Value of synovial fluid interleukin-1 β determination in predicting the outcome of psoriatic monoarthritis

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Abstract

Objective—To investigate the value of synovial fluid analysis in predicting the outcome of psoriatic monoarthritis.

Methods—In synovial fluid from knee joints of 18 patients with psoriatic monoarthritis lasting less than six months, white blood cell count, acid phosphatase, lysozyme, and interleukin (IL)-1 β were determined. ESR and serum C reactive protein were also measured. To define the outcome, the patients were monitored for at least three years and then subdivided into those with polyarthritis and those without.

Results—Among the blood and synovial fluid indices considered, synovial fluid IL-1 β was the only variable which differed between the patients who developed polyarthritis, within three years and those without polyarthritis after this time, at 20.82(SD 8.79) v 4.19(4.73) pg ml⁻¹, $P < 0.0001$. A correlation was found between synovial fluid IL-1 β concentrations and the number of affected joints after three years ($r = 0.739$, $P < 0.0001$).

Conclusions—Determination of synovial fluid IL-1 β at disease onset may be useful in revealing the outcome of psoriatic monoarthritis since, among the variables considered in our study, this was the only one capable of predicting the evolution of monoarticular psoriatic arthritis to polyarthritis.

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Synovial fluid analysis represents one of the most important laboratory investigations for the diagnosis of arthritis. It has also been proposed that it can predict the outcome of rheumatoid arthritis¹ and juvenile chronic arthritis,² both diseases characterised by subsets which differ in evolution and severity. Psoriatic arthritis has also been subdivided into subgroups according to its distribution and the number of joints involved.³ Although the type of onset is thought to be important for the prediction of psoriatic arthritis outcome, the pattern of joint involvement frequently changes with time, in particular when it is monoarticular.⁴

As in other arthropathies, laboratory investigations in psoriatic arthritis may be useful in the early prediction of the type of evolution. Since psoriatic monoarthritis is frequently associated with large effusions, synovial fluid

analysis may be considered in this context. Among inflammatory substances found in synovial fluid, increasing attention has recently been given to the cytokines.

Proinflammatory cytokines are thought to play a major role in chronic inflammation and joint destruction. Tumour necrosis factor (TNF) and interleukin (IL)-1 stimulate the proliferation of synoviocytes and the secretion of cartilage and bone degrading enzymes.⁵ The synovial fluid concentrations of IL-1 β have been found to be higher in psoriatic arthritis than in osteoarthritis and lower than in rheumatoid arthritis,⁶ thus suggesting a role for this cytokine in determining the type and severity of arthritis. Although results obtained in vitro suggest that cytokine measurement might have both diagnostic and prognostic value, until now very few reports have proposed in vivo synovial fluid cytokine measurement for the prediction of disease outcome.⁷

The aim of this study was to investigate the value of synovial fluid analysis in predicting the outcome of monoarticular psoriatic arthritis.

Methods

We examined the synovial fluid of 18 patients (10 female and eight male, mean age 47.1 years, range 18 to 60) with monoarticular onset of psoriatic arthropathy. Patients were required to satisfy the criteria of Moll and Wright for the diagnosis of psoriatic arthritis³ and to have had a disease duration of less than six months. The majority of patients (10/18 = 55.5%) were taking non-steroidal anti-inflammatory drugs (NSAIDs). None of the patients had received any intra-articular or systemic steroid or slow acting antirheumatic drugs (SAARDs) before the study.

Patients were first observed for six months and then monitored for a period of at least three years (range 36 to 40 months) to define the type of outcome. Only patients whose disease remained monoarticular in the first six months after onset were accepted. After three years, patients were subdivided, according to disease evolution, into a group with polyarthritis (five or more joints affected) and a group without polyarthritis (four or fewer joints affected).

Synovial fluid was aspirated from knee joints to dryness. Two millilitres of fluid from the knee were collected into lithium heparin for white blood cell count (WBC). The remaining synovial fluid was centrifuged at 3000 rpm for

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10 min and the supernatant was stored at -20°C in multiple small volumes. Total protein was measured by Biuret's method and IL-1 β was determined using a commercially available sensitive and specific enzyme linked immunosorbent assay (ELISA) (RD Systems; limit of detection 0.3 pg ml^{-1}). Acid phosphatase and lysozyme activities were measured using colorimetric methods. Paired blood samples were collected for determination of erythrocyte sedimentation rate (ESR, Westergren method) and serum C reactive protein (nephelometry). No patient had rheumatoid factor (nephelometry) in the serum.

