Methotrexate in Reiter’s disease

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SUMMARY Three cases of severe Reiter’s disease were treated successfully with methotrexate after failure of conservative therapy, including systemic corticosteroids in 2 instances. The usefulness and potential hazards of such therapy are discussed, and some evidence that corticosteroids may aggravate the dermatological manifestations of Reiter’s disease is presented.

Reiter’s disease as described by Reiter (1916) and a century earlier by Brodie (1818), is a systemic illness featuring asymmetric polyarthritis, conjunctivitis, urethritis, and mucosal and skin lesions. Of these latter the classical form is keratoderma blennorrhagica (KDB), and lesions clinically and histologically indistinguishable from psoriasis and pustular psoriasis are common. The syndrome is often complicated by sacroiliitis and spondylitis, and neurological or cardiovascular sequelae may occur in up to 30% and 10% of sufferers respectively (Good, 1974). Recently a very high prevalence of HLA B27 has been noted in this disease (Brewerton et al., 1973; Morris et al., 1974; Cross et al., 1975; Zachariae et al., 1975).

Effective therapy usually consists of bed rest, splinting, and intra-articular steroid to joints, local steroid therapy to skin lesions, non-steroidal anti-inflammatory drugs (NSAID), and patience. In some patients, however, a severe systemic illness may accompany florid skin lesions and polysynovitis, and systemic corticosteroid therapy may be introduced for symptomatic control. We describe here 3 patients to whom methotrexate was administered for severe illness, in 2 cases after systemic corticosteroids had failed to improve the course of the disease.

Case 1

A 20-year-old man first presented in August 1971 with urethritis and penile blisters following intercourse. After failure of penicillin, therapy with tetracycline was followed by improvement. Recurrence of urethritis was again successfully treated with tetracycline. However, the subsequent development of shoulder arthralgia, conjunctivitis, and a scaly scalp rash prompted the use of prednisone 15 mg/day, which was later ceased but then reintroduced as the condition relapsed. When seen at this hospital 2 months later he had an asymmetrical polyarthritis, painful cervical and lumbar spine, generalised pustular dermatitis, conjunctivitis, but no ulcers, and balanitis. Despite bed rest and local joint therapy the polyarthritis and spondylitis progressed, accompanied by frank KDB and a febrile systemic illness. Administration of salicylates, phenylbutazone, flufenamic acid, and teraclosacritin failed to influence the course of disease. In mid-November 1971 methotrexate 25 mg (0·3 mg/kg) in divided doses over 24 hours once per week was begun, and indomethacin was substituted for phenylbutazone. Rapid improvement in all clinical features followed, and by early January 1972 mild polyarthritis and minor skin lesions were controlled on salicylates, indomethacin, and methotrexate 12·5 mg/week. In March 1972 the patient returned to work and over the next 24 months required methotrexate 7·5–10 mg/week for control of disease, which was manifest as mild psoriasis. In 1974 methotrexate and NSAID were slowly reduced in dosage and then stopped. Subsequently he has remained well, with mild psoriasis controlled with topical steroid ointment and episodes of asymmetrical polysynovitis which have responded well to NSAID.

Case 2

In December 1975, a 32-year-old man after numerous sexual contacts developed balanitis, a blood-stained ejaculate, conjunctivitis, oral ulcers, and asymmetrical polyarthritis. Intra-articular steroid injections improved symptoms, but disease rapidly progressed. The patient had a high prevalence of HLA B27 and Reiter’s disease was diagnosed. Methotrexate 25 mg/week controlled the polyarthritis and skin lesions, while indomethacin controlled the oral ulcers. In 1977 methotrexate was ceased, and the disease has remained in remission for over 5 years.
metrical polyarthritis. Initial treatment over 2 months by bed rest, local joint therapy, salicylates, indomethacin, and phenylbutazone failed to influence these symptoms. In January 1976 prednisone was begun at a dose of 20 mg/day, subsequently being reduced. By April there had been no improvement in his polyarthritis, and an exacerbation of balanitis was accompanied by the development of KDB plus psoriatic-type paronychia with nail loss. Methotrexate 22.5 mg/week (0.3 mg/kg) was introduced, the prednisone dosage at this time being 9 mg/day. By July 1976 the keratodermia had resolved and there was moderate balanitis and mild synovitis. The erythrocyte sedimentation rate (ESR) had fallen from 50 to 4 mm/h. By September 1976, while the patient was on methotrexate 22.5 mg/week and prednisone 7.5 mg/day, only balanitis and penile warts were problems. Prednisone was reduced slowly and by January 1977 stopped entirely, clinical remission being maintained on methotrexate 20 mg/week. Subsequently he has remained well, but after 18 months’ therapy it has not been possible to reduce the methotrexate dosage.

