Regular Review

Treatment of severe rheumatoid arthritis

VERNA WRIGHT

The patient with intractable, destructive rheumatoid arthritis presents a most difficult problem for the physician. The chronicity of the condition coupled with its relentless progress may encourage the use of drastic measures in the patients who have failed to respond to second line agents, such as sulphasalazine, antimalarials (hydroxychloroquine or chloroquine), gold, or penicillamine.

In these circumstances the definition of failure should be applied strictly, for some patients' symptoms may be mechanical rather than due to active disease. As defined for trials of second line agents, active disease implies tenderness of over six joints, swelling of over three joints, early morning stiffness lasting over 45 minutes, an articular index of over 20, and an erythrocyte sedimentation rate greater than 28 mm in the first hour.¹ Failure may also have been due to the treatment being stopped because of minor side effects such as trace proteinuria. A patient may have been deprived of the potential benefit of the drug because no attempt has been made to reintroduce it cautiously. If the reason for withdrawal is failure to respond a combination of second line agents may be given. One report, for example, described a group of patients who failed to respond to conventional doses of penicillamine but did respond to an increased dose and to the addition of hydroxychloroquine.² On the other hand, gold and penicillamine given together increase the likelihood of side effects (F McKenna *et al*, paper given at XVI Congress of Rheumatology, Sydney, 1985). The reality is that we still do not have adequate treatment for this difficult group of patients, and every effort to find alternative drugs, such as a recent study of captopril,³ is to be welcomed.

It is patients of this type who receive steroids—yet they are the very people whose immobility (caused by severe disease) makes them likely to develop steroid osteoporosis with crush fractures. If the administration of steroids is contemplated they may best be given as pulse treatment combined with a second line agent.⁴ Indeed, a combination of second line drugs and corticosteroids may be appropriate, particularly in the elderly. In patients with refractory disease an attempt at immunological modification may be attractive though the rationale is muddled.⁵ Drugs used as immunomodulators have included azathioprine,⁶ cyclophosphamide,⁷ methotrexate,⁸ chlorambucil,⁹ levamisole,¹⁰ cyclosporin,¹¹ and thymopoietin.¹²

Azathioprine is a purine antagonist; it has replaced mercaptopurine in the treatment of rheumatoid arthritis. It decreases the antibody response, the synthesis of immunoglobulins, and the responsiveness of B lymphocytes.¹³ Among the immunosuppressants it is the drug of choice since it appears to be less toxic and is easier to handle than methotrexate or cyclophosphamide. In a trial of azathioprine against gold and cyclophosphamide the cytotoxic drugs facilitated steroid sparing and appeared to slow radiological

deterioration.¹⁴ Fewer side effects occurred with azathioprine than with cyclophosphamide. A daily dose of 2.5 mg/kg seems to have the most effect. Our own experience, however, showed a higher incidence of side effects,¹⁵ with an association between liver damage and abnormal immunoglobulins for patients on this drug.¹⁶ Patients with rheumatoid arthritis receiving azathioprine show increased chromosomal abnormalities,¹⁷ but concern that immunosuppression may encourage the induction of lymphomas, squamous cell carcinomas, and mesenchymal tumours (as in immunosuppressed transplant recipients) has not been substantiated.¹⁸

Methotrexate is useful in treating the skin lesions of psoriasis and no increased risk of cancer has been shown. There is, however, little evidence of its efficacy in controlled trials in rheumatoid disease. Chlorambucil has been shown in one controlled trial to be effective against rheumatoid arthritis,⁹ but in my view it is best reserved for late rheumatoid arthritis in the elderly.⁵ Cyclophosphamide may be the most effective of all the immunosuppressant drugs, but it also has the most potent side effects, including gastrointestinal intolerance, infertility, alopecia, marrow depression, increased infections, and haemorrhagic cystitis. The last complication demands immediate withdrawal of the drug, since it may progress to bladder fibrosis and even cancer of the bladder. The drug may inhibit new bone erosions and may produce regression of existing bone lesions.^{19,20} A threshold effect has been shown, and the daily dose needs to be about 1.3 mg/kg.^{7,21} When given in combination with prednisone clinical efficacy may be achieved with fewer side effects than when a higher dose of cyclophosphamide is used alone.²² There is little advantage in alternate day oral dosage, and intravenous treatment may produce severe systemic side effects, unless methylprednisolone is given at the same time.²³