For statistical analysis, Student's t test was used for the differences and Spearman's rank test for the correlations.

Results

After three years, the patients were subdivided in two groups according to the type of evolution (table 1). The first group (polyarthritis) consisted of six patients and the second group (non-polyarthritis) consisted of 12 patients. The number of patients who were taking NSAIDs was equally divided between the two clinical groups. Synovial fluid determinations, along with ESR and C reactive protein, measured at disease onset in both groups were compared. No differences were observed between the polyarthritis and the non-polyarthritis groups for ESR, C reactive protein, or synovial fluid measurements other than IL-1 β (table). In synovial fluid, IL-1 β was the only variable which differed significantly between the polyarthritis and the non-polyarthritis groups, at $20.82(\text{SD } 8.71)$ v $4.19(4.73)\text{ pg ml}^{-1}$ ($P < 0.0001$). A correlation was found between basal synovial fluid concentrations of IL-1 β and the number of

affected joints at the three year follow up ($r = 0.739$, $P < 0.0001$) (figure).

Discussion

As in other inflammatory joint diseases characterised by several subgroups with differing evolution and severity, in psoriatic arthritis the type of onset has been proposed to be useful in predicting disease outcome.⁸ However, when the onset is of the monoarticular type, the prediction may be difficult. In a recent study, Jones *et al*⁴ showed that 90% of psoriatic patients with monoarthritis pattern changed in the course of the disease, with 56.4% of patients presenting with monoarthritis and 75% of those presenting with oligoarthritis went on to develop polyarthritis. An early prediction of the evolution to polyarthritis is important because of the severity of this form of psoriatic arthritis. However, predicting the outcome on the basis of the number of joints affected at onset is disappointing. In our study, 27.7% of patients with monoarthritis remained unchanged after three years, while 33.3% developed polyarthritis. The difference between our data and those reported by Jones *et al*⁴ may lie in the different period from disease onset: three months in the Jones study and six months in ours.

Because of this uncertainty, attempts to predict disease outcome by means of laboratory investigation seem justified. The most common markers for joint inflammatory activity, such as ESR and C reactive protein, have been proposed by some investigators for predicting the evolution of rheumatoid arthritis. However, in our study these markers were not useful in identifying patients with monoarthritis who later developed polyarthritis. This lack of correlation may be in part due to the frequent unreliability of ESR and C

Synovial fluid and blood findings at the disease onset and outcome of psoriatic monoarthritis