**Case 3**

In May 1972 after venereal contact a 16-year-old youth developed dysuria with possible urethral discharge, asymmetrical polyarthritis, multiple buccal mucosal lesions, and KDB of hands and feet. Gonococcal and syphilitic infections were excluded. NSAID were prescribed, and the syndrome resolved in 2 months.

He remained completely well until October 1976, when he presented with dysuria, painful oral and nasal ulcers, conjunctivitis, asymmetrical polyarthritis, low lumbar pain, and a febrile systemic illness. Therapy with tetracycline, indomethacin, and ibuprofen was unsuccessful. He was admitted in November, when in addition to the above clinical features he developed classical KDB, lesions of pustular psoriasis with liquefying paronychia and punctate psoriasis. Toxic hepatitis was suggested by liver function tests and confirmed by biopsy. Bed rest, local joint therapy, full doses of NSAID, and steroid cream failed to influence these features. In late November 1976 methotrexate 22.5 mg/week (0.3 mg/kg) was introduced, with indomethacin as anti-inflammatory agent. There was an improvement in polyarthritis, balanitis, and mouth ulcers but an initial worsening of keratodermia. By January 1977 all features of his disease had improved. Liver function tests became normal. He was discharged and at nine months’ review was enjoying sustained improvement on a slowly reducing dose of methotrexate.

Laboratory investigations on the 3 patients showed normal haemoglobin, mild leucocytosis, and markedly elevated ESR, accompanied in 2 cases by thrombocytosis. Cultures of synovial fluid, urine, and urethral swabs failed to grow organisms; the Wassermann reaction and gonococcal complement fixation test were negative. Synovial fluid C3 and C4 were elevated in 2 cases, of the same order as an increase in serum complement. Each patient was found to have the antigen HLA B27; case 2 had HLA B13 in addition. Furthermore each patient had full haematological and liver function tests monitored, at first weekly and then monthly. These have all remained within normal limits.

Regular clinical follow-up has not detected development of cardiovascular or neurological complications of Reiter's disease, nor any evidence of pneumonia.

**Comment**

The clinical diagnosis of classical Reiter's disease in these 3 patients is supported by the presence of HLA B27 and the raised synovial fluid complement. The presence of the psoriasis-associated antigen HLA B13 in case 2 is interesting in view of the nature of the skin lesions. However, cases 1 and 3 show that this antigen is not essential for the expression of full dermatological features.

The indication for methotrexate in these cases was severe progressive skin and joint disease with systemic illness despite an adequate trial of conservative therapy and in 2 cases systemic corticosteroids. In these latter 2 cases joint disease persisted and skin lesions appeared to worsen with corticosteroid. The regimen followed was a modification of that of Weinstein and Frost (1971), with an initial dose of 0.3 mg/kg/week (0.2 mg/kg/m²/week) administered in 3 divided doses at 12-hourly intervals. In all cases the response was dramatic, ultimately allowing the sufferer to return to an essentially normal existence. It has been possible to withdraw the drug completely after 2 years in 1 case and to reduce the maintenance dosage relatively quickly in another, but in the third patient a moderately high maintenance dose has been necessary. No biochemical toxicity has occurred over 50 patient-months of treatment.

Methotrexate has a well established use in the treatment of severe psoriasis, and its value in psoriatic arthropathy has been known for the last 15 years. In each instance the tendency is to use a low maintenance dosage of the drug, about 5–15 mg/week, which contrasts with the dosage schedules used in neoplastic disease. In a recent review Weinstein (1977) has surveyed a large experience of the drug, mainly in the treatment of psoriasis, with
particular attention to hepatotoxicity. He concludes that some 3% of patients (with psoriasis) develop cirrhosis within the first 4 years of therapy. This histologically based review identified pre-existing abnormal liver biopsy, total cumulative dose of drug, obesity, and heavy alcohol intake as factors contributing to the development of cirrhosis; of these, alcohol was considered the major factor.

Of the 36 cases of methotrexate-induced pneumonitis reviewed by Sostman et al. (1976) 3 had psoriasis, 1 had ankylosing spondylitis and mycosis fungoides, 1 polymyositis, and 1 polymyositis and progressive systemic sclerosis. In 2 of the psoriatic cases pneumonitis appeared as a hypersensitivity phenomenon after a low total dose; in the third a much higher dose had been taken before development of pulmonary toxicity. All 3 patients recovered within 21 days after withdrawal of the drug. The potential for liver and pulmonary toxicity as well as other unwanted effects of cytotoxic therapy was considered acceptable for our cases, in which methotrexate therapy was indicated, despite the expectation of long-term therapy.

Methotrexate has been found by us to be a useful and well tolerated drug, indicated in severe resistant cases of Reiter's disease. Some evidence is presented that systemic corticosteroids may aggravate the dermatological symptoms with little benefit to the synovitis. This may apply particularly to patients with a psoriatic diathesis as determined clinically, by family history, or HLA typing.

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References


