Correspondence

Desensitisation to allopurinol

SIR, We read with interest the report by Kelsey *et al* of successful desensitisation to allopurinol.¹ We have recently treated a patient with massive tophaceous deposits, but no attacks of acute crystal synovitis, using this regimen, with useful lowering of uric acid and regression of tophi. The patient had chronic renal impairment which rendered alternative hypouricaemic therapy ineffective.²

The patient, a 73 year old woman, was found to have nodal osteoarthritis and hypertension in 1969; the serum urate at this time was 0.4 mmol/l. In 1963 after hip replacement she was referred for a rheumatological opinion with symptoms of median nerve compression, almost certainly due to walking stick pressure, and was found to have large tophaceous deposits in her fingers. She had a history of several years congestive cardiac failure treated with diuretics. When subsequently admitted for median nerve decompression her uric acid was 0.8 mmol/l, urea 24.4 mmol/l, and creatinine 185 µmol/l. Treatment with allopurinol 300 mg/day was started. Over the next two weeks she was unwell with malaise, gastrointestinal upset and subsequently developed a pruritic macular rash over the trunk and limbs. Her uric acid had fallen to 0.44 mmol/l, but the renal function was unchanged. Allopurinol was stopped, and her rash and other symptoms resolved. A further attempt to initiate allopurinol at 100 mg/day resulted in a prompt recurrence of the rash.

Over the next two years azapropazone and probenecid were tried without benefit, indeed her hyperuricaemia and tophi slowly enlarged and became increasingly painful. In 1986 she was admitted for management of an infected foot ulcer aggravated by subcutaneous tophi and peripheral oedema. Investigation showed uric acid 0.51 mmol/l, urea 18.8 mmol/l, creatinine 155 µmol/l. Attempts to control the oedema with increased diuretic therapy promptly increased her uric acid and caused the tophi to enlarge and ulcerate. It was decided to make a further attempt to reinstitute allopurinol, using the desensitisation regimen of Meyrier.³ This was completed without any recurrence of side effects, and she was eventually maintained on 200 mg/day. On this regimen her uric acid fell to 0.46 mmol/l and her tophi healed and have regressed markedly; her renal function is stable.

As Kelsey *et al* point out,¹ the significant incidence of adverse reactions with allopurinol limits its use. Such reactions are more common in patients with renal impairment, possibly because of greater accumulation of the allopurinol metabolite oxypurinol.⁴ It is possible that the initial adverse reaction in our patient was in part due to the high initial dose of allopurinol, and this illustrates the importance of starting the drug in low doses in the presence of renal impairment. Our case, however, also shows that should such a reaction recur on a low dose rechallenge, the patient can still be successfully desensi-

tised to the drug. As the source of stock preparations of allopurinol held by the hospital pharmacy differed in 1986 from 1983 we cannot exclude the possibility that there could be a difference in excipients to account for the absence of drug sensitivity in 1986. We agree that this regimen, though not without precedent,⁵ is a useful measure and deserves wider application when non-life-threatening sensitivity to allopurinol has occurred. It is particularly relevant in the context of renal impairment when other hypouricaemic agents usually prove ineffective.

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Oral methotrexate in the treatment of rheumatoid arthritis: Allergic agranulocytosis?

SIR, We have recently observed a patient who developed agranulocytosis after oral administration of methotrexate (MTX) in the treatment of rheumatoid arthritis (RA).

This 61 year old man had a 10 year history of progressive seropositive RA. The RA had been previously treated with auranofin, which had been discontinued because of an allergic exanthema. In September 1986 he was given a trial of oral MTX to control the progression of his disease. A dose of 15 mg MTX was to be given weekly. The patient, however, was accidentally administered 45 mg MTX over three days. Other concurrent medications were fluocortolone, ketoprofen, and oral ferrous sulphate.

