Annals of the Rheumatic Diseases, 1985, **44**, 215–219

Anti-Ro(SSA) positive rheumatoid arthritis (RA): a clinicoserological group of patients with high incidence of D-penicillamine side effects

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SUMMARY The clinical, laboratory, histological, and radiological manifestations of 90 Greek patients with anti-Ro(SSA) negative rheumatoid arthritis (RA) were compared with those of 15 Greek patients with anti-Ro(SSA) positive RA. Anti-Ro(SSA) positive RA patients had the same articular and extra-articular manifestations as anti-Ro(SSA) negative patients. However, they were predominantly females with lower rheumatoid factor titres and a high incidence of positive minor salivary gland biopsy specimens for Sjögren's syndrome. Finally, anti-Ro(SSA) positive RA patients frequently experienced penicillamine side effects.

Key words: Sjögren's syndrome, antibodies to Ro(SSA).

Antibodies to the soluble ribonucleoprotein (Ro(SSA))[1] extractable cellular antigen occur predominantly in patients with primary Sjögren's syndrome (SS)[2–4] and systemic lupus erythematosus (SLE),[5] particularly in seronegative lupus,[6] subacute lupus,[7] and lupus patients with histological manifestations of SS.[8] This antibody has also been described in rheumatoid arthritis (RA) patients with sicca syndrome[9] and in some patients with systemic sclerosis.[10] In a recent Greek study this antibody occurred in 25% of SLE patients, in approximately 10% of scleroderma patients, in 40% of SS patients, and in 15% of RA patients. A major feature was that anti-Ro positive RA patients experienced a high frequency of D-penicillamine side effects.[11]

In this study we compare the clinical, laboratory, histological, and radiological manifestations of anti-Ro(SSA) positive RA patients with those of anti-Ro(SSA) negative RA patients and examine the response of the two groups to penicillamine treatment.

Accepted for publication 2 November 1984.
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We confirm that anti-Ro(SSA) positive RA patients constitute a subgroup of RA patients with different serological and histological manifestations and a high incidence of D-penicillamine side effects.

Materials and methods

Sera of 105 consecutive unselected patients with definite or classical RA[12] who were diagnosed and followed up in our clinic were examined by double immunodiffusion and counterimmunoelectrophoresis techniques for antibodies to Ro(SSA) cellular antigen as previously described.[13] Antibodies were detected in 15 patients who composed the anti-Ro(SSA) positive group. The remaining 90 patients constituted the anti-Ro(SSA) negative group.

From the medical records the age, sex, disease duration, articular (arthritis of small and large joints) and extra-articular manifestations (rheumatoid nodules, splenomegaly, lymphadenopathy, pleurisy, xerophthalmia, xerostomia, and vasculitis) were recorded and compared in the two groups (Tables 1 and 2). The admission rheumatoid factor (RF) titres, serum C-reactive protein (CRP) levels, erythrocyte

Table 1 *Biographical information*

	Anti-Ro(SSA) negative	*Anti-Ro(SSA) positive*
Number of patients	90	15
Male/female	22/78	1/14
Age (years)	53·6±13·8*	49·2±9·7
Disease duration (years)	8·4±10·4	8·3±6·6
Follow up (years)	1·1± 0·6	1·2±0·5

*Mean±standard deviation.

Table 2 *Clinical diseases of the two groups of patients*

Manifestations	*Anti-Ro(SSA) negative (% with disease)*	*Anti-Ro(SSA) positive (% with disease)*
Arthritis (small joints)	24·4	20
(small and large joints)	75·5	80
Subcutaneous nodules	10	6·6
Pleurisy	7·7	13·3
Splenomegaly	3·3	6·6
Lymphadenopathy	18·8	20
Interstitial lung disease	29	22
Vasculitis	3·3	0
Xerophthalmia	16·6	26·6
Xerostomia	20	20
Lip biopsy specimens (lymphoid infiltrates)	9·5	53·8*

*$\chi^2=12·18$, $p<0·005$.

