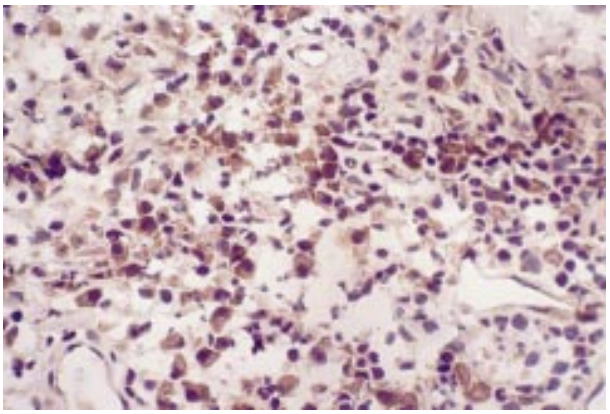

Figure 2 Immunohistochemical staining using anti-AM antibody. AM was positive in endothelial cells in the RA synovium. Original magnification ×200.

AM and ET-1 were positive around the perivascular and endothelial cells in the synovial tissue from patients with RA (fig 2, web extra fig W2). In contrast, the synovial tissue from patients with OA was negative. AM reduced constitutive production of IL6 from RA synoviocytes dose dependently. A high concentration of AM ($\geq 10^{-8}$ mmol/l) significantly reduced constitutive production of IL6 compared with a low concentration of AM ($\leq 10^{-9}$ mmol/l) ($p=0.0029$). TNFα dose dependently induced production of IL6 from RA synoviocytes (data not shown). AM did not reduce IL6 production induced by TNFα (data not shown).

Our study showed that the concentration of total and mature AM in synovial fluids was significantly higher in patients with RA than in patients with OA. In addition, by immunohistochemical staining, AM and ET-1 were shown to be positive around the perivascular area, the endothelial cells, and synoviocytes in RA synovial tissue. We have reported that osteoclasts are present in synovial tissues from patients with RA and that IL6 and soluble IL6 receptors in synovial fluids may participate in osteoclast formation.[8] Thus, IL6 is responsible for joint destruction in the presence of soluble IL6 receptor through osteoclastogenesis. In this study we showed that AM reduced constitutive production of IL6 from RA synoviocytes dose dependently. Thus, our results suggest that AM in patients with RA inhibits both synovitis and osteoclastogenesis through the inhibition of IL6 production.

Additional figures can be found on the website at www.annrheumdis.com

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Abnormal IgA levels in patients with rheumatoid arthritis

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The dominant antibody at mucous membranes and in exocrine secretions is IgA. It has been implicated in the pathogenesis of rheumatoid arthritis (RA), possibly due to immune complex formation.[1 2] If IgA is important in RA pathogenesis one might predict that patients with abnormal levels would have different characteristics from the "normal" IgA population. Limited work published on patients with high IgA levels has suggested that there is an increase in erythrocyte sedimentation rate (ESR), microscopic haematuria, and both distal interphalangeal joint involvement and unilateral sacroiliitis, even though patients fulfil the American College of Rheumatology (ACR) criteria for RA and have no other evidence of spondyloarthropathy.[3]

Primary selective IgA deficiency is the most common hypogammaglobulinaemia in the general population, with a prevalence of around 1:500.[4] It is associated with increased risk of autoimmune disease[5] and, possibly, with RA.[6] Primary IgA deficiency may result from impaired switching from class IgM to IgA.[7] Secondary IgA deficiency may be caused by drugs such as D-penicillamine, sulfasalazine, and gold. The few descriptions of primary IgA deficiency and RA have been single case studies and a longitudinal study is needed to determine if these cases represent a subgroup.

