Methotrexate in rheumatoid arthritis

Those immersed in the clinical practice of rheumatology have watched with wry amusement the recent enthusiastic endorsement of methotrexate (MTX) by the academic community. Long recognized as a valuable weapon against rheumatoid arthritis (RA) by clinically oriented rheumatologists who have followed the work of such pioneers as Mackenzie and Scherbel[1] at the Cleveland Clinic, MTX is finally achieving general acceptance. Its efficacy appears comparable to that of the other slow-acting agents, such as gold and d-penicillamine. Furthermore, its safety will prove superior to that of the other cytostatic agents used to treat RA, such as azathioprine and cyclophosphamide, as well as gold and d-penicillamine. The feared spectre of hepatotoxicity has failed to materialize* in patients treated with low-dose pulse (single weekly dose less than 15 mg) MTX as long as other assaults on the liver (especially alcohol) are avoided. This experience differs substantially from that with MTX treatment of psoriasis, in which larger doses appear to be necessary.

It is difficult to see why it has taken so long for MTX to emerge. Perhaps the almost homeopathic-appearing doses (7.5 mg weekly on the average) have contributed to a certain reticence on the part of therapists to claim efficacy. It seems unlikely that significant immunosuppression is achieved at these levels, but the same can be said of most other modalities acknowledged to be effective in RA (cyclophosphamide and perhaps azathioprine being notable exceptions). Similarly, MTX has never been noted to possess potent anti-inflammatory activity in the tradition of the strong prostaglandin or leukotriene inhibitors, but these agents cannot be shown to modify the course of RA. However, inability to explain theoretically (or in some cases, even to clearly demonstrate) beneficial effects of therapy has not stopped widespread use of any of the currently popular drugs; why should MTX be any different?

This is the age of the blinded, controlled trial, and if there is any disease in which this methodology is necessary to prove efficacy of treatment, it is RA. A look at the subjective nature of the outcomes assessed will suffice to underscore this statement. Clearly, the positive results of several double-blinded, controlled trials of MTX in RA will make this treatment a mainstay in moderately severe disease, as it has been at the Cleveland Clinic since the middle 1960s. The real lesson of MTX is that this was too long delayed, and this mistake should not be made in the future with other promising therapies.

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Reference

1. Mackenzie AH, Scherbel AL. Management of rheumatoid arthritis in the surgical patient. Orthop Clin North Am 1971; **2**:277–299.

* See the paper by Mackenzie in this issue (pp 129–135)