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<0.001) 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.

Psoriatic arthritis (PsA) is characterised by synovitis which has many pathogenic factors such as proinflammatory and anti-inflammatory cytokines. Interleukin (IL) 13 is a protein secreted by activated T cells, which modulates human monocyte and B cell function in vitro. This cytokine inhibits production of proinflammatory molecules, such as IL12, by activated human monocytes. The role of IL13 in arthritis is not clear, as both relevant and negligible amounts of this cytokine have been observed in the serum and synovial fluid (SF) of patients with rheumatoid arthritis (RA), whereas, in patients with PsA, it has only been investigated in a small group. Moreover, the relation between its concentration in SF and serum in PsA has not yet been determined.

We studied the pattern of IL13 production in SF and serum of patients with PsA and compared it with the pattern in patients with RA and osteoarthritis (OA), investigating its relation to a proinflammatory cytokine (IL12).

PATIENTS AND METHODS

We studied 35 patients with PsA, diagnosed by the presence of psoriasis and seronegative peripheral arthritis, with a knee joint effusion. We also studied 36 patients with RA, classified according to Arnett’s criteria and 15 patients with primary OA, with knee joint effusion. For all patients, we evaluated the main clinical and laboratory variables, including the 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

Table 1 shows the main data for all the patients and controls, and fig 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 group (0.6/1–3.5).

Statistical analysis

Categorical variables were analysed by the χ² test or Fisher’s exact test. The results were expressed as median (25th–75th centile), and the significance of the differences determined using the Mann-Whitney test for unpaired samples and Wilcoxon’s test for paired samples. The significance of any correlation was determined by the Spearman’s rank correlation coefficient; p<0.05 was considered significant.

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 ($r_s=0.651$; $p<0.0001$) in RA and with SF IL12 levels ($r_s=0.390$; $p<0.03$) 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...
Cytokines were lower in SF from patients with PsA than in OA, suggesting a role for this cytokine in joint inflammation.

These results agree with those of Isomaki et al
14, 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 al
8 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,
9 but we have no results to support this hypothesis.

The relation between SF and serum IL13 levels has been poorly investigated in PsA.
10 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 arthritides. 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,
15 which are known to play a major role in PsA, as well as in RA.
16 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.
16 Moreover, CD4+ helper/inducer is the predominant T cell subset in PsA and RA synovial tissues.
18 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.
19 This could be due to differences in the number and/or activation state of molecules on the T cell surface or to disease duration.

All these findings confirm that the differences between articular involvement in PsA and RA are mostly qualitative rather than quantitative. 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.
15 According to our results, the occurrence and concentrations of different cytokines were lower in SF from patients with PsA than in those with RA.
15 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.

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