

CONCISE REPORTS

T cell derived cytokines in psoriatic arthritis synovial fluids

Gerald Partsch, Ernst Wagner, Burkhard F Leeb, Hans Bröll, Attila Dunky, Josef S Smolen

Abstract

Objective—The aim of this study was to investigate the concentrations of T cell derived cytokines in the synovial fluids (SFs) of patients with psoriatic arthritis (PsA) in comparison with rheumatoid arthritis (RA) and osteoarthritis (OA).

Methods—Th1 type cytokines (interleukin 2 (IL2), tumour necrosis factor β (TNF β), and interferon γ (INF γ)) and Th2 type cytokines (IL4, IL10) were measured by means of enzyme linked immunosorbent assays.

Results—IL2 was usually not detectable in any of the disease groups. TNF β was found in 3 of 31 PsA SFs (mean (SEM) 11.1 (2.3) pg/ml) and in a significantly lower concentration than in 20 of the 40 RA SFs (42.2 (15.6) pg/ml; $p < 0.002$). INF γ was measurable in 2 of 10 PsA and 6 of 16 RA SFs ($p > 0.05$). IL4 was present at low concentrations in 4 of 22 PsA SFs (0.41 (0.8) pg/ml), and in 15 of 20 RA SFs (0.63 (0.09) pg/ml; $p < 0.01$). IL10 was found in 4 of 27 PsA SFs (12.3 (0.9) pg/ml) and in 27 of 32 RA SFs (37.3 (4.9) pg/ml; $p < 0.0001$). In all OA SFs cytokine concentrations were below the limit of detection.

Conclusion—The pattern of T cell derived cytokines in PsA SFs was similar to that of RA SFs. However, both the frequency and the concentrations of cytokines were lower in PsA SFs than in RA SFs, while OA SFs generally lacked any detectable T cell

cytokines altogether. The presence of Th1 and Th2 cell derived cytokines in PsA SFs suggests the presence of activated T cells in the inflamed joint tissues and their participation in the immunoinflammatory events. (*Ann Rheum Dis* 1998;57:691-693)

T cells are important cellular components in the development of inflammatory joint diseases such as rheumatoid arthritis (RA).^{1,2} Psoriatic arthritis (PsA), an inflammatory seronegative disease of unknown aetiology, is also characterised by the infiltration of joints and involved skin by activated T cells.³ The synovial membranes of PsA and RA cannot be differentiated from each other by immunohistology.⁴

Activated T cells belong to two major subpopulations, which may be differentiated by their cytokine profiles: Th1 cells produce the proinflammatory cytokines interleukin 2 (IL2), tumour necrosis factor β (TNF β), and interferon γ (INF γ), while Th2 cells synthesise the anti-inflammatory cytokines IL4 and IL10.⁵ As the role or presence of T cell derived cytokines in PsA is still unknown, we investigated them and compared them with those in RA and osteoarthritis (OA).

Methods

PATIENTS

Synovial fluids (SFs) from 35 patients with PsA, 60 patients with RA⁶, and 25 patients with

Ludwig Boltzmann
Institute of
Rheumatology and
Balneology,
Vienna-Oberlaa,
Austria
G Partsch
J S Smolen

5th Medical
Department
(Rheumatology,
Metabolic Diseases
and Rehabilitation),
Wilhelminenspital,
Vienna, Austria
E Wagner
A Dunky

2nd Department of
Medicine, Centre for
Rheumatic Diseases,
Municipal Hospital
Vienna-Lainz, Austria
B F Leeb
J S Smolen

2nd Medical
Department
(Rheumatology and
Osteology),
Kaiser-Franz-Josef-
Hospital, Vienna,
Austria
H Bröll

Correspondence to:
Dr G Partsch, Ludwig
Boltzmann Institute of
Rheumatology, PO Box 78,
A-1107 Vienna-Oberlaa,
Austria.