		Onset										
		Synovial fluid						Blood		Outcome		
Patients	Age (Years)	Volume (ml)	WBC ($\times 10^3$ mm $^{-3}$)	TP (g dl $^{-1}$)	AP (U litre $^{-1}$)	LZ (mg litre $^{-1}$)	IL-1 β (pg ml $^{-1}$)	ESR (mm h $^{-1}$)	CRP (mg d $^{-1}$)	Follow up (months)	Subgroup	Number of affected joints
1	28	43	13.6	4.5	4.5	11.0	33.5	18	1.2	40	polyA	10
2	24	25	28.0	4.5	11.0	10.0	10.0	42	1.0	36	polyA	6
3	50	60	5.0	4.2	10.0	15.1	15.0	20	0.8	40	polyA	6
4	42	20	20.0	4.9	4.0	7.0	24.7	18	2.9	40	polyA	7
5	56	40	7.0	4.3	16.0	17.0	26.3	28	1.9	39	polyA	8
6	42	41	14.1	4.8	9.0	8.0	15.4	15	0.8	39	polyA	6
Mean (SD)	40.33 (12.36)	33.17 (9.54)	14.62 (8.48)	4.53 (0.27)	9.08 (4.45)	11.35 (3.95)	20.82 (8.71)	23.05 (10.01)	1.41 (0.82)			
1	30	85	14.3	5.1	7.1	7.0	2.0	10	0.4	36	non-polyA	1
2	39	6	3.2	3.7	8.9	9.2	12.0	15	0.9	40	non-polyA	3
3	31	155	33.9	5.3	9.0	7.1	2.5	12	0.6	38	non-polyA	1
4	18	15	8.7	3.8	3.9	7.2	3.5	19	1.8	39	non-polyA	2
5	56	60	17.7	5.4	11.1	15.1	12.0	25	1.7	40	non-polyA	2
6	60	15	7.5	4.9	15.0	16.9	1.0	26	1.4	38	non-polyA	4
7	48	15	3.8	3.4	5.0	6.0	11.5	8	0.4	40	non-polyA	1
8	36	36	7.5	3.8	6.0	7.0	1.0	18	0.6	39	non-polyA	1
9	21	30	3.0	4.7	10.0	12.0	0.7	13	0.9	36	non-polyA	2
10	29	40	7.3	5.0	11.0	9.1	0.5	8	0.5	40	non-polyA	2
11	58	35	4.3	3.7	12.0	13.0	0.3	12	0.4	36	non-polyA	1
12	27	5	9.1	6.0	15.1	10.0	3.3	30	1.8	40	non-polyA	2
Mean (SD)	37.75 (14.51)	43.50 (42.13)	10.02 (8.72)	4.52 (0.86)	9.51 (3.61)	9.97 (3.55)	4.19 (4.73)	16.31 (7.31)	0.92 (0.54)			
P*	NS	NS	NS	NS	NS	NS	<0.0001	NS	NS			

WBC, white blood cells; TP, total protein; AP, acid phosphatase; LZ, lysozyme; IL-1 β , interleukin-1 β ; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; polyA, polyarthritis.

* Difference between the values found at the disease onset (first six months) in the PsA subgroup developing polyA and in non-polyA subgroup (Student's test).

Correlation between synovial fluid interleukin 1β (IL-1β) at onset and the number of affected joints at outcome.

reactive protein as markers of disease activity in psoriatic arthritis.⁹

Among the blood and synovial fluid variables considered in our study, only IL-1β was able to predict the evolution of monoarticular psoriatic arthritis into polyarthritis. Patients who developed polyarthritis had synovial fluid levels of IL-1β at the baseline observation that were significantly higher than in the group whose arthritis remained monoarticular or evolved to oligoarthritis or spondyloarthritis. Indeed, synovial fluid IL-1β concentrations and the number of joints involved were highly correlated. Although the small number of patients with polyarthritis may limit the validity of our conclusions, synovial fluid IL-1β seems to be a potential marker of the type of evolution of psoriatic arthritis. The reasons why IL-1β levels can permit early prediction of evolution to polyarthritis are not clear. Possibly IL-1β is more closely related to the genetic predisposition of the patients than the other markers. The observation that monocytes from both normal individuals and rheumatoid arthritis patients varied considerably in the amount of IL-1 released in response to lipopolysaccharide stimulation¹⁰ raised the possibility that monocytes may be genetically programmed to produce higher or lower amounts of IL-1 or other cytokines in response to a given stimulus. In fact, HLA-DR antigens are involved in the interaction with lipopolysaccharide on the cell surface, and high or low IL-1 and tumour necrosis factor secretory responses have subsequently been shown to be associated with certain HLA-DR

haplotypes.¹¹ Gene polymorphisms in the population have been demonstrated mainly for TNFα, but also for IL-1α, IL-1ra, and IL-1β,¹² and some of these polymorphisms are associated with certain, mainly autoimmune, diseases. Increased frequency of the less common gene polymorphisms of IL-1ra, associated with higher IL-1ra and lower IL-1α production, has also been found in psoriasis.¹³

In conclusion, since it has been widely demonstrated that some of the various psoriatic subgroups are associated with class I and II major histocompatibility complex (MHC) molecules¹⁴ and because of the HLA localisation of cytokine genes and the biological activities of the gene products, one can hypothesise that cytokine measurements in synovial fluid of psoriatic arthritis may reveal at an early stage a genetic predisposition of psoriatic patients to different types of evolution.

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