Combined suppressive drug treatment in severe refractory rheumatoid disease: an analysis of the relative effects of parenteral methylprednisolone, cyclophosphamide, and sodium aurothiomalate

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SUMMARY A trial was designed to assess the effects of intramuscular sodium aurothiomalate or intravenous cyclophosphamide, or both, in combination with intravenous 'pulse' methylprednisolone in severe intractable rheumatoid arthritis. Thirteen patients with severe, active rheumatoid arthritis, unresponsive to conventional therapeutic regimens showed improvement in synovitis after receiving a single intravenous bolus of methylprednisolone (15 mg/kg). Early morning stiffness and Ritchie articular index remained improved over pretreatment values after 12 weeks. There was an early fall in the erythrocyte sedimentation rate, which returned to baseline levels by four weeks. A concomitant intravenous pulse of cyclophosphamide (1 g/m² body surface area) given to eight patients did not confer any additional benefit. Six patients received sodium aurothiomalate, up to 100 mg intramuscularly a week, and in these patients the early improvement in synovitis induced by methylprednisolone was maintained. Thus between 12 and 24 weeks the Ritchie articular index, visual analogue pain score, erythrocyte sedimentation rate, haemoglobin, and immunoglobulin G were significantly better in the patients treated with gold and methylprednisolone than in those treated with methylprednisolone alone, irrespective of whether they had received cyclophosphamide. Methylprednisolone pulse therapy given at the start of gold treatment results in early improvement in synovitis, maintained until the usual delay in achieving a therapeutic effect from gold has elapsed.

Key words: rheumatoid arthritis, pulse therapy, synacthen test

Effective suppression of severe rheumatoid disease resistant to conventional treatment presents a difficult problem. By analogy with therapeutic regimens used in malignant disease, especially of the lymphoreticular system, with which rheumatoid disease has some features in common,¹ it seemed possible that combinations of drugs in biologically effective doses might allow sufficient disease suppression to be achieved without unacceptable toxicity. Intermittent intravenous (IV) boluses or 'pulses' of methylprednisolone (MP) have been used for many years to suppress immunologically mediated disease. Renal allograft rejection can be prevented² and idiopathic glomerulonephritis^{3,4} or the glomeru-

lonephritis associated with systemic lupus erythematosus⁵ have responded well to this form of treatment, which has been shown to be superior to high dose oral steroids. This approach has been extended to other autoimmune conditions, notably rheumatoid arthritis (RA), where it has been shown that IV pulses of MP produce relief of symptoms and improvement in laboratory tests lasting for up to three months.^{6,7} Oral cyclophosphamide has been shown to be of benefit in the treatment of active RA over an eight month period.⁸ When given for RA vasculitis as an intermittent IV bolus combined with MP, the side effects of cyclophosphamide are reduced without loss of therapeutic effect.⁹ Sodium aurothiomalate is accepted by many as the standard against which other forms of suppressive treatment for RA should be compared, but it may need to be given for several months before noticeable

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symptomatic improvement occurs. Once induced, remission may be prolonged for months.¹⁰

We suggest that MP given alone or combined with cyclophosphamide may induce a clinical remission in severe, active RA, which could then be maintained in the medium to long term by gold treatment.

Patients and methods

Patients entering the study fulfilled the American Rheumatism Association criteria for classical or definite RA, and all had severe, active, seropositive and erosive disease. Active disease was defined by the presence of at least three of the following five criteria: (a) erythrocyte sedimentation rate (ESR, Westergren) >50 mm/1st h; (b) Ritchie articular index (RAI) >25 (maximum score obtainable on our modified version was 78); (c) early morning stiffness (EMS) >30 minutes; (d) visual analogue pain score on 100 mm horizontal scale (VAPS) >30; (e) haemoglobin <110 g/l. Twelve of the 13 patients analysed fulfilled at least four of these criteria. All patients had failed to respond to an adequate trial of at least one other second line drug in conventional doses, including gold (at least six months' treatment, including six weeks receiving 50 mg intramuscularly (IM) weekly), D-penicillamine (at least six months' treatment, including six weeks receiving 500 mg daily), azathioprine (at least three months' treatment, including six weeks receiving 150 mg daily), and hydroxychloroquine (at least three months' treatment receiving 400 mg daily).

Patients who had received systemic corticosteroids during the previous two years and those with dyspepsia or a history of intolerance to corticosteroids or gold salts were excluded from the study.

No drugs other than non-steroidal anti-inflammatory compounds, simple analgesics, or drugs for non-rheumatological conditions were allowed in the month before entry into the study.