Accepted for publication
12 August 1998

Table 1 Demographic data of the patients (mean (SEM))

	PSA	RA	OA
Number of patients (F/M)	6/29	47/13	12/13
Age (y)	50.5 (2.5)	60.9 (1.5)	57.6 (3.6)
Treatment			
DMARDs			
MTX	12	13	0
Gold salts	1	7	0
Chloroquine	0	7	0
D-penicillamine	0	5	0
Azathioprine	0	6	0
Prednisolone in addition (<10 mg/day)	3	13	0
NSAID	22	22	25
Duration of disease (y)	9.5 (0.9)	8.6 (1.1)	NA
Number of swollen joints	4.9 (0.9)	6.8 (0.7)	NA
Number of tender joints	6.9 (1.2)	7.7 (0.8)	NA
Morning stiffness (min)	27.4 (8.3)	52.6 (10.0)	NA
ESR (mm 1st h)	41.0 (3.6)	45.7 (3.8)	19.5 (2.8)
CRP (mg/l)	17.3 (4.2)	33.2 (5.3)	13.7 (1.6)
SF leucocytes $\times 10^3/\mu\text{l}$	14.6 (3.0)	19.0 (2.3)	5.6 (1.7)
RF in SFs (IU/ml)	19.0 (4.0)	84.0 (23.3)	11.9 (0.9)

NA = not analysed

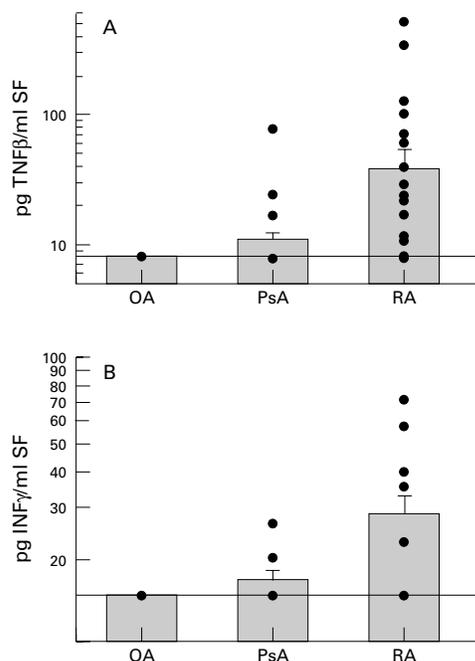


Figure 1 Concentrations of Th1 cell derived cytokines in synovial fluids ((shaded bars) mean concentration (SEM); solid line shows limit of detection). (A) TNF β of patients with osteoarthritis (OA, n = 6), psoriatic arthritis (PsA, n = 31), and rheumatoid arthritis (RA, n = 40); (B) INF γ of patients with osteoarthritis (OA, n = 9), psoriatic arthritis (PsA, n = 10), and rheumatoid arthritis (RA, n = 16).

OA⁷ were analysed. Table 1 gives details of the patients.

At the time of arthrocentesis swollen and tender joints, morning stiffness, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) were determined as markers of disease activity in PsA and RA. In addition, the leucocyte counts and rheumatoid factor (RF) values in the SFs were measured.

The SFs were obtained from knee joint effusions, treated with hyaluronidase (20 μ g/ml SF; H-2251 sheep testes, type III, Sigma, St Louis, MO, USA), centrifuged, and the supernatant used to determine the cytokines.

CYTOKINE ASSAYS

All of the test kits for T cell derived cytokines were commercial "sandwich" enzyme linked immunosorbent assays (ELISA) and were used according to the manufacturers' instructions. The lower limits of detection were as follows: for IL2 (Research and Diagnostic Systems (R and D), Minneapolis, USA; Quantikine) 31 pg/ml; for IL4 (R and D, Quantikine HS with high sensitivity) 0.25 pg/ml, for IL10 (Medgenix Diagnostics SA, Fleurus, Belgium) 11 pg/ml; for TNF β (Bender MedSystems, Vienna, Austria) 7 pg/ml, and for INF γ (Endogen, Cambridge, MA, USA) 15 pg/ml.

STATISTICAL ANALYSIS

The parameter free two tailed Mann-Whitney U test for independent samples was used to analyse statistical significances as indicated; p values below 0.05 were considered significant. Similar results were obtained with the χ^2 test. All concentrations are presented as mean (SEM).

