factor, demonstration of its presence in the synovial tissue of patients with RA,[4] and suppression of collagen induced arthritis by its inhibitor suggest that it may have a role in the angiogenesis of RA.[5] TNF up regulates the production of VEGF.[6] No data are available on the effect of sTNFr on VEGF. Thus we studied the effect of sTNFr monotherapy on VEGF and MMPs in patients with RA.

Ten patients with RA (all women, nine seropositive, mean age 35.2 years, mean duration of disease 6.2 years)[7] were studied. They received 25 mg of sTNFr (etanercept) twice weekly subcutaneously. No other disease modifying antirheumatic drugs were given. Plasma samples were collected at baseline and then weekly for the first 1 month and monthly thereafter for the next 3 months. Clinical assessment included 28 swollen joint count, 28 tender joint count, duration of early morning stiffness, physician's and patient's global assessment, and Health Assessment Questionnaire. VEGF, MMP-1, and TIMP were measured by sandwich enzyme linked immunosorbent assay (ELISA; R&D, Minneapolis, USA). C reactive protein was measured by turbidimetery. Non-parametric tests were used for correlation and intergroup comparison.

There was a good correlation between the levels of C reactive protein and those of VEGF ($p<0.001$) and MMP ($p<0.002$). After treatment the levels of MMP fell significantly (fig 1A) as compared with baseline values as early as 2 weeks after the start of treatment. The levels of TIMP-1 however remained unchanged (fig 1B). VEGF levels also fell but to a lesser degree (fig 1C). These effects paralleled changes in clinical parameters like tender joint count or swollen joint count (figs 1D and E).

MMPs cause tissue destruction because of their proteolytic abilities. Our data of more than 50% decrease in MMP-1 within 2 weeks of the start of treatment suggest that TNF blockade down regulates production of MMPs. Recently, sTNFr treatment has been shown to reduce MMP expression in the synovial membrane.[3] Anti-TNF antibody has also been shown to have similar effect on MMPs.[8] An ideal treatment will be one which increases levels of TIMP and reduces levels of MMP. Unfortunately, most data,[3 8] including ours, show that TIMP levels are either not affected or are reduced to a smaller degree than MMPs with TNF blockade. Even this change is likely to tilt the balance in favour of TIMP and thus prevent action of MMPs and tissue damage.

As far as we know, our study is the first to demonstrate the effect of sTNFr on plasma VEGF in patients with RA, even though the effect was mild. Reduction in serum VEGF levels was also reported with the use of anti-TNF antibody.[6] However, serum VEGF levels may be confounded by VEGF released by platelets, which may increase with the thrombocytosis of inflammation. Hence we measured plasma VEGF levels.

Thus sTNFr has significant and early effect on mediators of tissue damage.

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Cytokine profile of bronchoalveolar lavage in systemic sclerosis with interstitial lung disease: comparison with usual interstitial pneumonia

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Interstitial lung disease (ILD), which often develops in systemic sclerosis (SSc), is associated with a better prognosis than idiopathic usual interstitial pneumonia (UIP) because only a limited number of patients with SSc progress to end stage fibrosis.[1 2] Mechanisms driving the fibrotic evolution of ILD are still poorly understood,

Table 1 IL8, IL10, and IL18 BALF levels in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD) or usual interstitial pneumonia (UIP), and in control subjects

	SSc-ILD	UIP	Controls
IL8 (pg/ml)	24.5 (6.5–46.6)*	34.95 (19.4–52.2)*	13.7 (8.8–16.5)
IL10 (pg/ml)	1.5 (0.0–6.25)*	0.50 (0.3–0.5)	0.0 (0.0–0.0)
IL18 (pg/ml)	100.7 (42.1–153.8)	56.4 (19.9–114.4)	47.6 (24.5–214.3)

*Significant difference with respect to controls (Mann-Whitney U test, $p \leqslant 0.05$).
Data are expressed as pg of cytokine per ml of recovered BAL fluid. Median values and 25th–75th centile intervals are shown.