METHODS AND RESULTS

Serum immunoglobulins were measured in 352 patients (aged 18–75) attending a rheumatology outpatient department over a six year period. All patients fulfilled the ACR criteria for diagnosis of RA.[8] Patients with selective hypergammaglobulinaemia (>240 IU/ml) or primary selective IgA deficiency (<50 IU/ml) were identified as the two study cohorts. These

Table 1 Comparison of clinical features in patients with RA with normal and abnormal IgA levels. Value of the clinical feature (95% confidence interval) shown where a range is given

Variable	High IgA group (n=22)	Low IgA group (n=8)	RA controls (n=277)
Male:female	7:15	2:6	88:189
Mean age at assessment	56.0 (52 to 60)	56.8 (43 to 71)	52.1 (48 to 57)
Mean age of onset	50.0 (45 to 55)	49.8 (37 to 62)	46.3 (45 to 49)
No with 1st degree relative with RA	11 (20)	5 (7)*	99 (277)
Median Steinbrocker score	2.3 (1.9 to 2.6)	2.0 (1.4 to 2.6)	2.1 (2.0 to 2.2)
Mean tender joint count	8.9 (6.6 to 11.3)	10.0 (5.0 to 15.0)	9.0 (7.7 to 10.3)
No with nodules	3 (20)	0 (7)	53 (275)
Mean CRP	49.7 (32.0 to 67.3)	62.9 (31.7 to 94.0)	45.2 (39.7 to 50.7)
No with positive RA latex (>1/40)	11 (20)	6 (7)	168 (275)
No with positive ANF (>1/40)	5 (20)	2 (7)	54 (275)
Mean ESR over 18 months	40.6 (32.1 to 49.0)	33.0 (20.4 to 45.6)	29.9 (26.2 to 32.9)
Mean CRP over 18 months	40.8 (28.4 to 53.1)	31.5 (15.0 to 48.0)	29.1 (26.4 to 32.7)
Mean tender joint count over 18 months	7.6 (6.1 to 9.2)	7.3 (2.9 to 11.7)	7.2 (6.0 to 8.4)
Long term follow up			
Mean HAQ score	1.7 (1.1 to 2.2) (15)		1.5 (1.4 to 1.6)
No with one or more large joints replaced	8 (21)	3 (8)	87 (276)
Mean no of large joints replaced per patient	0.8 (0.2 to 1.3)	0.75 (0.2 to 1.7)	0.9 (0.7 to 1.1)
No died over 15 years	8	2	61

*OR 4.5, 95% CI 0.8 to 34.1, p=0.053 (compared with RA controls).

were compared with patients with RA (n=277) with normal IgA levels. No patients had been treated with immunosuppressant drugs at the time of IgA determination. Measurements of disease activity and disability were made at 0, 6, 12, and 18 months. A long term follow up assessment (including Health Assessment Questionnaire[9] and joint surgery) was made at about 12 years. Mortality was assessed after 15 years.

Of 352 patients, eight had a primary selective IgA deficiency, a point prevalence of 2.3%. A further three had a low IgA as part of combined immunoglobulin deficiency. Twenty two patients had a selective IgA hypergammaglobulinaemia, a point prevalence of 6.3%, with a further 28 having a high IgA combined with abnormal levels of IgG or IgM. The IgA deficient patients were more likely to have a first degree relative with RA than the overall RA population and none of this group had RA nodules compared with 29% of RA controls (table 1). There was a tendency for the high IgA group to have a higher ESR and C reactive protein over the first 18 months than the low IgA group and controls. The long term outcome data demonstrated no significant difference in joint damage, joint replacement surgery, or mortality.

DISCUSSION

As far as we know, this study is the first to examine long term outcome in patients with RA with abnormal IgA levels, and to investigate the prevalence of IgA deficiency. The latter has been associated with other autoimmune diseases, suggesting that it may predispose a person to autoimmune dysfunction. Although most cases of primary IgA deficiency are spontaneous, familial cases have been described. In our study, IgA deficient patients were more likely to have a history of RA in first degree relatives, suggesting inheritance of a predisposing factor. Though numbers were small, no similar published study was found. The lack of power caused by small sample sizes might have prevented us demonstrating more significant differences. None the less, the findings are of interest. As in previous work the high IgA group possibly had more active disease. However, there was little overall difference between the patients with abnormal IgA levels and the controls. These findings do not support a role for IgA as a key factor in the pathogenesis of RA, or its clinical presentation.

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