Table 3 *Laboratory results in the two groups*

	Anti-Ro(SSA) negative	*Anti-Ro(SSA) positive*
Anaemia (% with disease)	8·8	20·0
Leucopenia (% with disease)	3·3	6·6
CRP (mg/l)	42·3± 40·4*	35·8±48·3
RF (titre)	132·6±296·3	43·3±44·3†

Mean±standard deviation.
†$t=2·62$, $p<0·01$.

sedimentation rate, anaemia (Hb<9 g/dl), leucopenia (leucocytes<4×10^9/l), and thrombocytopenia (platelets<100×10^9/l) were also analysed (Table 3). Finally, effectiveness and side effects of penicillamine treatment were recorded (Table 4).

Seventeen anti-Ro negative RA patients and nine anti-Ro positive RA patients were evaluated for interstitial lung disease with a respiratory questionnaire,[14] physical examination, chest roentgenogram, spirometry, and arterial blood gas analysis. We considered the presence of positive findings in at least two of the three parameters: clinical, roentgenological, and functional, to be evidence of diffuse interstitial lung disease.

The hand *x*-rays of 30 anti-Ro(SSA) negative and anti-Ro(SSA) positive RA patients were reviewed without knowledge of other clinical or serological features using the grading system proposed by Larsen (Table 5).[15] The presence of at least one lesion of a particular grade at any location on either hand was used for grading.

Labial minor salivary glands were biopsied randomly on 42 anti-Ro(SSA) negative RA patients and 13 anti-Ro(SSA) positive patients. Haematoxylin and eosin stained slides were blindly read and graded according to Tarpley's classification.[16] Only biopsy specimens with infiltrates greater than 2+ were considered positive.

For statistical analysis the χ^2 test and Student's *t*-test were used.

Table 4 *Penicillamine treatment: effectiveness and side effects*

	Anti-Ro(SSA) negative	*Anti-Ro(SSA) positive*
Number of patients	47	13
Side effects (no. of patients)	4	8*

*$\chi^2=13{\cdot}97$, $p<0{\cdot}005$.

Table 5 *Grading of the radiological lesion in the hand x-rays in the two groups*

	Anti-Ro(SSA) negative	*Anti-Ro(SSA) positive*
Number of patients	21	9
Erosions		
<grade 3	11	1
>grade 3	10	8*

*Not statistically significant.

Results

The male to female ratio, the mean age, the disease duration, and duration of follow up of the two groups of patients are given in Table 1. The only difference was that anti-Ro(SSA) positive RA patients were predominantly females, while anti-Ro(SSA) negative RA affected males to females in a 1:3 ratio.

The incidence of articular and extra-articular manifestations and the histological changes in the minor salivary glands of the two groups of patients are given in Table 2. The pattern of arthritis and the incidence of extra-articular manifestations were similar, while anti-Ro(SSA) positive RA patients more often had lymphoid infiltrates in the labial salivary gland biopsy specimens compared with the anti-Ro(SSA) negative group.

The only laboratory parameter which differed significantly (Table 3) was the serum rheumatoid factor titre ($t=2{\cdot}62$, $p<0{\cdot}01$) which was lower in the anti-Ro(SSA) positive group. The severity of the radiological erosions tended to be greater in the anti-Ro(SSA) positive group, though this difference did not reach statistical significance (Table 5).

Forty-seven anti-Ro(SSA) negative RA patients and 13 anti-Ro(SSA) positive RA patients were treated with D-penicillamine for more than six months (mean duration follow up was 13·8 months). The D-penicillamine dose did not exceed 500 mg daily. Eight of the 13 anti-Ro(SSA) positive RA patients developed side effects within six months of treatment, consisting primarily of skin rashes, decreased taste sensation, fever, leucopenia, and proteinuria. In contrast 4/47 anti-Ro(SSA) negative RA patients developed side effects. One of these patients developed proteinuria, another myasthenia gravis, and two patients had loss of taste sensation (Table 4). Table 6 shows the side effects in the Ro(SSA) positive group in more detail.

