

## CONCISE REPORT

# Autoantibodies in biological agent naive patients with psoriatic arthritis

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**Background:** Anti-tumour necrosis factor  $\alpha$  (anti-TNF $\alpha$ ) treatment may be associated with the production of autoantibodies, including lupus-specific autoantibodies.

**Objective:** To investigate the prevalence of autoantibodies in biological agent naive patients with psoriatic arthritis (PsA).

**Methods:** 94 consecutive, prospectively collected, biological agent naive patients with PsA at the University of Toronto PsA clinic underwent clinical and laboratory assessment. Disease activity was assessed by the number of actively inflamed joints, and the Psoriasis Activity and Severity Index (PASI) score. Antinuclear antibodies (ANA), rheumatoid factor (RF), double stranded DNA (dsDNA), Ro, La, Smith, and RNP were tested. Descriptive statistics and non-parametric tests were used to analyse the data.

**Results:** 44/94 (47%) patients with PsA were ANA positive ( $\geq 1/40$ ); 13/94 (14%) had a clinically significant titre of  $\geq 1/80$ . Three per cent had dsDNA antibodies, 2% had RF and anti-Ro antibodies, 1% had anti-RNP antibodies, and none had anti-La or anti-Smith antibodies.

**Conclusions:** The background prevalence of ANA  $\geq 1/80$  in patients with PsA was 14%, with very few patients having specific lupus antibodies. This should serve as a baseline figure for the frequency of autoantibodies in biological agent naive patients with PsA for studies of the use of anti-TNF $\alpha$  agents.

Psoriatic arthritis (PsA) has been classified as a seronegative spondyloarthritis. The inflammatory response is thought to be immune driven, with an immunomodulatory cascade and cytokine profile qualitatively similar to that of rheumatoid arthritis.<sup>1</sup> Seven to 77% of patients with PsA have been reported to have antinuclear antibodies (ANA), which are thought to react with stratum corneum antigens.<sup>2-4</sup> Other previously described immunological abnormalities include the presence of antiepidermal keratin and anticytokeratin-18 antibodies.<sup>5</sup>

Anti-tumour necrosis factor  $\alpha$  (anti-TNF $\alpha$ ) treatment is increasingly being advocated for the treatment of PsA. Observational studies have suggested that these biological treatments are associated with the production of autoantibodies, including lupus-specific autoantibodies. Indeed, Feletar *et al* reported the development of autoantibodies in 8/16 patients with PsA treated with infliximab over a 54 week trial.<sup>6</sup> However, the background prevalence of these antibodies in PsA is not well delineated. Thus, this study aimed at investigating the prevalence of autoantibodies, including lupus-specific autoantibodies, in biological agent naive patients with PsA followed up in a longitudinal clinic.

## METHODS

### PsA clinic

The University of Toronto Psoriatic Arthritis clinic was established in 1978 and comprises the largest group of patients with PsA followed up prospectively. Patients are referred to the clinic by family physicians, dermatologists, internists, rheumatologists, other physicians, and the Psoriasis Education and Research Centre.<sup>7</sup> Patients are admitted to the PsA clinic if they have an inflammatory arthritis associated with psoriasis. Patients with nodular rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, reactive arthritis, gout, and grade 4 osteoarthritis are excluded. To date, 632 patients have been followed up prospectively and tracked in the database. Because routine clinical assessment does not include evaluation of lupus-specific autoantibodies, 94 prospectively collected, consecutive, biological agent naive patients with PsA assessed over a 2 month period (September to October 2002) were included in the current investigations.

### Clinical assessments

At each visit patients underwent a complete assessment according to a standard protocol. Clinical history included features related to PsA, concurrent illnesses, and drugs. Physical examination included a general medical examination with emphasis on skin, nails, peripheral and axial joints. The number of actively inflamed and clinically damaged joints was recorded at each visit.

