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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.

tolerated and efficiently controlled the clinical and biological activity of RA in patient 2, who fulfilled the American College of Rheumatology 50 response criteria and showed a marked decrease in serum levels of rheumatoid factor. However, results for FS were disappointing, because no increase in neutrophil count or modification of infection rates could be detected (table 1). In patient 1, a decrease in neutrophil count was observed at week 12, but without any clinical anomaly. Biological controls showed no modification of levels of anti-G-CSF antibodies, no appearance of anti-granulocyte antibodies, and no large granular lymphocyte proliferation.[4]

DISCUSSION

Several factors might account for the lack of efficacy of rituximab in the treatment of FS. Firstly, although different autoreactive B cells may be involved in the pathology of FS, the inability of rituximab to bind to plasma cells, which are CD20 negative, might prevent it from acting on FS. Nevertheless, the efficacy of rituximab in certain conditions associated with autoantibodies is not correlated with a reduction of these antibodies, which would suggest that in addition to autoantibody production, other roles of B cells (immunoglobulins, antigen presentation, T cell cooperation) are important in the pathogenesis of such diseases.[3] Secondly, a subpopulation of T lymphocytes having an antigranulocyte activity may exist independently of B cells in some forms of FS.[5]

In conclusion, the lack of efficacy of rituximab in these two patients with FS raises some important questions about the mechanisms responsible for FS and the best therapeutic strategy to adopt.

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Antinuclear and antiphospholipid autoantibodies in patients with peripheral arterial occlusive disease

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According to the Chapel Hill Consensus Conference, large peripheral arteries are only affected by giant cell vasculitis and, in rare cases, by polyarteritis nodosa.[1 2] Vasculitis becomes apparent through involvement of typical organs (lung, kidney, skin) or raised C reactive protein (CRP) level or erythrocyte sedimentation rate (ESR). Thus, a specific diagnostic effort to exclude vasculitis as an underlying disease in patients with peripheral arterial occlusive disease (PAOD) may be unnecessary. On the other hand, there is increasing evidence that humoral immunity may have a role in the pathogenesis of atherosclerosis.[1 2 9] Antinuclear antibodies were reported in 70% of patients with severe coronary heart disease (CHD), compared with in only 17% in the control group.[3] Thus, we prospectively studied the importance of autoantibody determination in patients with symptomatic PAOD.

METHODS AND RESULTS

Six hundred and ninety eight patients (mean (SD) age 68 (10) years) referred for treatment of PAOD between 1998 and 1999 were included. In 121 patients with PAOD (aged 61 (12) years) with a low atherosclerotic risk profile, or with rarefied distal arteries without media calcinosis, or with raised ESR or CRP not due to a local infection, the following autoantibodies were determined: antinuclear antibodies (ANA) by an indirect immunofluorescence technique; antibodies against extractable nuclear antigens (Scl-70, RNP, SSA, SSB, Jo-1, SM) by western blot; double stranded DNA antibodies, antineutrophil cytoplasmic antibodies (c- and pANCA), and antiphospholipid antibodies (cardiolipin, phosphatidylserine (APSA), and β_2-glycoprotein) by enzyme linked immunoassay. To stratify the importance of autoantibody determination all patients with increased autoantibody concentration were clinically and sonographically followed up for 24 (6) months for evidence of vasculitides or collagen disease. A multivariate logistic regression analysis was performed to evaluate the importance of CRP and ESR in patients with autoantibody concentrations above the appropriate reference value.

Thirty eight of the 121 patients had increased autoantibody concentrations (table 1). ANA were the most common autoantibodies detected in 14 patients followed by APSA in 11, and β_2-glycoprotein antibodies in 12. Patients with increased autoantibody concentration did not differ in their PAOD stages and affected segments, but in patients with increased autoantibody concentrations the ESR was higher ($p = 0.0043$). The ESR at 2 hours was associated with an odds ratio of 7.1 (95% confidence interval 1.5 to 33.8) in determination of increased autoantibody concentrations. During the follow up of 24 (6) months no vasculitides or collagen diseases could be detected by clinical examination or by nailfold capillary microscopy, pulmonary or gastrointestinal imaging in the 38 patients.

DISCUSSION

The group of 121 patients with PAOD analysed is a group selected individually from all the patients, but represents those patients in whom possible vasculitis may be present.