Table 6 *Penicillamine side effects in the Ro(SSA) positive RA patients*

Patient	*Sex*	*Age*	*Duration of disease before treatment (years)*	*Duration of treatment (months)*	*Effectiveness*	*Side effects*
1	Male	50	6	5	+	Mouth ulcers rash
2	Female	62	5	1·5	+	Fever
3	Female	54	2	4	+	Butterfly rash
4	Female	60	15	1	*	Decreased taste sensation
5	Female	46	1·5	6	+	Transient skin rash
6	Female	46	4	4	+	Proteinuria, skin rash
7	Female	23	0	4	−	Pruritic rash, decreased taste sensation, leucopenia
8	Female	32	5	2	+	Pruritic rash

*Impossible to evaluate because penicillamine was discontinued.

Discussion

In the last decade studies on the antibodies to cellular (nuclear and cytoplasmic) antigens have provided additional diagnostic, prognostic, and pathogenetic clues for the autoimmune rheumatic diseases.[17] Our study showed that Greek RA patients have a higher incidence of antibodies to Ro(SSA) cellular antigen compared with that of other RA patient groups tested by the same method.[2 11]

The high incidence of antibodies to Ro(SSA) cellular antigen in Greek RA patients points towards two possibilities: either Greek anti-Ro(SSA) positive RA patients possess a genetic make up which predisposes them to develop this clinicoserological picture or the environmental factor which triggers this subset of RA is more common in Greece.

Alexander *et al.*[9] linked the presence of anti-Ro(SSA) with the development of Sjögren's syndrome, but no comment was made about the other differences between the anti-Ro(SSA) positive and anti-Ro(SSA) negative RA patients. We have also found an association with Sjögren's syndrome, but in this study anti-Ro(SSA) positive RA patients also differ in other aspects. The important observation made in this study was that anti-Ro(SSA) positive RA patients constitute a different clinicoserological group of RA patients who cannot tolerate D-penicillamine treatment. These patients, as compared with anti-Ro(SSA) negative RA patients, are predominantly females with similar clinical and radiological erosive arthritis but a higher incidence of the histological features of Sjögren's syndrome. Furthermore, rheumatoid factor titres are lower than in anti-Ro(SSA) negative RA patients. It appears that anti-Ro(SSA) positive RA patients have features which overlap with SS. SS predominantly affects females who more commonly have antibodies to Ro(SSA) antigen.[18 19] Females with SS have a high incidence of the alloantigen HLA-DR3,[20] while RA is associated with HLA-DR4.[21] We speculate that anti-Ro(SSA) positive RA patients have a combination of the genetic factors characterising these individual diseases.

Our observation that the antibody to Ro(SSA) is a marker for penicillamine intolerance in RA patients supplements the observation of Panayi *et al.*,[22] that RA patients with the HLA-DR3 alloantigen have a greater risk of developing D-penicillamine side effects. A strong association between the anti-Ro(SSA) and HLA-DR3 has been previously demonstrated.[23] Prospective immunogenetic studies on anti-Ro(SSA) positive and anti-Ro(SSA) negative RA patient groups are now under way to confirm this association. Why anti-Ro(SSA) positive RA patients and DR3 RA patients develop penicillamine side effects is a very intriguing question. Penicillamine controls RA inflammation possibly by suppressing T lymphocyte function.[24 25] It can be postulated that penicillamine-induced immunosuppression in RA patients with more aggressive autoimmune disease (lymphocytic infiltration of the exocrine glands, anti-Ro(SSA) antibody, leucopenia, etc.) further distorts the already aberrant immunoregulation of these patients, resulting in additional immunological side effects, such as skin rashes, fever, and proteinuria.

We thank Ms E Papanikolaou and Mrs J Wright for excellent secretarial assistance.

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