but, recently, on the basis of animal models, a pathogenetic role has been ascribed to an imbalance in the local Th1/Th2 response, with an expansion of the Th2 profile.[3]

METHODS AND RESULTS

We studied the cytokine profile of bronchoalveolar lavage fluid (BALF) of 28 patients with SSc-ILD (6 men, 22 women; mean (SD) age 50.3 (8.9) years). All patients with SSc satisfied the preliminary American College of Rheumatology (ACR) criteria for classification of the disease,[4] and respiratory disease was defined on the basis of functional tests and high resolution computed tomography findings as at least grade 1 severity, according to the disease severity scale for SSc.[5] Seven (25%) patients with SSc had limited and 21 (75%) diffuse disease. All were positive for antinuclear antibodies; 18 for anti-topoisomerase I, and one for anti-RNA polymerase I and III. Results were compared with those obtained in 13 patients with UIP (10 men, three women; mean (SD) age 56 (16.8) years; all newly diagnosed, previously untreated patients); and nine normal controls (seven men, two women, mean (SD) age 42.7 (12.1) years).

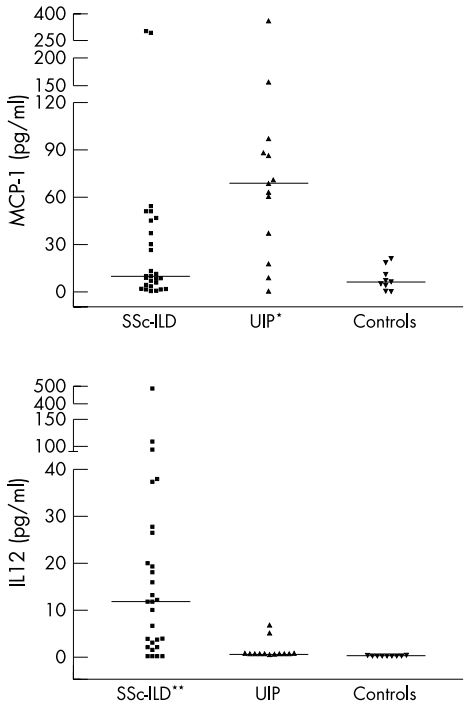

Figure 1 MCP-1 and IL12 BALF levels in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD) or patients with usual interstitial pneumonia (UIP), and in control subjects. Data are expressed as pg of cytokine per ml of recovered BALF. Median values and 25th–75th centile intervals are shown. *Significant difference with respect to controls (Mann-Whitney U test, $p \leqslant 0.05$); **significant difference with respect to both UIP and controls (Mann-Whitney U test, $p \leqslant 0.05$).

The following cytokines were assessed on concentrated (by ultrafiltration) BALF: two proinflammatory chemokines interleukin (IL)8 and monocyte chemotactic protein-1 (MCP-1), two Th1 related factors IL12 and IL18, and one anti-inflammatory Th2 related cytokine IL10. Data, expressed as medians (25th–75th centile) were analysed with the Mann-Whitney U test (Kolmogornov-Smirnov test, $p \leqslant 0.05$).

Table 1 shows that BALF levels of IL8 were increased in patients with SSc-ILD and UIP in comparison with controls ($p = 0.05$ and $p = 0.004$). In addition, a trend towards an increase of IL8 levels in UIP compared with SSc-ILD was found ($p = 0.07$). Levels of MCP-1 were markedly and significantly raised only in patients with UIP in comparison with both SSc-ILD and controls (fig 1). For the Th1 related cytokines, IL18 values did not differ significantly among the groups (table 1), but higher levels were detected in control BALFs. These findings suggest a relatively high constitutional release of IL18 in physiological conditions. On the contrary, IL12 was almost undetectable in BALF from controls, but it was markedly increased in patients with SSc-ILD ($p = 0.0008$) (fig 1). Moreover, IL10 levels were higher in SSc-ILD than in controls ($p = 0.02$; table 1). Finally, no differences in the BALF cytokine levels were seen among patients with SSc-ILD according to their clinical or serological subset ($p > 0.05$).

