

LETTERS

On the treatment of rheumatoid arthritis with M&Ms (Motrin & methotrexate)

To the Editor:

The efficacy of low-dose, pulse methotrexate (MTX) in the treatment of rheumatoid arthritis (RA) has been established in both short-term and long-term clinical trials (1,2). The safety profile of this drug regimen appears, thus far at least, to be very favorable (3), particularly in comparison with the safety profiles of some of the other second-line and third-line agents that are currently used to treat RA. This has prompted some leading rheumatologists in the US to recommend that MTX be the therapeutic choice after failure of gold therapy (oral or injectable) due to a lack of efficacy or to toxic reactions. Indeed, some of our colleagues are selecting MTX immediately after failure of an adequate trial of nonsteroidal antiinflammatory drugs (Motrin and related compounds), bypassing the various gold preparations, hydroxychloroquine, and penicillamine.

At the 51st Annual Meeting of the American Rheumatism Association (June 1987), the results of 2 trials were presented, in which the efficacy of weekly intramuscular injections of MTX was compared with that of weekly intramuscular injections of gold. The investigators concluded that MTX is at least as effective as parenteral gold, and is as safe, or safer, over the *short* term (4,5). When these and similar studies are published in well-refereed journals, further impetus will be given to the newer prescribing practices outlined above. This trend can be expected to be further augmented after Food and Drug Administration approval of MTX for the treatment of RA, which will then permit advertising and active promotion by industry.

It is a clinical impression, now supported by the results of a well-executed, double-blind trial (6), that withdrawal of MTX predictably gives rise to a severe flare of the RA, usually within weeks. Thus, once a patient is committed to this course of treatment, it may be expected that the MTX will have to be continued *indefinitely*, unless a spontaneous remission supervenes or another agent is added. It is reasonable to expect that RA patients may be the largest group of patients (without malignant disease) to be exposed to prolonged therapy with the drug. Although pulse MTX was first introduced for treatment of psoriasis, the effectiveness of MTX on the skin lesions of psoriasis is less dramatic and sustained than it is on the synovitis of RA. It is likely that far more RA patients than psoriasis patients will be maintained on a prolonged treatment regimen with MTX.

The nature and incidence of possible adverse effects that might be associated with prolonged administration of MTX to a large patient population with a chronic disease that requires continued treatment is not known. Many years ago, patients with ankylosing spondylitis were treated with radiotherapy of the spine, and the results were excellent. Only 20 years later was it appreciated that in patients so treated, there was an excessive incidence of deaths from acute leukemia. It would seem prudent, therefore, that the currently accepted "pyramid" of therapeutic strategy in RA, with nonsteroidal antiinflammatory drugs at the base and the

antiproliferative drugs at the apex, not be abandoned quite yet. Certainly, in the case of younger patients, gold, hydroxychloroquine, and penicillamine are worthy of a trial, even though these agents are slower in onset of effect and require greater effort on the part of the treating physician and more forbearance by the patient with active disease.

All therapeutic approaches should be explored so that the initiation of MTX therapy can be deferred for as long as possible—at least until more patient-years of experience with the long-term use of MTX in RA have been obtained. Perhaps a major role for MTX, which should be evaluated in future studies, would be as a "bridging" drug: It would be used to achieve rapid control of disease activity, after which a slow-acting, noncytotoxic agent would be introduced, in a manner analogous to that for which corticosteroids are currently used.

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Immune thrombocytopenia in association with oral gold treatment

To the Editor:

Auranofin has been found to be useful and relatively well tolerated in the treatment of rheumatoid arthritis. In a study of 3,475 patients taking auranofin, toxic reactions, including thrombocytopenia, were generally mild (1). We report a case of severe thrombocytopenia developing 3 months after the start of auranofin therapy in a patient with a 20-year history of mild, seronegative, erosive rheumatoid arthritis which was not previously treated with slow-acting antirheumatic drugs other than hydroxychloroquine.

In March 1987 the patient, a 69-year-old woman, was admitted to the hospital because of a 3-day history of easy

bruising and petechiae on her legs. Apart from mild synovitis involving the finger joints and the right ankle, clinical examination results were unremarkable. She had been taking auranofin (3 mg twice a day) and diclofenac sodium (50 mg 3 times a day), and she was receiving monthly injections of cyanocobalamin for pernicious anemia.

