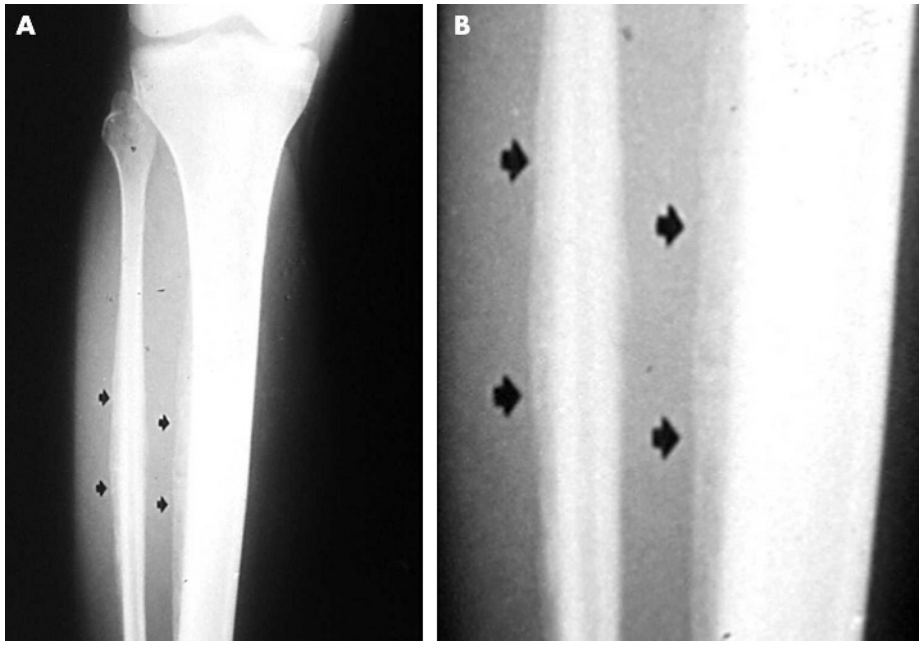

Figure 1 (A) Bone radiography of the right lower leg with periostal new bone formation (arrow). (B) A magnified view.

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Presence of rheumatoid factor and antibodies to citrullinated peptides in systemic lupus erythematosus

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Rheumatoid factor (RF) is found commonly in patients with systemic lupus erythematosus (SLE), and has been associated with a more benign disease course.[1 2] Anti-citrullinated peptide antibodies (ACPA) are more specific for rheumatoid arthritis (RA).[3–5] Several assays for ACPA detection have been developed: among others, an enzyme linked immunosorbent assay (ELISA) for anti-cyclic citrullinated peptide (anti-CCP) antibodies[3] and a line immunoassay (LIA) for antibodies to peptide A (pepA) and peptide B (pepB), two synthetic citrullinated peptides.[4] Few reports exist about the presence of ACPA in SLE. Although patients with SLE are often part of the control group when determining the specificity of ACPA for RA, SLE alone is seldom studied. Mediwake *et al* found that 3/66 patients with SLE were positive for anti-CCP1 antibodies; two of them had erosive arthritis.[6] We investigated the presence of RF and three different ACPA (anti-CCP, anti-pepA, and anti-pepB antibodies) in SLE.

Two hundred and thirty five patients with SLE, meeting American College of Rheumatology (ACR) revised criteria for classification of SLE,[7 8] were prospectively included in four European centres. The study investigated associations between symptoms and specific antinuclear reactivities and has been reported elsewhere.[9] Serum was available for further analysis in 201 patients. The male to female ratio was 25:176. The mean age was 40 years. The study was