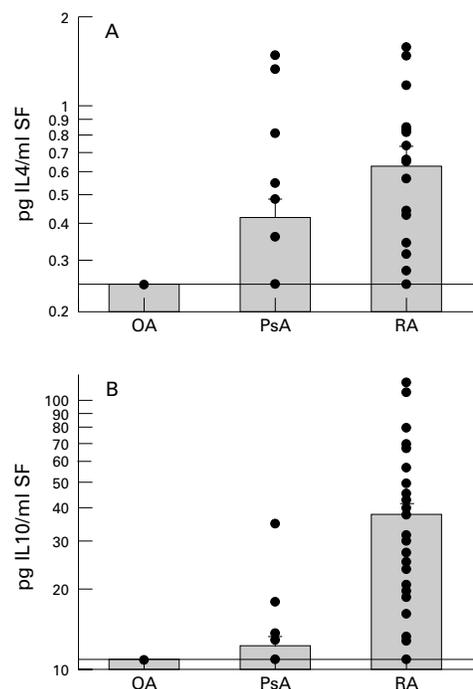


Figure 2 Concentrations of Th2 cell derived cytokines in synovial fluids ((shaded bars) mean concentration (SEM); solid line shows limit of detection). (A) IL4 of patients with osteoarthritis (OA, n = 15), psoriatic arthritis (PsA, n = 22), and rheumatoid arthritis (RA, n = 20); (B) IL10 of patients with osteoarthritis (OA, n = 16), psoriatic arthritis (PsA, n = 27), and rheumatoid arthritis (RA, n = 32).

Results

In all OA SFs cytokine concentrations were below the limits of detection.

INTERLEUKIN 2

IL2 was not detectable in PsA SFs or RA SFs (with two exceptions).

TUMOUR NECROSIS FACTOR β

Three of 31 (10%) PsA SFs contained TNF β (mean 11.1 (2.3 pg/ml)) as did 20 of 40 (50%) RA SFs (mean 42.2 (15.6) pg/ml; p < 0.002 compared with PsA), (fig 1A).

INTERFERON γ

INF γ was found in 2 of 10 (20 %) PsA SFs (mean 16.7 (1.2 pg/ml)) and in 6 of the 16 (45%) RA SFs (mean 28.2 (5.3) pg/ml; p > 0.05 compared with PsA), (fig 1B).

INTERLEUKIN 4

IL4 (fig 2A) was found in 4 of 22 (18%) PsA SFs (mean 0.41 (0.08 pg/ml)) but in significantly lower concentrations (p < 0.01) than in 15 of the 20 (75%) RA SFs (mean 0.63 (0.09) pg/ml).

INTERLEUKIN 10

IL10 (fig 2B) was detected in only 4 of 27 (15%) PsA SFs (mean 12.3 (0.9) pg/ml), but in 27 of 32 (84%) RA SFs where it was also found in much higher concentrations than in the PsA SFs (mean 37.3 (4.9) pg/ml; p < 0.0001).

Discussion

In this study T cell derived cytokines were detected in 10 to 20% of PsA SFs. However, the frequencies and values of TNF β , IL4, and

IL10 were significantly higher in RA. The concentrations of $\text{INF}\gamma$ did not statistically differ in PsA and RA SFs even though it is also produced by CD8^+ cells, which are increased in PsA SFs.⁸ None of these lymphokines was found in OA SFs.

From a quantitative point of view, the Th1 derived cytokines $\text{TNF}\beta$ and $\text{INF}\gamma$ were found in much higher concentrations than the Th2 lymphokine IL4. This indicates that Th1 cytokines may be a major factor in the inflammation of PsA. This has been accepted for arthritis in other seronegative spondylarthropathies and for RA.^{9,10} The sensitivity of the assay used permitted the detection of lower concentrations of IL4 than was previously possible.¹¹

In contrast, IL10 was readily found, although of all the cytokines analysed it is the only one that is also readily produced by non-T cells.¹² The lower frequency and concentrations of IL10 in PsA SFs may therefore be because of the lower numbers of macrophages in the synovial membranes of PsA compared with RA patients.¹³

The presence of lymphokines in SFs has its synovial membrane correlate in RA. Moreover, we have also observed that the same proinflammatory monokines that are characteristic of RA, namely $\text{TNF}\alpha$ and $\text{IL1}\beta$ are also found in PsA SFs, albeit at lower concentrations and frequencies.¹⁴ These observations in conjunction with the findings reported here indicate that the psoriatic joint inflammation bears similarities to rheumatoid inflammation, but to a lesser extent. This is well in line with both the potential of PsA to be a destructive, erosive joint disease and its generally more benign nature compared with RA.¹⁵

Because of the lack of validated criteria for disease activity in PsA, the same criteria were used for both PsA and RA.¹⁶ This represents a somewhat limiting factor in our study, as the parameters chosen may not reflect disease activity to the same extent in the two diseases.