Laboratory studies showed a normochromic normocytic anemia, a hemoglobin level of 7.4 gm/dl, a white blood cell count of 6.3×10^9 /liter, and thrombocytopenia (platelet count 5×10^9 /liter). One month previously, the hemoglobin level had been 10 gm/dl, the white blood cell count had been 5.0×10^9 /liter, and the platelet count had been 244×10^9 /liter. A bone marrow aspirate and a sample taken by trephine showed numerous megakaryocytes. A direct test of platelet-associated immunoglobulin gave a positive result, with 5,350 molecules of IgG per platelet (normal <200) (2). The indirect Coombs' platelet test result was slightly positive, with no further increase in platelet immunoglobulin on addition of auranofin. Investigations of plasma electrolytes, urea, creatinine, liver function, clotting profile, fibrinogen level, and fibrinogen degradation products produced normal results. Rheumatoid factor and antinuclear antibody were absent. The HLA phenotype was A2,3;B8,35;Bw6;DR3,4.

The auranofin and diclofenac sodium therapy was discontinued. She was transfused with 2 units of packed red blood cells, and treatment with prednisolone (60 mg daily) was instituted. Ranitidine (150 mg twice a day) was given because of the possibility of upper gastrointestinal bleeding, although this was not documented. The hemoglobin level has since remained stable. The platelet count returned to a normal level within 1 week, and there was a gradual decrease in platelet-associated immunoglobulin, which reached the normal range some 8 weeks later. The platelet count remained normal as the dosage of prednisolone was gradually reduced.

This case illustrates that the sudden onset of severe thrombocytopenia, well recognized as a complication of parenteral gold therapy, may also occur with auranofin. Although it is not recommended that hematologic monitoring be conducted as frequently in patients taking auranofin as in those receiving parenteral gold, our patient's case highlights the importance of instructing patients to immediately report any unusual bleeding. It has been suggested that parenteral gold induces platelet-specific autoantibodies which cause the thrombocytopenia (3), and an association with the HLA-DR3 alloantigen has been documented (4). The increased level of platelet-associated IgG, its decrease with steroid therapy, and the presence of HLA-DR3 suggest that similar immunogenetic mechanisms were operative in our patient, despite the structural differences between the oral and parenteral gold derivatives.

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Wegener's granulomatosis with acute pericardial tamponade

To the Editor:

We recently saw a patient who had Wegener's granulomatosis associated with acute, life-threatening cardiac tamponade. To our knowledge, this is the first report of this complication occurring in Wegener's granulomatosis.

The patient, a 59-year-old white man, was admitted to the hospital because of hemoptysis, dyspnea, and fever of 2 days duration. Two months earlier, a routine physical examination, including complete blood count, urinalysis, chest radiograph, and electrocardiogram, had shown no abnormalities. Five weeks prior to admission, he developed bilateral otitis media. Three weeks later, symmetric arthritis involving his wrist, shoulder, and knee joints developed, along with 1-2 hours of morning stiffness and episcleritis. His medical history was significant for well-controlled essential hypertension of 10 years duration.

On physical examination, his blood pressure was 140/80 mm Hg, pulse rate was 92/minute, temperature was 102.8°F orally, and respiratory rate was 20/minute. His skin was without vasculitic lesions or rashes. There was no evidence of otitis, scleritis, sinus tenderness, or oral or nasal mucosal lesions. Cardiac rhythm was regular, with a normal S1 and S2. A grade I/VI systolic ejection murmur was heard at the lower left sternal border, but no gallops or rubs were noted. Abdominal and neurologic examinations revealed no abnormalities. Muscle strength was normal. Bilateral knee effusions were present.

Admission laboratory studies revealed a white blood cell count of $16,800/\text{mm}^3$, with 81% neutrophils, a hemoglobin level of 8.7 gm/dl, a reticulocyte count of 3.4%, and a platelet count of $870,000/\text{mm}^3$. Urinalysis revealed 1+ protein and 50-100 red blood cells per high power field. The blood urea nitrogen level was 28 mg/dl and the creatinine level was 1.4 mg/dl. Creatinine clearance was 42 ml/minute, with 2.1 gm protein/24 hours. The erythrocyte sedimentation rate (Westergren) was 126 mm/hour. Analysis of arterial blood gases, with the patient breathing room air, revealed a pH of 7.54, Pco_2 of 27 mm Hg, and Po_2 of 68 mm Hg. Results of an electrocardiogram, sinus radiographs, serum electrolyte studies, total protein studies, protein electrophoresis, liver function tests, complement studies, and direct and indirect Coombs' tests were normal or negative. Antinuclear antibodies were present in a speckled pattern (titer 1:64), but