Initial enthusiasm for levamisole has been tempered by the frequency of side effects. Idiosyncratic reactions (agranulocytosis, mouth ulcers, rash, and an influenza-like illness) may occur in about a fifth of patients with rheumatoid arthritis. This frequency may be decreased by altering the dosage, but a weekly dose of 150 mg seems the minimum to achieve an effect.²⁴ Cyclosporin A has been suggested for these patients, but it is unlikely to find a place in the treatment of rheumatoid arthritis.¹¹ Thymopoietin is a synthetic pentapeptide which replaces differentiation of T and B lymphocytes in many different ways.²⁵ It does not cause allergy and is said to be the active moiety of the thymic hormone extract. A recent controlled trial compared the effects of slow intravenous injections with placebo. Patients given the drug showed improvement in some clinical variables, but laboratory variables did not alter, and the disease relapsed two to four weeks after stopping treatment.¹³

Apart from using drugs, four other methods have been

used to achieve immunosuppression—thoracic duct drainage, plasmapheresis, total lymphoid irradiation, and total body irradiation. Thoracic duct drainage has been evaluated in America and Japan.^{26,27} Clinical variables improved, and nodules regressed within a week, but the improvement was only temporary. This cumbersome procedure is unlikely to find a place in routine treatment. Plasmapheresis is expensive. Uncontrolled initial studies in rheumatoid arthritis suggested considerable improvement.²⁸ A controlled study, however, showed no more clinical improvement than was seen in patients receiving identical hospital treatment without plasma exchange, despite a clear reduction in levels of circulating immune complexes.²⁹ Lymphapheresis, a variant of the procedure in which lymphocytes rather than circulating immune complexes are selectively removed, similarly showed less impressive results from a controlled study³⁰ than initial uncontrolled reports.³¹

Total lymphoid irradiation, using protocols originally designed for Hodgkin's disease, has been evaluated at Stanford³² and at Harvard,³³ and the approach has been reviewed by Calin.³⁴ The Stanford group undertook a double blind randomised trial at 2000 rads and 200 rads. Alleviation of joint activity was greater in the high dose group at three and six months after radiotherapy and was accompanied by a reduction in T lymphocyte function and numbers. Possibly prednisone may have played a synergistic part in the improvement. Complications (seen only in the high dose group) included transient neutropenia, thrombocytopenia, pericarditis, pleurisy, and susceptibility to herpes zoster infections. The Harvard group found comparable improvement in the short term, but the patients soon showed a recrudescence of disease activity. Calin's explanation of this difference is that the treatment schedule may have allowed repopulation of irradiated areas by unirradiated lymphocytes. At Stanford 2000 rads were given in fragmented doses to two portals, one above (mantle) and one below (inverted Y) the diaphragm, the course being completed within five to six

weeks. At Harvard three portals were used (the mantle, the para-aortic/splenic, and the pelvic) giving 3000 rads over 14-16 weeks.

Total body irradiation is an alternative system which has also been used in other non-malignant conditions such as polymyositis³⁵ and myasthenia gravis.³⁶ Anecdotal reports suggest that it has no part to play in the management of rheumatoid arthritis. Comparative studies of different regimens are required. Dequeker *et al* are comparing total lymphoid irradiation with a combination of azathioprine and cyclophosphamide at a daily dose of 1 mg/kg of each drug (paper to XI International Congress of Rheumatology, Sydney, 1985). Their preliminary results suggest that there is little to choose between the two regimens in efficacy, but that the combined drug treatment may be more toxic. Neither the optimal time nor the optimal dose pattern for such irradiation has been established—and the places of hypoxic cell sensitisers, radiation protectors, hypothermia, and hyperthermia still require controlled evaluation.

