Correspondence

5-Fluorouracil in progressive systemic sclerosis: Is it safe?

SIR, Satisfactory drug treatment for progressive systemic sclerosis (PSS) is not available. A recent report by Casas *et al* presented evidence of the efficacy of 5-fluorouracil (5-FU) in this disease.¹ This report prompted us to undertake a similar trial. Here we report some major untoward side effects due to 5-FU within a short period of starting this trial, seen at doses even less than those used by Casas *et al*.¹

So far 11 patients with PSS have been entered into this trial. Patients were previously on various drug regimens, including D-penicillamine, nifedipine, captopril, high dose pulse dexamethasone or low dose daily oral prednisolone, or both. They had, however, not shown any significant improvement. After a wash out period of two weeks each patient was given 5-FU in a dose of 10 mg/kg daily for the first five days (instead of 12.5 mg/kg daily used by Casas *et al*).¹ This was followed by four doses of 10 mg/kg on alternate days. Subsequently the patients received a weekly maintenance dosage of 10 mg/kg. So far 11 patients have been given five to 20 pulses of 5-FU. Major toxicity developed in three patients necessitating discontinuation of the treatment. One of these, a 45 year old woman, developed severe headache, anorexia, nausea, and vomiting after the third pulse. Her blood counts were normal at this stage. After the seventh pulse she developed extensive mucosal ulcers, profuse bloody diarrhoea with dehydration, high fever, epistaxis, and septicæmic shock. On that day she showed severe pancytopenia (total white blood cell count $0.4 \times 10^9/l$, platelet count less than $50 \times 10^9/l$, and haemoglobin 60 g/l). Complete blood counts were normal immediately before this pulse. Severe diarrhoea persisted with a clinical picture resembling pseudomembranous colitis, but the stool culture was negative. She recovered after prolonged supportive therapy in addition to parenteral antibiotics and high dose corticosteroids.

Two other patients developed marked weakness, severe bloody diarrhoea, mucosal ulceration, abdominal pain, severe alopecia, and diffuse erythematous lesions on the face after the fifth pulse. These episodes lasted for eight to 10 days. Both patients recovered when treatment was discontinued and combined antibiotics and symptomatic treatment were administered.

An additional six patients showed minor side effects, including reversible leucopenia (in one patient after three pulses), mild thrombocytopenia (in two patients after 15 pulses), vomiting (two patients), anorexia (four patients), mild diarrhoea (two patients), skin pigmentation (two patients after the induction phase), and headache (three patients in the induction phase). Only two of the 11 patients did not have any side effects.

The duration of the present study is too short to assess

the beneficial effects of 5-FU, but these observations indicate that 5-FU in the recommended dose is probably not safe. We therefore recommend the reappraisal of the dosage schedule of 5-FU in patients with PSS. An important observation was that the three cases most severely affected developed toxicity after five to seven pulses (induction phase). Some modification in the dosage and duration of the induction phase in this schedule might therefore have reduced toxicity.

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Reference

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SIR, The observation by Malaviya *et al* that serious toxicity may result from the use of 5-fluorouracil (5-FU) in the treatment of scleroderma is important and emphasises the potential harm that may result from the use of an unproved treatment. In our initial study we observed no serious toxicity.¹ From the information available we cannot readily explain why these investigators observed such serious toxicity and we did not. The role of genetic factors, nutritional status, comorbid conditions, total drug dose, etc remains speculative.

At present we are conducting an international collaborative double blind study. For this study our original protocol has been modified to comply with the currently accepted standards for 5-FU administration in the USA.^{2,3} Currently, we give 12 mg/kg daily for four days, 6 mg/kg every other day for four doses, then 12.5 mg/kg for the weekly maintenance dose. No single dose exceeds 1000 mg. Furthermore, if significant toxicity occurs the drug treatment is withheld until the toxicity resolves and is restarted at 75% of the original dose. If toxicity recurs the dose is reduced further or the drug discontinued.

To date 33 patients have completed the study, of whom 21 received 5-FU; an additional 15 patients completed the inductive phase (a total of eight doses) but did not continue in the study for a variety of reasons (finances, side effects compliance, etc). Although side effects have been observed with increased frequency in the 5-FU treated patients, they have been much less severe than those described by Malaviya *et al*. This may be in part owing to the dose modifications mentioned above.