DISCUSSION

Data presented here suggest the presence of a different BALF cytokine profile in SSc-ILD than in UIP. In particular, we found that patients with SSc-ILD had increased levels of IL12, a cytokine shown to attenuate bleomycin induced lung fibrosis in rats.[6 7] This might suggest a protective activity of IL12 with respect to the fibrotic evolution in SSc-ILD. In addition, we found that MCP-1 was significantly raised in UIP BALF but only slightly increased in SSc-ILD. Moreover, MCP-1 BALF levels correlated significantly ($p = 0.004$) with BALF eosinophil counts that are known to be a prognostic factor in SSc-ILD. In fact, MCP-1 has been shown to provoke chronic fibrogenic lung inflammation in animal models of lung fibrosis induced by bleomycin, radiation, or FITC.[8–10] Finally, levels of the anti-inflammatory IL10 were higher in SSc-ILD than in controls.

In conclusion, the BALF cytokine profile in SSc-ILD seems to express a more favourable balance between fibrotic (MCP-1) and anti-fibrotic or anti-inflammatory factors (IL12 and IL10) than that in UIP, and this may account for the better prognosis of interstitial damage associated with SSc. Further longitudinal studies are necessary to confirm

whether a different cytokine phenotype might be considered predictive of clinical outcome.

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Gout in liver transplant patients receiving tacrolimus

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Hyperuricaemia and gout have been reported in organ transplant patients treated with cyclosporin, an immunosuppressant inhibiting calcineurin.[1 2] Tacrolimus, another calcineurin inhibitor, is nowadays widely used in place of cyclosporin. Hyperuricaemia has been seen in patients receiving tacrolimus[3] but, to our knowledge, only rare cases of gout have been mentioned so far.[4]

Since 1998, 31 patients (22 men, 9 women; current mean age 53 years (range 24–67)) have regularly received tacrolimus for immunosuppression after liver transplantation in the surgical department of Lausanne University Hospital. The mean duration of follow up with tacrolimus treatment was 27.8 months (range 7–57).

In two cases the first manifestations of gout appeared after liver transplantation when these two patients were receiving tacrolimus for immunosuppression.

CASE REPORTS

Patient 1

A 31 year old man received a liver transplant in November 1998. He was treated with tacrolimus at a daily dose of 6 mg, as well as prednisone. He also was receiving treatment with furosemide. In July 1999 he presented episodes of acute arthritis of the right wrist and both elbows. The serum uric acid level was 421 µmol/l and creatinine 105 µmol/l. Gout was not diagnosed until March 2000, when he started to have severe compression of the right median nerve, owing to a voluminous mass located in the anterolateral part of the wrist (fig 1A), which was suspected to be tumoral. Histological examination of the resected material revealed typical gouty tophi (fig 1B). After surgery, he was treated with allopurinol and colchicine. To treat hypertension, he received furosemide and losartan; this latter drug was chosen because it has been shown to have uricosuric properties[5] and has proved to be beneficial in hypertensive gouty subjects.[6]

Patient 2

A 25 year old woman who received a transplant in 1996 for type 1 A glycogen storage disease has been treated with tacrolimus since then. Attacks of podagra and arthritis of the left wrist occurred 5 years later when she was receiving tacrolimus 4 mg/day. No tophi could be seen. The serum level of uric acid was 452 µmol/l and of creatinine 190 µmol/l. From the time of diagnosis she has been receiving allopurinol 100 mg/day, and the attacks of gout have resolved.

DISCUSSION

In a large series of patients who had received a liver allograft, hyperuricaemia was detected in about half, in both cyclosporin and tacrolimus treated patients.[4] It was assumed that both drugs can impair renal uric acid excretion.[3 4]

In our series of liver transplant recipients receiving tacrolimus, gout was directly related to tacrolimus treatment in two. In case No 1, large tophaceous deposits developed