Letters to the Editor

Infliximab therapy in patients with secondary Sjögren's syndrome: Functional evaluation

Sirs,

Sjögren's syndrome (SS) is a chronic inflammatory disease characterised by a decrease in lacrimal and salivary secretion also called autoimmune epithelitis. The prevalence of SS is relatively high: for the primary disease it is 1/2500, while secondary Sjögren's syndrome may be found in up to 30% of patients with systemic lupus erythematosus (SLE) and in up to 20% in patients with rheumatoid arthritis (RA) (1).

It would be useful to find a therapeutic agent that inhibits the inflammatory process in the salivary glands and prevents further destruction of residual function. The therapeutic options available so far, however, such as immunosuppressive agents or corticosteroids, are limited, not highly effective and characterised by several undesirable side effects (2). Treatment is most often aimed at increasing saliva production by means of sialagogous drugs.

TNF-α plays a central role in the pathogenesis of inflammatory processes; it modulates the secretion of cytokines such as IL-8, and upregulates the expression of adhesion molecules (ICAM) on endothelial cells and of integrins on granulocytes with a consequent increase in the recruitment of polymorphonuclear cells at the sites of inflammation (3).

Steinfeld *et al*. have recently showed that infliximab may be useful for the treatment of SS (4). Studies performed so far, however, have not evaluated the effect of therapy on the function of infiltrated glands. We report our experience with the use of infliximab (Remicade®) in 4 female patients with RA and secondary SS (mean age:49, range: 34-60 years) diagnosed according to the criteria of the American Rheumatology Association (ARA). The following parameters were evaluated: complete blood cell count, renal and liver function tests, ESR, CRP, ANA, ENA, anti-dsDNA antibodies and ophthalmologic assessment with Schirmer's test and tear film break-up time (BUT). At the time of the study all patients were being treated with methotrexate or cyclosporin A and were showing disease progression. Written informed consent was obtained from all patients.

Infliximab was given according to the protocol used in the ATTRACT study: 3 mg/kg in infusion at the following time points: 0, 2, 6, 14, 22 and 30 weeks in combination with methotrexate or cyclosporin A.

To evaluate the effect of therapy on the function of salivary glands, scintigraphy was performed immediately before the beginning of treatment and was repeated after 3 months. Dynamic images were acquired after the injection of 185 MBq of 99mTcO4 for 32 minutes. 16 min after the injection lemon juice (2 ml) was given orally. Time activity curves were generated to evaluate the uptake and secretion pattern.

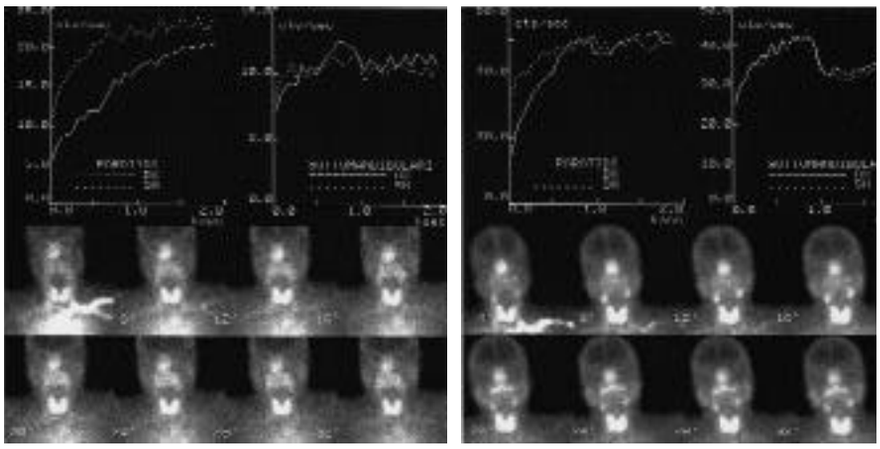

Fig. 1. Salivary gland scintigraphy in a patient with rheumatoid arthritis and secondary Sjögren's syndrome before (**A**) and after (**B**) treatment with infliximab. The uptake curves (DX: right,S:left) of the baseline study show decreased and delayed uptake and no significant response to lemon juice. The images show severe reduction of pertechnetate uptake in the all major salivary glands,comparable to background activity. The study after therapy shows, both in the curves and in the images, increase in tracer uptake and the appearance of a response to lemon juice in all major salivary glands,being particularly evident in the submandibular glands.

All patients reported a definite improvement in joint pain and dryness of the mouth and eyes. ESR and CRP decreased significantly during the treatment period. Saliva formation and secretion,as detected by salivary glands scintigraphy improved (Fig. 1). Given the low number of patients,statistical analysis was not performed. Infliximab was well tolerated and side effects were not observed. No patients had to interrupt the therapy, no opportunistic infections were observed, and no patient became anti-dsDNA antibody positive during treatment.

In conclusion our study on a small group of patients indicates that the use of infliximab, in combination with methotrexate or cyclosporin A is safe and effective in improving symptoms and salivary gland function. Sa1ivary g1and scintigraphy can monitor the efficacy of immune treatment on residual salivary function. Moreover, by repeating the scintigraphy at different time points, we may be able to identify the optimal duration and dosage of therapy for cost-effective treatment. These results suggest that infliximab could have a role in the treatment of patients with Sjögren's syndrome and studies in a larger series of patients are needed.