With the limited information we have any order of preference for these treatments must be subjective. Mine would be sulphasalazine, penicillamine or gold, hydroxychloroquine or chloroquine, combination treatment, captopril in the first place. Pulsed steroids may be used for acute exacerbations with a second line agent; and long term oral steroids in the elderly. Bed rest and pulsed steroids should be tried before resorting to cytotoxic agents; when these are needed my order of immune modulating drugs would be azathioprine or methotrexate, chlorambucil, then cyclophosphamide. If vasculitis complicated the picture and threatened life or limb I would opt for cyclophosphamide. The non-drug means of achieving immunosuppression have produced valuable information but remain the special province of a few research centres.

VERNA WRIGHT

Professor of Rheumatology,
University of Leeds, Leeds LS2 9PJ

- Dixon JS, Bird HA, Pickup ME, Wright V. A human model screening system for the detection of specific antirheumatoid activity. *Semin Arthritis Rheum* 1982;12:185-90.
- Martin MFR, Dixon JS, Hickling P, Bird HA, Golding J, Wright V. A combination of D-penicillamine and hydroxychloroquine for the treatment of rheumatoid arthritis. *Ann Rheum Dis* 1982;41:208.
- Martin MFR, Surrall KE, McKenna F, Dixon JS, Bird HA, Wright V. Captopril—a potential new treatment for rheumatoid arthritis. *Lancet* 1984;ii:1325-7.
- Neumann V, Hopkins R, Dixon JS, Bird HA, Wright V. Pulsed methylprednisolone in rheumatoid arthritis—alone or in combination. *British Journal of Rheumatology* 1984;23:118-9.
- Bird HA, Wright V. Immunoactive drugs. In: *Applied drug therapy of the rheumatic diseases*. Bristol: Wright, 1982:162-81.
- Mason RM, Curry HLF, Barnes CG. Azathioprine in rheumatoid arthritis. *Br Med J* 1969;ii:420-1.
- Co-operating Clinics Committee of the American Rheumatism Association. A controlled trial of cyclophosphamide in rheumatoid arthritis. *N Engl J Med* 1970;283:833-89.
- Gubner R, August S, Ginsberg V. Therapeutic suppression of tissue reactivity. II. Effect of aminopterin in rheumatoid arthritis and psoriasis. *Am J Med Sci* 1951;221:176-82.
- Hatchuel R. Efficacité et mode d'action du chlorambucil dans la poly-arthrite rhumatoïde. Etude contrôlée en double insu. A propos 47 observations. Memoire pour l'obtention du Certificat d'Etudes Speciales en Rheumatologie, Paris.
- European League Against Rheumatism. Levamisole. Proceedings of a symposium, June 1978. *J Rheumatol* 1978;5 (suppl 4).
- Graf U, Marbet U, Muller W, Thiel G. Cyclosporin A—Wirkungen & Nebenwirkungen bei der Behandlung der Chronischen Polyarthritiden und der Psoriasisarthritis. *Immun Infekt* 1981;9:20.
- Bunch TW, O'Duffy JD. Disease-modifying drugs for progressive rheumatoid arthritis. *Mayo Clin Proc* 1980;55:161-79.
- Malaise MG, Franchimont P, Bach-Anderson R, *et al*. Treatment of active rheumatoid arthritis with slow intravenous injections of thymopentin. *Lancet* 1985;ii:832-6.
- Curry HLF, Harriss J, Mason RM, *et al*. Comparison of azathioprine, cyclophosphamide, and gold in treatment of rheumatoid arthritis. *Br Med J* 1974;iii:763-6.
- Dixon JS, Bird HA, Sitton NG, Pickup ME, Leatham PA, Wright V. Serum biochemistry in relation to the action of azathioprine in rheumatoid arthritis. *Agents Actions* 1983;13:373-9.