Table 1 Characteristics of ACPA positive patients with SLE

Patient No	RF	Anti-CCP	Anti-PepA	Anti-PepB	Fine antinuclear reactivities	SE	Rx	RA crit	Clinical signs
1	1280	186	3+	3+	SSB, Ro60	0	−	−	Arthritis, proteinuria, leucopenia, lymphopenia
2	640	9	−	1+	RNP-C	0	−	+	Butterfly rash, photosensitivity, arthritis, lymphopenia
3	0	168	−	−	dsDNA	NA	NA	NA	Butterfly rash, oral ulcers, arthritis, proteinuria, cellular casts
4	0	83	−	−	SmB, dsDNA	NA	NA	NA	Butterfly rash, photosensitivity, oral ulcers, arthritis, pleuritis, leucopenia
5	80	2	−	1+	Histones, dsDNA	NA	NA	NA	Butterfly rash, arthritis, proteinuria, cellular casts
6	0	76	−	−	SmB, RNP-A, RNP-C, ribosomal P, histones	1	NA	+	Arthritis, pericarditis, pleuritis, proteinuria, thrombopenia, leucopenia, haemolytic anaemia
7	40	64	−	−	SmD, SmB, RNP-C, RNP-70k, ribosomal P	1	NA	−	Butterfly rash, photosensitivity, pleuritis, arthritis, leucopenia
8	0	58	−	−	Negative	0	NA	−	Butterfly rash, photosensitivity, lymphopenia, leucopenia
9	320	110	−	−	SmB, RNP-70k, RNP-A, RNP-C, histones, dsDNA	0	−	+	Arthritis, leucopenia
10	320	78	1+	1+	SmB, RNP-70k, RNP-A, RNP-C	0	+	+	Arthritis, pleuritis, lymphopenia
11	80	56	−	−	RNP-A, histones, ribosomal P	1	−	−	Butterfly rash, photosensitivity, lymphopenia, leucopenia
12	640	52	−	−	RNP-70k, RNP-A	0	+	+	Butterfly rash, oral ulcers, arthritis, cellular casts, proteinuria, lymphopenia, leucopenia
13	320	>1600	2+	2+	Ro60	0	+	+	Butterfly rash, arthritis, lymphopenia

RF titres and anti-CCP2 concentrations (U/ml, cut off point 42 U/ml) are given. Anti-pepA and anti-pepB antibodies were scored −,1+, 2+, or 3+. Fine antinuclear reactivities are noted. Shared epitope (SE) status is recorded as the presence of 0, 1, or 2 copies (0, 1, 2). Radiographic data (Rx) are listed as the presence (+) or absence (−) of erosions. ACR classification criteria for RA (RA crit) were noted as fulfilled (+) or not (−). Clinical symptoms being part of the ACR criteria for SLE are listed. NA= not available.

approved by the local ethics committees. Informed consent was obtained from all patients.

Fine antinuclear reactivities were determined with INNO-LIA-ANA Update (Innogenetics, Ghent, Belgium) and by indirect immunofluorescence on *Crithidia luciliae*. RF was detected using the latex fixation method (Becton Dickinson, Sparks, Maryland, USA). Titres ⩾160 were considered positive, which corresponds to a specificity for RA of 95.9% in an independent control cohort, consisting of 146 patients with rheumatic complaints but no RA (data not shown). Anti-CCP2 antibodies were detected by ELISA (Immunoscan RA, mark 2, Eurodiagnostica, Arnhem, Netherlands). A cut off value of 42 U/ml was used. Anti-pepA and anti-pepB antibodies were detected by a research LIA (Innogenetics).[4] During each run, a strip was developed using a control serum, providing a cut off intensity for each antigen line. In the control population mentioned earlier, all three ACPA had a specificity of at least 98.5%.[5] The RA associated HLA-DR shared epitope (SE) was determined with INNO-LiPA (Innogenetics).

χ^2 Tests were used to determine associations. Antibody frequencies were compared using the McNemar test.

Anti-CCP2 antibodies were found in 11/201 (5.5%) patients, anti-pepA antibodies 3 (1.5%) patients, and anti-pepB antibodies in 5 (2.5%) patients. Table 1 shows the characteristics of patients positive for ACPA. Anti-CCP2 antibodies were significantly more frequent then anti-pepA antibodies ($p = 0.008$), but not anti-pepB antibodies ($p = 0.109$). It is important to notice that in an independent control cohort all three ACPA obtained comparable specificities of at least 98.5%.[5] Apparently, the different substrates behave differently in SLE. RF was found in 26 (12.9%) patients, which was significantly more frequent than anti-pepA ($p<0.001$), anti-pepB ($p<0.001$), and anti-CCP2 antibodies ($p = 0.006$). Although the diagnosis in the ACPA positive patients was SLE, and all fulfilled classification criteria for SLE,[7 8] ACR criteria for RA[10] were also fulfilled in 6/10 evaluable patients, with 3/10 carrying an SE allele; radiographic erosions were present in 3/7 evaluable patients.