Patients were admitted to hospital for two weeks. On admission a full clinical examination was performed and the following recorded: body weight, duration of EMS, VAPS, grip strength (GS), RAI, and range of joint movement, in particular shoulder abduction and knee flexion. Laboratory investigations included full blood count, ESR, C reactive protein (CRP), and immunoglobulins G, A, and M. A short synacthen test was performed on admission and after 24 weeks.

Patients were randomly allocated to one of four groups and received treatment as follows: group A—methylprednisolone sodium succinate 15 mg/kg body weight, given as a single IV bolus in 100 ml of isotonic saline over 30 minutes. Group B—As for

group A together with cyclophosphamide 1 g/m² body surface area as an IV bolus immediately before the MP. Group C—As for group A with IM sodium aurothiomalate as follows: day 1—test dose 10 mg, day 5—50 mg, day 9—100 mg, day 13—100 mg. Group D—As for group C with cyclophosphamide 1 g/m² as an IV bolus as in group B.

Patients were rested in bed for the first week and then gradually mobilised during the second week.

After discharge from hospital groups C and D continued to receive gold injections 50 mg weekly. Clinical and laboratory assessments were repeated at 2, 4, 8, 12, 16, 20, and 24 weeks. After 12 weeks all patients in all four groups were offered a second pulse of MP, and those requesting this were readmitted to hospital for a further two week period. Other treatment continued unchanged.

STATISTICAL ANALYSIS

The Mann-Whitney U test for non-parametric data was used to analyse the unpaired data as follows: (1) The effect of a single pulse of MP and two weeks hospitalisation on the clinical and laboratory parameters of active RA. The combined baseline values for all groups were compared with the combined values for all groups at 2, 4, 8, and 12 weeks. (2) The effect of the addition of an IV pulse of cyclophosphamide to the MP. The values for groups A and C (no cyclophosphamide) were combined and compared with the combined values for groups B and D (cyclophosphamide treated), at 2, 4, 8, and 12 weeks. (3) The effect of adding gold to either MP or MP plus cyclophosphamide pulse therapy. The combined values for groups A and B (no gold) were compared with the combined values for groups C and D (gold treated) at 4, 8, 12, 16, 20, and 24 weeks.

Results

Seventeen patients were entered and 13 patients completed the study. Table 1 shows the demographic details.

Of the initial 17 patients, two group A patients withdrew because they felt the treatment was ineffective, one after two weeks and the other after

Table 1 Demographic data of patients in the study. Mean values (range) are given

Group	Age (years)	Duration of disease (years)
A (4F, 1M)	56 (44–69)	12.6 (2–27)
B (4F)	55.5 (42–63)	12.3 (6–18)
C (3F, 1M)	61 (54–74)	12.7 (5–17)
D (2F, 2M)	61 (52–72)	12.3 (3–24)

12 weeks; one group C patient entered as a penicillamine 'failure' developed an acute exacerbation of synovitis six weeks after stopping the drug and subsequently restarted penicillamine; one group D patient was withdrawn because of the development of the nephrotic syndrome after 310 mg of gold. A renal biopsy showed minimal change glomerulonephritis and the nephrosis has since slowly resolved. Side effects attributable to the MP within the 24 hour period after the infusion were frequent but usually minor and included (occurrences in parentheses) facial flushing (four), feelings of faintness or clamminess (three), headaches (one), palpitations (one), bitter taste in mouth (three), depression (one), and an exacerbation of synovitis (two). One patient with a history of two previous myocardial infarctions and stable angina had a small anterolateral myocardial infarction within 36 hours of the infusion. Five of the eight patients treated with cyclophosphamide had nausea or vomiting, or both, within 12 hours of the infusion. In six of these

eight patients there was a mild neutropenia after two weeks (mean neutrophil count $1.38 \times 10^9/l$, range $0.92-1.95 \times 10^9/l$), which reverted to normal by four weeks.

EFFECT OF A SINGLE IV PULSE OF MP

We compared the baseline entry values of body weight, duration of EMS, VAPS, GS, RAI, range of shoulder abduction and knee flexion, haemoglobin, ESR, CRP, IgG, IgA, and IgM in all groups and found no significant differences.

When the combined baseline values for all groups were compared with the combined values for all groups at 2, 4, 8, and 12 weeks there were significant improvements in EMS, VAPS, and RAI within 12 weeks after a single pulse of MP (Figs 1a-c). The mean value for the ESR fell two weeks after the pulse was given from 81 mm/1st h to 63 mm/1st h but this was not statistically significant ($p=0.06$). All short synacthen tests were normal on entry into the study and again after 24 weeks.

Fig. 1 Effect of intravenous methylprednisolone (15 mg/kg) on measurements of disease activity in patients with rheumatoid arthritis in groups A, B, C, and D combined ($n=17$). (a) Early morning stiffness (EMS); (b) visual analogue pain score (VAPS); (c) Ritchie articular index (RAI).