Fig. 1 shows the peripheral neutrophils and precursors of this patient before, during, and after the administration of

Fig. 1 Number of peripheral neutrophils and precursors before, during, and after the administration of oral methotrexate. The dose of 15 mg MTX was given on three consecutive days with the first dose on day 0 (marked with three arrows). (PMN=polymorphonuclear cells; PB=peripheral blood.)

oral MTX. Platelets remained above $180 \times 10^9/l$ and haemoglobin above 98 g/l throughout this period.

Fourteen days after the first dose of MTX, the patient was admitted to hospital after presenting with diarrhoea, vomiting, severe stomatitis, and complaints of a fever the night before admission. On the first hospital day the patient developed pneumonia and sepsis due to *Pseudomonas aeruginosa*, which responded well to intravenous piperacillin and tobramycin. Bone marrow cytology from the third hospital day showed a hypercellular marrow with an increased percentage of immature white cells. He was discharged in good condition on the 14th hospital day.

After discharge, blood was taken for a lymphocyte transformation test, the results of which are shown in Table 1. Stimulation with MTX alone induced only a slight lymphoproliferation of blood mononuclear cells (MNCs). Leucovorin alone did not affect spontaneous incorporation of [3 H]thymidine into the DNA of the lymphocytes. In contrast, strong lymphoproliferation occurred when MNC cultures were stimulated with low dose MTX (0.5 µg/ml) and supplemented with a tenfold dose of leucovorin (5 µg/ml) to overcome the toxic effect of MTX. Higher doses of MTX with comparable doses of leucovorin led to significantly lower proliferative responses. The MNCs of a patient with RA who had received oral MTX for several months without side effects served as a negative control. The MNCs of this patient did not show any in vitro lymphoproliferation to MTX even when leucovorin was added in higher doses to the cell culture. The positive control experiments with common mitogens such as phytohaemagglutinin, concanavalin A, and pokeweed mitogen showed comparable proliferative responses in both patients.

Pancytopenia¹ and immune haemolytic anaemia² are known adverse effects of MTX therapy. Earlier reports indicated that the haematological side effects of MTX were generally dose related.^{3,4}

Table 1 Lymphoproliferation of blood mononuclear cells after stimulation with methotrexate (MTX), phytohaemagglutinin (PHA), concanavalin A (con A), and pokeweed mitogen (PWM)

Stimulus	Incorporation of [3 H]thymidine into DNA (Δ cpm $\times 10^3$) [*]	
	Patient 1 [†]	Patient 2 [‡]
0.5 µg MTX	3 237 (1621)‡	1 365 (383)
0.5 µg Leucovorin (LV)	785 (222)	924 (272)
0.5 µg MTX+0.5 µg LV	18 270 (2985)	1 872 (386)
0.5 µg MTX+5 µg LV	25 996 (3882)	1 846 (432)
1 µg MTX	2 292 (175)	886 (108)
1 µg LV	360 (124)	253 (102)
1 µg MTX+1 µg LV	3 280 (394)	1 227 (383)
1 µg MTX+5 µg LV	20 091 (2075)	1 482 (264)
5 µg MTX	3 080 (1224)	1 222 (468)
5 µg LV	898 (216)	927 (232)
5 µg MTX+5 µg LV	17 569 (2073)	1 339 (227)
PHA 12.5 µg/ml	22 333 (2513)	28 344 (3142)
Con A 25 µg/ml	16 727 (2675)	21 742 (2348)
PWM 5 µg/ml	16 230 (1226)	17 878 (2176)

^{*} Δ cpm=cpm of stimulated cultures-cpm of unstimulated cultures.

[†]Patient 1: agranulocytosis after MTX therapy; patient 2: receiving MTX therapy without side effects.

[‡]Data are expressed as mean (SD) of net cpm.

Many case reports of pancytopenia after treatment with low dose oral MTX have appeared.^{5,6} To our knowledge there have been no reports of haematological adverse reactions to MTX due to an allergic pathogenesis.

In our patient we cannot exclude the toxic effects of MTX as the cause of his agranulocytosis, especially in light of the erroneous dosage. The results of the lymphocyte transformation test, however, present at least partial evidence for an allergic pathogenesis.

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