### Serological assessment

Routine laboratory assessment included ANA, using indirect immunofluorescence with Hep-2 cell line as substrate (BioRad Laboratories Ltd, Canada) and rheumatoid factor (RF) by nephelometry (Latex RF test kit, Dade Behring Marburg GmbH, Germany). All patients also had double stranded DNA (dsDNA) by both a Farr assay (using calf thymus DNA, radioimmunoassay, Trinity Biotech Inc, Ireland) and enzyme linked immunosorbent assay (ELISA; ENA ELISA Test System, Zeus Scientific Inc, USA). Autoantibodies to Ro, La, Smith, and RNP were assessed by ELISA (ENA ELISA Test System, Zeus Scientific Inc, USA). Because previous studies have reported an ANA titre of 1/40, but a clinically significant positive ANA titre is usually considered as  $\geq 1/80$ , both titres are reported in this study.

### Statistical analysis

Data were described using means (standard deviation) and proportions. Patients with and without autoantibodies were

**Abbreviations:** ANA, antinuclear antibodies; dsDNA, double stranded DNA; ELISA, enzyme linked immunosorbent assay; PASI, Psoriasis Activity and Severity Index; PsA, psoriatic arthritis; RF, rheumatoid factor; TNF $\alpha$ , tumour necrosis factor  $\alpha$

**Table 1** Patient characteristics (ANA+ defined as  $\geq 1/40$  and included in group Ab+)

Feature	Total (n = 94)	Ab+ (n = 48)	Ab- (n = 46)	p Value
Men/women	52/42	25/23	27/19	0.52
Age (years)	52.4 (13.2)	52.5 (12.4)	52.4 (14.1)	0.96
Age at presentation (years)	43.6 (12.3)	43.8 (11.6)	43.5 (13.1)	0.92
Age at onset of psoriasis (years)	30.7 (13.1)	30.7 (12.8)	30.8 (13.6)	0.97
Age at onset of PsA (years)	37.1 (12.8)	37.8 (13.6)	36.3 (12.0)	0.57
Duration of psoriasis (years)	21.7 (12.0)	21.8 (13.0)	21.6 (11.1)	0.94
Duration of PsA (years)	15.3 (10.6)	14.7 (10.5)	16.0 (10.9)	0.57
Skin before joints, No (%)	70 (75)	35 (73)	35 (76)	0.72
Arthritis pattern at assessment (n):				
Distal	1	1	0	0.45
Oligoarthritis	14	9	5	
Polyarthritis	25	14	11	
Back only	5	2	3	
Back and distal	2	2	0	
Back and oligo	8	3	5	
Back and poly	39	17	22	
Active joint count	6.1 (8.1)	5.0 (6.2)	7.2 (9.6)	0.18
Clinically damaged joint count	8.8 (11.7)	10.3 (12.6)	7.2 (10.5)	0.20
Radiological damaged joint count	6.9 (8.5)	7.9 (9.6)	5.8 (7.1)	0.24
PASI score	4.6 (5.4)	5.4 (6.3)	3.7 (4.2)	0.14

Results are shown as mean (SD) unless otherwise stated.  
Ab+, autoantibodies present; Ab-, autoantibodies absent.

compared using Fisher's exact test and the Wilcoxon rank sum test.