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Bleeding tendency and relapsing small vessel thromboses in a patient with secondary antiphospholipid syndrome

Sirs,

We would like to present the complex clinical case of a female patient who originally suffered from both haemorrhagic diathesis due to multiple coagulation defects and primary antiphospholipid syndrome (PAPS), was later diagnosed with systemic lupus erythematosus (SLE), and finally succumb-

ed to catastrophic APS (CAPS). The precipitating factors for CAPS are debatable.

Since 1968, when the patient was 16, a bleeding tendency attributed to a decreased activity of coagulation factors II and V and the presence of inhibitors to factor IX had been apparent. The factor V deficiency was not further defined. The patient has been regularly taking the antifibrinolytic agent cyclocapron during menses.

Her diagnosis of PAPS was established in 1989 (age 37 years), based on the following clinical and laboratory criteria: a history of one stillbirth and one foetal loss, livedo reticularis and highly increased IgG aCL (1). A mild decline in renal function was noted in 1992, followed by moderate hypertension in 1994.

In April 1996, SLE was diagnosed due to Coombs positive haemolytic anaemia, thrombocytopenia, positive ANA and anti-dsDNA antibodies, renal affection (creatinine 263 mmol/L) with haematuria and proteinuria, arthritis and arthralgias (2). Echocardiography showed hypertensive myocardial changes and aortic and mitral valve lesions. Treatment with a high dose of methylprednisolone was instituted with rapid improvement. The dose was gradually tapered to the maintenance dose of 8 mg o.d. Renal biopsy was abandoned because of haemorrhagic diathesis. However, upon steroid therapy the bleeding disorders vanished and treatment with the antifibrinolytic was withdrawn.

The patient was readmitted to our hospital in April 1997 because of rapidly progressive renal insufficiency (creatinine 470 mmol/L on admission) and congestive heart failure. The results of immunoserological tests were as follows: highly positive IgG aCL, positive LA and ANA, negative anti-ENA and anti-dsDNA, positive direct and indirect Coombs test, normal C3 and slightly lowered C4 complement component. Echocardiography revealed pericarditis, dilated and poorly contractile left ventricle and haemodynamically significant aortic stenosis and regurgitation. Despite aggressive treatment, including haemodialysis, she died a few days later. Heart rupture found on autopsy was considered the direct cause of death.

Pathomorphologic changes were consistent with CAPS. Additionally, in several organs, including the kidneys, signs of chronic thrombotic microangiopathy were seen (3). Glomerulonephritis was estimated as WHO class IIA (4). No overt vasculitic lesions or granular vascular immune complex deposits, typical of SLE, were noted.

In analysing the clinical course, three points deserve to be noted. First, the patient had concomitant bleeding disorders and APS for a long period of time. A paradoxical bleeding tendency in patients with antiphospholipid antibodies has already been reported (5, 6). Second, despite the fact that the patient later fulfilled the ARA diagnostic criteria for SLE (secondary APS), post-mortem histomorphological changes suggested that a thrombotic tendency related to APS was the major cause of renal and heart failure. Anticoagulant therapy was not introduced for the treatment of APS due to the patient's haemorrhagic diathesis.

Third, it is not clear why upon steroid treatment the bleeding disorders disappeared and the thrombotic tendency escalated. It may be speculated that decreased activity of coagulation factors II, V and IX were secondary to the autoantibodies directed towards them, and that steroids suppressed their production (7). Additionally, it is also possible that the deficiency of factor V was due to patient's pseudohomozygosis for activated protein C resistance (APC-R), which paradoxically predisposed to thrombosis (8).

The ultimate precipitating factor for CAPS was most probably infection, as in the majority of such cases (9, 10). In fact, autopsy confirmed bilateral pneumonia, already suspected clinically. This clinical case illustrates the complexity of haemostatic disorders that may coexist in patients with secondary APS, and the potential danger of steroid therapy in such circumstances.

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A case of Takayasu's arteritis with parenchymal pulmonary involvement associated with spondylarthropathy

Sirs,

We report a case of a woman affected by Takayasu's arteritis (TA) with pulmonary parenchymal involvement and spondylarthropathy (SpA). The association of TA with SpA has been already reported, but pulmonary involvement was found in only one of these patients (1). Although the large and medium branches of the pulmonary arteries may be affected in TA (2), pulmonary parenchymal involvement, caused by vasculitis of the small and medium vessels, is very rare (3).

A 17-year old Caucasian female presented in June 1999 with a twelve-month history of arthralgia of her knees, shoulders and bilateral buttock pain. There was tenderness over her sacroiliac and sterno-costal joints. ESR was 57 mm/1sthour, CRP 2.4 mg/dl; antinuclear antibodies, rheumatoid factor and-HLA-B27 were negative. Radiographs showed grade-3 bilateral sacroiliitis (4) and erosive pubitis. Other causes of SpA were excluded and her condition was classified as undifferentiated spondylarthropathy (4). She was started on sulphasalazine 1 g *bid*.

At her periodic review (August 2001) she reported no joint symptoms, but mild exertional dyspnoea and remitting neck pain. On examination radial pulses were absent, BP was undetectable in her upper limbs and a right carotid bruit was audible; ESR was 33 mm/1sthour, CRP 2.1 mg/dl. Arteriography demonstrated stenosis of the brachio-