EFFECT OF A SINGLE IV PULSE OF CYCLOPHOSPHAMIDE

When the values for groups A and C (no cyclophosphamide) were combined and compared with the

combined values for group B and D (cyclophosphamide treated) at 2, 4, 8, and 12 weeks there were no statistically significant differences, suggesting that a single pulse of cyclophosphamide did not confer

Fig. 2 Comparison of measurements of disease activity in groups A and B (no gold) ■—■ and groups C and D (gold treated) ●—● during 24 weeks after intravenous methylprednisolone (15 mg/kg). (a) Ritchie articular index (RAI); (b) visual analogue pain score (VAPS); (c) grip strength; (d) shoulder abduction; (e) erythrocyte sedimentation rate (ESR); (f) haemoglobin; (g) immunoglobulin G. Error bars indicate the standard error of the mean.

additional benefit over a single pulse of MP in decreasing disease activity, at least over a 12 week period.

EFFECT OF THE ADDITION OF GOLD

As the therapeutic benefit of gold salts in RA usually takes several weeks or months to become apparent we compared the combined mean values for each parameter in groups A and B (no gold) and groups C and D (gold treated) at 2, 4, 8, 12, 16, 20 and 24 weeks after the pulse of MP with or without cyclophosphamide and initiation of gold treatment. Two group A and one group B patient received further pulses of MP at 12 weeks, whereas no patient in groups C or D elected to have this. Despite this, groups C and D (gold treated) showed better overall improvement.

When the clinical indices of disease activity were examined, there was a difference between the combined groups in favour of gold treatment in terms of RAI as early as week 4 (Fig. 2a), and this was statistically significant from week 16 ($p=0.03$). At weeks 20 and 24 the group C/D patients complained of significantly less overall pain in their joints (VAPS) ($p=0.02$ and 0.03 respectively) (Fig. 2b). At week 16 GS was significantly higher in the gold treated group (Fig. 2c), and the range of glenohumeral joint movement had increased ($p=0.05$; Fig. 2d). There were no significant changes over the 24 week observation period in the following parameters: knee flexion (range group A/B $126-138^\circ$, range group C/D $116-125^\circ$), body weight (range group A/B $58.0-60.7$ kg, range group C/D $56.8-64.7$ kg), and EMS (range group A/B $21.7-56.0$ minutes, range group C/D $21.4-47.1$ minutes).

When the laboratory indices of disease activity were examined, from week 12 there was a significant difference in the ESR between the combined groups in favour of the gold treated group, which was maintained until the end of the study (Fig. 2e). The mean haemoglobin concentration was significantly higher in the group C/D patients at 24 weeks ($109 \nu 99$ g/l, $p=0.01$) (Fig. 2f). Although the absolute value of serum IgG did not change in the group C/D patients, the concentration tended to rise in the group A/B patients, so that at weeks 16 and 20 the differences were significant ($p=0.05$ and $p=0.02$ respectively; Fig. 2g). There were no significant differences between the groups in serum IgA (range group A/B $2.2-4.7$ g/l, range group C/D $3.0-4.5$ g/l), nor in serum IgM (range group A/B $1.8-2.8$ g/l, range group C/D $0.6-1.1$ g/l). Similarly, there were no significant differences between the groups in serum CRP (range group A/B $0.038-0.1$ g/l, range group C/D $0.057-0.123$ g/l).

Discussion

This study confirms the findings of others that pulse MP is an effective short term treatment for most patients with active RA.^{6,7} Moreover pulse MP therapy given at the start of chrysotherapy may eliminate the 'lag' period before the improvement in disease due to gold becomes apparent. There have been two recent comparable studies. Neumann *et al* observed a beneficial clinical effect when pulsed MP was given at the start of treatment with penicillamine or sulphasalazine,¹¹ and Hansen *et al* found clinical benefit and early falls in the ESR, VAPS and RAI after pulsed MP given before gold penicillamine, or azathioprine.¹² In both these studies, however, three IV pulses of MP were given. We used only a single IV pulse of MP at the start of treatment, which in most patients produced a sustained improvement. In some of the patients not receiving gold the effect was short lived and a second dose of MP was given after 12 weeks if the patient elected to receive this. The situation is not clear. There is some evidence that MP given in this way may be immunosuppressive and after infusion there is a profound peripheral blood lymphopenia after four hours followed by a return of lymphocytes to normal levels by 24 hours. Alternatively, MP may merely induce a sufficiently prolonged anti-inflammatory effect, which lasts until the suppressive effect of gold becomes manifest.

