsA and RA, T helper lymphocytes are abundant in peripheral blood and synovial membrane and fluid, although there are some quantitative differences. In fact, a CD4 surplus and a deficiency of suppressor CD8 cells have been shown in the peripheral blood of patients with RA, whereas this ratio was not as high in patients with PsA as in controls.11 Moreover, CD4 helper inducer is the predominant T cell subset in PsA and RA synovial tissues.10 In contrast with the vast surplus of CD4 cells in synovial tissue, this subset is not predominant compared with CD8 cells in SF of patients with PsA or RA.10,12 This could be due to differences in the number and/or activation state of molecules on the T cell surface or to disease duration.10

All these findings confirm that the differences between articular involvement in PsA and RA are mostly quantitative rather than qualitative. This is also emphasised by the observation that SF from patients with PsA and RA have a similar pattern of T cell derived cytokine production.11 According to our results, the occurrence and concentrations of different cytokines were lower in SF from patients with PsA than in those with RA.11

The relation between SF levels of IL13 and IL12 in PsA supports the hypothesis that the production of these two molecules is balanced, but that endogenous IL13 production is insufficient for optimal inhibition of the cytokines involved in joint inflammation, suggesting a role for IL13 in the treatment of arthritis, as has been demonstrated in animal models.14 Moreover, it should be stressed that IL13 is a protein secreted by activated T cells that modulates B cell function in vitro and plays an important part in their proliferation and differentiation.15 This property could account for the high local IL13 levels observed in patients with PsA and RA, characterised by B lymphocyte proliferation, compared with patients with OA.

In conclusion, this report suggests that the local or systemic pattern of IL13 production may be related to the clinical pictures of PsA, RA, and OA, reflecting the different pathogenic mechanisms involved in inflammatory and degenerative joint diseases.

Authors’ affiliations
A Spadaro, T Rinaldi, V Riccieri, G Valesini, Department of Medical Therapy, Rheumatology Unit, University of Rome “La Sapienza”, Italy
E Taccari, Rheumatology Unit, II Faculty of Medicine, University of Rome “La Sapienza”

Correspondence to: Dr A Spadaro, Dipartimento di Terapia Medica, Divisione di Reumatologia, Università di Roma “La Sapienza”, Azienda Polyclinico Umberto I, Viale dei Poli clinici 155, 00161 Roma, Italia, a.spadaro.reuma@virgilio.it

Accepted 4 July 2001

REFERENCES

www.annrheumdis.com
Interleukin 13 in synovial fluid and serum of patients with psoriatic arthritis

A Spadaro, T Rinaldi, V Riccieri, G Valesini and E Taccari

doi: 10.1136/ard.61.2.174

Updated information and services can be found at:
http://ard.bmj.com/content/61/2/174

References
This article cites 12 articles, 3 of which you can access for free at:
http://ard.bmj.com/content/61/2/174#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Immunology (including allergy) (5144)
- Degenerative joint disease (4641)
- Musculoskeletal syndromes (4951)
- Osteoarthritis (931)
- Connective tissue disease (4253)
- Inflammation (1251)
- Rheumatoid arthritis (3258)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/