These authors state that 'the recommended dose (of 5-FU) is probably not safe'. Recommended by whom? We have made no recommendations for the use of 5-FU in the treatment of scleroderma. Our findings were stated as preliminary and published to encourage further controlled

studies. 5-FU remains an unproved treatment for scleroderma and its use outside properly conducted clinical studies is strongly discouraged. The report of Malaviya *et al* emphasises that no matter how promising a new treatment appears it must be critically evaluated before patients are subjected to its potentially harmful effects.

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Sarcoidosis or primary Sjögren's syndrome?

SIR, We were interested to read the case report by Melsom and coworkers.¹ We have been following up a patient who presented a similar difficult diagnosis.²

A 59 year old woman was seen in 1983 complaining of a recurrent non-deforming, non-destructive arthritis since 1970. The sicca syndrome was obvious, with a Schirmer's test of 0, positive rose bengal staining, and keratoconjunctivitis. Antinuclear antibodies were not detected and latex agglutination was negative. Despite a normal erythrocyte sedimentation rate there were 20×10^9 cells/l (89% lymphocytes) in the synovial fluid of the left knee, and the synovial biopsy specimen was considered non-specific in spite of the presence of few epithelioid cells.

Clinically, the differential diagnosis lay between sarcoidosis and Sjögren's syndrome. As the labial gland biopsy specimen showed acinar atrophy with fibrosis and a mild infiltration of lymphocytes Sjögren's syndrome was suggested.

Two years later cervical lymph adenopathy developed, and biopsy showed non-caseating granulomata with multinucleate giant cells. The Mantoux test was negative, the angiotensin converting enzyme raised, and scintigraphy with gallium showed mediastinal and splenic uptake.

This patient presented in a similar fashion to the one reported, but the prolonged course of the articular disease with sicca syndrome before the appearance of the cervical adenopathy is in contrast.

We confirm that sarcoidosis may mimic Sjögren's

syndrome in the absence of features suggestive of sarcoidosis in the lip biopsy specimen.

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SIR, We have read the report of Melsom *et al* of a patient with sarcoidosis and a lip biopsy consistent with Sjögren's syndrome (SS).¹ Although no granulomata were present in minor salivary gland histological sections, the authors concluded that early involvement of these tissues by sarcoid mimicking SS was the most likely explanation for this finding. We have recently encountered a patient with similar clinical and histological features, in whom, however, we reached different conclusions.

The patient was a 62 year old woman with a 12 year history of recurrent polyarthralgia, anterior uveitis, and skin lesions suggestive of erythema nodosum. During the past three years she had presented a typical sicca syndrome. When she was referred to our clinic physical examination was normal except for the absence of saliva around the base of the lingual frenulum. Schirmer's test showed decreased lacrimation (5 cm). Lip biopsy disclosed periductal fibrosis, acinar atrophy, and a moderately intense but diffuse lymphoplasmacytic infiltrate, consistent with histological class III (3+) on Tarpley's classification.² Routine laboratory studies were normal and immunological markers were not detected. Chest radiographs and thoracic computed tomography showed bilateral hilar adenopathies. This posed the differential diagnosis between lymphoma and sarcoidosis in a patient with SS. The presence of uveitis did not necessarily favour sarcoidosis as it has been described in patients with SS.³ A mediastinoscopy directed biopsy of one of these nodes was thus performed. The pathological study showed multiple non-caseating granulomata as did a bronchoscopy directed bilateral transbronchial biopsy. The Mantoux test was negative. Mycobacterial and fungal microbiological studies were negative. We reviewed the lip biopsy sections thoroughly but still found no evidence of sarcoid infiltration.

Lip biopsy is an established method for histological confirmation of sarcoidosis.⁴ Even though the presence of granulomata is indispensable for this purpose, sarcoidosis may in some cases show non-specific findings, such as scattered lymphoplasmacytic infiltrates and multinucleated cells.⁵ Both of these may also be encountered in SS.⁶ Giotaki *et al* recently reviewed 60 lip biopsy specimens from 32 patients with sarcoidosis and 28 patients with SS.⁵