Side effects attributable to MP were usually minor, but one patient had palpitations and another a small myocardial infarction shortly after the pulse of MP. Neumann *et al* also mention that one of their patients was withdrawn from their study owing to myocardial infarction.¹¹ They felt that the pulse therapy was not responsible, but no details were given. We would advise caution in the use of MP for the treatment of patients with a history of ischaemic heart disease in view of the positive inotropic effect of the drug on the myocardium. We performed short synacthen tests on all patients to detect possible suppression of the hypothalamic-pituitary-adrenal axis but found no evidence of this.

Oral cyclophosphamide has been of benefit in severe intractable RA,¹⁵⁻¹⁷ but the possibility of inducing serious long term side effects, such as haemorrhagic cystitis,¹⁸ carcinoma of the bladder and leukaemia or lymphoma,^{19,20} has caused concern. There are few published data on the use of intermittent IV pulses of cyclophosphamide in active RA, although when combined with MP it has improved rheumatoid vasculitis, with a low incidence of side effects.⁹ We hoped that the combination of cyclophosphamide, with or without gold, and MP might have an additional synergistic effect on

rheumatoid synovitis. The addition of a single pulse of cyclophosphamide to the MP, however, conferred no more benefit than a single pulse of MP, but caused no serious side effects. Minor side effects such as nausea and vomiting occurred in five of eight patients. The degree of neutropenia was acceptable. Continuous high dose oral administration of cyclophosphamide is often limited by toxicity. It is possible that more frequent, intermittent IV boluses may be more beneficial than the single IV bolus we used. One complication of gold treatment occurred in the patient who developed nephrosis after 310 mg, which gradually resolved after withdrawal of the gold.

Our study suggests that in severe, active RA, when treatment with gold is contemplated, a single IV pulse of MP given at the onset of treatment is usually effective in inducing an early remission of synovitis before the effect of the second line agent. Neumann *et al* used three alternate day pulses of IV MP over five days,¹¹ and Hansen *et al* used three IV pulses of MP on consecutive days.¹² We agree with Hansen *et al*¹² that this may be no more beneficial in most patients than a single IV bolus and suggest that as there are potential risks from this form of treatment that a single pulse of MP should be tried in the first instance. Subsequently, it may be appropriate to repeat the pulse therapy after an interval, depending on the individual clinical response. In our experience the side effects of this form of treatment for severe RA are usually minor. We would, however, urge caution in patients with ischaemic heart disease.

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Alterations in appendicular skeletal mass in patients with rheumatoid arthritis, psoriatic arthritis, and osteoarthritis

SIR, Cooper *et al* in their recent article on skeletal mass in rheumatoid arthritis, psoriatic arthritis, and osteoarthritis stated that lumbar bone mass is reduced in rheumatoid arthritis, irrespective of corticosteroid treatment.¹

For this statement they quoted, without any personal experience, one published reference.² In our opinion, however, this statement does not reflect the results of other reports concerning lumbar bone mass in rheumatoid arthritis. From the same author as the one referred to by Cooper *et al* there is a previous study of early rheumatoid arthritis, in which no diminution of bone mass could be shown when patients with rheumatoid arthritis were compared with controls.³ In our own study we found a normal lumbar bone mass when female, postmenopausal patients with rheumatoid arthritis were compared with controls matched for sex, age, and menopausal state, irrespective of corticosteroid treatment.

Moreover, when discussing the appendicular skeleton as measured by single photon absorptiometry the authors refer to 'one single study', whereas there are many studies of peripheral bone mass at the radial site in rheumatoid arthritis, treated with corticosteroids or not.^{4–11} Some authors report a decreased peripheral bone mass in rheumatoid arthritis while others do not.

As the assessment of bone mass in arthritis is difficult owing to a variety of interfering factors, such as sex, age, menopausal state, disease activity and duration, local destruction, treatment (especially corticosteroid treatment), I feel that the discussion should have been expanded, with a better use of the available publications and a discussion of current controversies.

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SIR, As Dr Verstraeten indicates studies of bone mass at different anatomical sites in rheumatoid arthritis have produced conflicting results, and we stated this in our report. It was not our purpose to write an exhaustive review of published work but to highlight some of the inconsistencies, which are, quite naturally, open to various interpretations. We reported our own measurements of appendicular bone mass in three different polyarthropathies and considered these to be of interest. Dr Verstraeten's comments on corticosteroid treated patients do not really apply in this context owing to the deliberate exclusion of such patients from our study.

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Correction: Combined suppressive drug treatment in severe refractory rheumatoid disease: an analysis of the relative effects of parenteral methylprednisolone, cyclophosphamide, and sodium aurothiomalate. In the paper by Drs M T Walters and M I D Cawley (*Ann Rheum Dis* 1988; **47**: 924–9) we regret that the first line of the second paragraph of the Discussion was omitted. The first sentence of this paragraph should have read 'The mode of action of both gold and MP in this situation is not clear'.