## RESULTS

Table 1 shows the clinical features of the 94 biological agent naive consecutive patients with PsA seen over 2 months. Forty four of 94 (47%) patients with PsA were ANA positive ( $\geq 1/40$ ). However, only 13/94 (14%) had a clinically significant titre of  $\geq 1/80$ . Three per cent of patients with PsA had dsDNA autoantibodies; 1 patient had a level of 18 U/ml by the Farr method (normal  $< 7$  U/ml) and 268 IU/ml by ELISA (normal  $< 150$  IU/ml). Two patients had values of 295 and 341 IU/ml by ELISA, but did not have any dsDNA antibodies by the Farr assay. None of these patients had any features to support a diagnosis of systemic lupus erythematosus. Two per cent of patients were RF positive with titres of 39 and 290 IU (normal  $< 20$  IU). These patients clearly had PsA manifesting as polyarthritis with distal interphalangeal joint involvement, digital tenosynovitis, dactylitis, psoriasis, calcaneal spurs, and non-marginal syndesmophytes in the thoracolumbar spine. Anti-cyclic citrullinated peptide antibodies were not assessed in these patients. Two per cent of patients had anti-Ro antibodies, 1% had anti-RNP antibodies, none had anti-La or anti-Smith antibodies. There was no significant difference between patients with PsA with ANA titres of  $\geq 1/40$  and  $\geq 1/80$  compared with patients without autoantibodies for mean ages at presentation, at onset of psoriasis, at onset of PsA, disease pattern, duration, activity, damage, or Psoriasis Activity and Severity Index (PASI) score (table 1).

## DISCUSSION

The reported frequency of ANA in the general population is 31.7% at  $\geq 1/40$  serum dilution, corroborated by a second study reporting 34.9% at  $\geq 1/32$ .<sup>8,9</sup> Previous estimates of the prevalence of ANA in PsA have varied between 3% and 77%.<sup>2-4,10-13</sup> Sonnichsen *et al* initially reported a prevalence of 77%, but subsequent publications from the same group did not support their earlier results.<sup>4,14,15</sup> The ANA prevalence studies were performed over different time periods ranging from the 1970s to this current study. The discrepancy among these prevalence estimates may be secondary to variations in technique over time, use of less sensitive substrates, and variable thresholds for interpretation of ANA studies. Indeed

when we analysed the whole University of Toronto PsA cohort at their first clinic visit 23% had a positive ANA  $\geq 1/40$  and 17% had a positive RF. When the presence of ANA was examined at any time during their follow up, 53% of the patients with PsA had an ANA  $\geq 1/40$  and 21% had a positive RF after a mean follow up of 7 years. These values also represent a varied period of ANA evaluation between 1978 and 2004. Our current prospective results are most relevant to the anti-TNF era. Forty seven per cent of our patients with PsA were ANA positive ( $\geq 1/40$ ), but only 14% (13/94) had a clinically significant titre of  $\geq 1/80$ .

We then compared patients with and without autoantibodies. There was no statistical difference between patients with PsA with ANA titres of  $\geq 1/40$  and  $\geq 1/80$  compared with patients without autoantibodies for mean age at presentation, at onset of psoriasis, at onset of PsA, disease pattern, duration, disease activity, damage, or PASI score. This counters the previously held notion that there is a high incidence of ANA in adults and children with destructive joint disease.<sup>10</sup> These older studies may have been biased as they were retrospective in nature or had a smaller sample size.

Finally, in addition to the high prevalence of ANA, we found a low but clinically important prevalence of lupus-specific antibodies. The recognition of this phenomenon before the initiation of a biological agent is important. Using the University of Toronto PsA cohort, Feletar *et al* reported the development of autoantibodies in 8/16 patients with PsA treated with infliximab over a 54 week trial.<sup>6</sup> The role of anti-TNF agents in precipitating autoantibody production needs to be interpreted on the basis of the background prevalence of these autoantibodies among patients with PsA.

## CONCLUSION

In a cohort of 94 consecutive biological naive patients followed up in a longitudinal PsA clinic, we found 47% of patients with PsA were ANA positive ( $\geq 1/40$ ), 14% (13/94) of whom had a titre of  $\geq 1/80$ , which is higher than the general population. Furthermore, 3% had anti-dsDNA antibodies, 2% had RF and anti-Ro, 1% had anti-RNP antibodies, while none had anti-LA or anti-Smith antibodies. In an era where there is increasing concern about the association of autoantibodies with anti-TNF $\alpha$  drugs, these results should serve as baseline

figures for the frequency of autoantibodies in patients with PsA for studies using biological agents.

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