- Harvey C, Dixon JS, Bird HA. Serum IgA concentration and hepatotoxicity in rheumatoid arthritis treated with azathioprine. *Br Med J* 1983;287:534.
- Hunter T, Vrowitz MB, Gordon DA, Smythe HA, Ogryzlo MA. Azathioprine in arthritis: A long term follow-up study. *Arthritis Rheum* 1975;18:15-20.
- Hoover R, Fraumeni JR. Risk of cancer in renal treatment recipients. *Lancet* 1973;ii:55-7.
- Hazleman BL, De Silva M. The comparative incidence of malignant disease in rheumatoid arthritis exposed to different treatment regimens. *Ann Rheum Dis* 1982;41 (suppl):12-7.
- Rownes AS, Sowa JM, Segelman LE. Controlled trial of cyclophosphamide in rheumatoid arthritis. *Arthritis Rheum* 1976;19:563-73.
- Co-operating Clinics Committee of the American Rheumatism Association. A controlled trial of high and low doses of cyclophosphamide in 82 patients with rheumatoid arthritis. *Arthritis Rheum* 1972;15:434 (abstract).
- Smyth CJ, Bartholomew BA, Mills BM. Cyclophosphamide therapy for rheumatoid arthritis. *Arch Intern Med* 1975;135:789-93.
- Hall ND, Bird HA, Ring EFJ, Bacon PA. A combined clinical and immunological assessment of four cyclophosphamide regimens in rheumatoid arthritis. *Agents Actions* 1979;9:97-102.
- Huskisson EC, Adams JG. An overview of the current state of levamisole in the treatment of rheumatoid diseases. *Drugs* 1980;19:100-4.
- Laym CY, Goldstein G. Functional effects of thymopentin on cytotoxic lymphocyte precursor units. *J Immunol* 1980;124:1861-3.
- Paulus HE, Macheder HI, Levine S, Yu DTY, MacDonald NS. Lymphocytic involvement in rheumatoid arthritis. Studies during thoracic duct drainage. *Arthritis Rheum* 1977;20:1249-62.
- Veio T, Tanaka S, Tominaga Y, Ogana H, Sakurami T. The effect of thoracic duct drainage in lymphocyte dynamics and clinical symptoms in patients with rheumatoid arthritis. *Arthritis Rheum* 1979;22:1405-12.
- Wallace DL, Goldfinger D, Gratti R, *et al*. Plasmapheresis and lymphoplasmapheresis in the management of rheumatoid arthritis. *Arthritis Rheum* 1979;22:709-10.
- Rothwell RS, Gordon PA, Davis P, *et al*. A controlled study of plasma exchange in the treatment of severe rheumatoid arthritis. *Arthritis Rheum* 1980;23:785-90.
- Karsh J, Klippel JH, Plotz PH, Wright DG, Flye W, Decker JS. Lymphopheresis in rheumatoid arthritis: a randomised trial. *Arthritis Rheum* 1980;23:701-2.
- Karsh J, Wright DG, Klippel JH, Decker JL, Deisseroth AB, Flye MW. Lymphocyte depletion by continuous flow centrifugation in rheumatoid arthritis. *Arthritis Rheum* 1979;22:1055-9.
- Strober S, Tanay A, Field E, *et al*. Effect of total lymphoid irradiation in intractable rheumatoid arthritis: a double-blind randomised trial. *Ann Intern Med* 1985;102:441-9.
- Trentmann DE, Belli JA, Anderson RJ, *et al*. Clinical and immunologic effects of fractionated total lymphoid irradiation in refractory arthritis. *N Engl J Med* 1981;305:976-82.
- Calin A. Irradiation in the management of rheumatoid disease. *Br J Hosp Med* 1985;34:261-5.
- Hubbard WN, Walport MJ, Halnan KE, Beane RP, Hughes GRV. Remission from polymyositis after total body irradiation. *Br Med J* 1982;284:1915-6.
- Engel WK, Lichter AS, Galdi AP. Polymyositis: remarkable response to total body irradiation. *Lancet* 1981;ii:658.