Our data suggest that the presence of ACPA does not exclude a diagnosis of SLE. It remains to be evaluated whether ACPA in SLE predispose for a chronic RA-like arthritis in this case.

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Lack of efficacy of rituximab in Felty's syndrome

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Felty's syndrome (FS) is defined by the coexistence of rheumatoid arthritis (RA), neutropenia, and splenomegaly. The mechanisms underlying the neutropenia of FS may involve both cellular and humoral immunity, with a possible role of granulocyte-colony stimulating factor (G-CSF) antibodies.[1] Various disease modifying antirheumatic drugs have been used to treat FS, but with varying success[2] as this syndrome may arise in response to the excessive immune reaction found in RA. Interest has focused recently on a new biological tool in the treatment of RA, rituximab, a chimeric monoclonal antibody specific for human CD20 which targets B lymphocytes.[3] Accordingly, we investigated here the safety and efficacy of rituximab in two patients presenting with active RA and severe and refractory FS.

METHODS AND RESULTS

Two men, were studied, aged 67 (patient 1) and 53 (patient 2) years, with a duration of RA of 6 and 11 years, respectively. FS had been diagnosed respectively 5 and 3 years ago, and RA remained active in both patients despite corticotherapy and respectively one (sulfasalazine) and two (sulfasalazine and methotrexate) previous disease modifying antirheumatic drugs. Anti-tumour necrosis factor treatment was not used because of neutropenia and the risk of severe infection. The absolute neutrophil count was persistently less than 0.8×10^9/l and complicated with recurrent sinopulmonary infections. There was no suggestion of congenital hypogammaglobulinaemia and, in particular, no sign of selective IgG2 immunodeficiency. Blood and bone marrow immunophenotyping did not disclose any features of myelodysplasia or lymphoproliferation, or any large granular lymphocytes. No other classical cause of neutropenia, such as toxicity, chronic infection, vitamin deficiency, or liver disease, was present. Anti-G-CSF (IgG) antibodies, which were determined by enzyme linked immunosorbent assay (ELISA),[1] were detected in one patient without previous administration of haematopoietic factor (G-CSF).

Owing to the presence of refractory RA associated with severe FS, rituximab was administered as an intravenous infusion at a dose of 375 mg/m^2 once weekly for 4 weeks. Concomitant treatment consisted of prednisone (15–20 mg/day) for more than 12 months in both patients and methotrexate (20 mg/week) since March 2003 in patient 2. The duration of follow up was 6 months. Rituximab was well

Table 1 Clinical and biological features of two patients with FS treated with rituximab

Normal range	DAS28 <2.6	Neutrophil count 1800–7500 $\times10^9$/l	ESR <8 mm/1st h	CRP <4 mg/l	CD19+ cells 200–400/mm^3	IgG 7.2–14.7 g/l	IgM 0.48–3.10 g/l	RF (IgM) (ELISA) <11 IU/ml	IgG anti-GCSF (ELISA) <20 IU/ml
Patient 1									
W0	6.64	460	60	20.5	149	11.2	2.63	12	28
W1	5.97	300	100	81.6	5	11.5	2.69	16.5	26
W2	7.38	360	72	55.6	1	11.7	2.5	11	26
W3	7.91	170	63	29.8	0	10.5	2.34	ND	21
W4	7.68	230	67	54.8	2	10.6	2.28	7	ND
W12	6.68	170	65	38.2	2	12.1	2.65	ND	ND
W24	6.5	150	55	25	2	11.5	2.40	ND	ND
Patient 2									
W0	7.52	150	39	90.2	67	15.8	0.97	60	0
W1	7.13	150	56	191	ND	ND	ND	ND	0
W2	5.16	140	37	98.1	ND	ND	ND	ND	0
W3	3.73	ND	ND	11.6	ND	ND	ND	ND	0
W4	2.94	50	20	24.3	9	11.1	0.41	29	0
W12	2.92	140	14	18.8	0	9.5	0.34	26.5	0
W16	2.17	410	15	41.1	0	8.42	0.58	12.5	ND
W24	1.74	260	8	8.4	1	8.14	0.24	14	ND

W0, biological data were obtained before first infusion of rituximab.
DAS28, 28 joint count Disease Activity Score; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; RF, rheumatoid factor, ND, not determined.