Our conclusions are in agreement with earlier observations about similarities between the histological changes in PsA and RA.⁴ The diversity in genetic associations as well as the probable heterogeneity in the hitherto unknown aetiological events and the nature of eliciting (and/or perpetuating) antigens may govern the differences between the two diseases.

The results obtained suggest that T cells participate actively in the immunoinflammatory events in PsA. Thus targeting T cells may be an important therapeutic approach in this disease. This notion is supported by the efficacy of cyclosporin A, a compound that targets T cell lymphokine gene activation in PsA.¹⁷

This study was supported by grants from the Austrian Ministry of Health, Sports and Consumer Protection (ZI 236.065/3-II/A/6/91) and the City of Vienna (Department of Urban Development, Planning and Scientific Affairs). The authors are grateful to Ing Christine Schwarzer for her excellent laboratory work and to Erika Karner for expert secretarial assistance.

- Panayi GS, Lanchbury JS, Kingsley GH. The importance of the T cell in initiating and maintaining the chronic synovitis of rheumatoid arthritis. *Arthritis Rheum* 1992;35:246-9.
- Smolen JS, Tohidast-Akrad M, Gal A, Kunaver M, Eberl G, Zenz P, *et al.* The role of T-lymphocytes and cytokines in rheumatoid arthritis. *Scand J Rheumatol* 1996;25:1-4.
- Panayi GS. Immunology of psoriasis and psoriatic arthritis. *Baillieres Clin Rheumatol* 1994;8:419-27.
- Soren A, Waugh TR. Changes in the synovial membrane in psoriatic arthritis. *Rev Rhum* 1982;49:671-6.
- Dechanet J, Risoan MC, Banchereau J, Miossec P. Interleukin 4, but not interleukin 10, regulates the production of inflammation mediators by rheumatoid synovio-cytes. *Cytokine* 1995;7:176-83.
- Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
- Altman R. Classification of disease: osteoarthritis. *Semin Arthritis Rheum* 1991;20 (suppl 2):40-7.
- Costello P, O'Farrelly C, Bresnihan B, FitzGerald O. Characterisation of CD8^+ T cells in psoriatic arthritis synovial effusions. *Br J Rheumatol* 1996;35 (suppl 1):160.
- Schlaak JF, Pfers I, Meyer zum Büschenfelde K-H, Märker-Hermann E. Different cytokine profiles in the synovial fluid of patients with osteoarthritis, rheumatoid arthritis and seronegative spondylarthropathies. *Clin Exp Rheumatol* 1996;14:155-62.
- Simon AK, Seipelt E, Sieper J. Divergent T-cell cytokine patterns in inflammatory arthritis. *Proc Natl Acad Sci USA* 1994;91:8562-6.
- Miossec P, Navilat M, Dupuy d'Angeac A, Sany J, Banchereau J. Low levels of interleukin-4 and high levels of transforming growth factor β in rheumatoid synovitis. *Arthritis Rheum* 1990;33:1180-7.
- Howard M, O'Garra A, Ishida H, Malefyt RDW, de Vries J. Biological properties of interleukin 10. *J Clin Immunol* 1992;12:239-47.
- Veale D, Yanni G, Rogers S, Barnes L, Bresnihan B, Fitzgerald O. Reduced synovial membrane macrophage numbers, ELAM-1 expression, and lining layer hyperplasia in psoriatic arthritis as compared with rheumatoid arthritis. *Arthritis Rheum* 1993;36:893-900.
- Partsch G, Steiner G, Leeb BF, Dunky A, Bröll H, Smolen JS. Highly increased levels of tumor necrosis factor- α and other proinflammatory cytokines in psoriatic arthritis synovial fluid. *J Rheumatol* 1997;24:518-23.
- Gladman DD. Natural history of psoriatic arthritis. In: Wright V, Helliwell P, eds. *Psoriatic arthritis*. Baillieres Clin Rheumatol 1994;8:379-94.
- Leeb BF, Witzmann G, Ogris E, Studnicka-Benke A, Andel I, Schweitzer H, *et al.* Folic acid and cyanocobalamin levels in serum and erythrocytes during low-dose methotrexate therapy of rheumatoid arthritis and psoriatic arthritis patients. *Clin Exp Rheumatol* 1995;13:459-63.
- Olivieri I, Salvarani C, Olivieri I, Cantini F, Macchioni L, Padula A, *et al.* Therapy with cyclosporine in psoriatic arthritis. *Semin Arthritis Rheum* 1997;27:36-43.