Immunosuppressive therapy in polymyositis

S. CURRIE AND J. N. WALTON

From the Regional Neurological Centre, The General Hospital, Newcastle upon Tyne

SUMMARY Immunosuppressive drugs were given to seven patients with polymyositis. The *in-vitro* activity of peripheral blood lymphocytes had previously been studied in five of these patients with findings suggestive of disturbed immunological processes. Some improvement occurred in five cases, but only in two was the improvement marked and sustained. In this small series of cases, the response to treatment was best in a patient with polymyositis who showed no evidence of involvement of tissues or organs other than muscle and in a second case with subacute polymyositis occurring in association with an unidentified connective tissue disorder. The response was less satisfactory in two patients with dermatomyositis, in two with polymyositis associated with systemic sclerosis, and in one in whom the muscle disorder complicated rheumatoid arthritis. At present such treatment is usually given only in cases which are resistant to, or intolerant of, steroids. The relative values of steroid and immunosuppressive therapy are discussed; a combination of the two in moderate doses may eventually prove to be the best initial treatment for the disorder.

Polymyositis is an acquired disorder in which necrosis of skeletal muscle fibres occurs with or without inflammatory cell infiltration; the skin may also be involved (dermatomyositis). In most cases steroid therapy in adequate dosage is followed by remission (Rose and Walton, 1966). However, such improvement is neither invariable nor predictable. An initial response to this therapy may not be sustained or the condition may be refractory on relapse. Other cases are controlled only at the cost of unacceptable side-effects. For these reasons, alternative therapy must occasionally be considered. Polymyositis probably has an immunological basis; evidence consistent with this view was recently summarized and was supported by the results of work carried out in this centre (Currie, Saunders, Knowles, and Brown, 1971). The action of steroid derivatives may be immunosuppressive as well as anti-inflammatory (Schwartz, 1969). American physicians have reported successful treatment with immunosuppressive agents in small numbers of cases (Malaviya, Many, and Schwartz, 1968; McFarlin and Griggs, 1968). The drugs which they used were methotrexate and azathioprine. The theoretical and practical aspects of the use of immunosuppressive drugs in general have been fully discussed by Schwartz (1965, 1969). Our own experience of treating polymyositis with such agents has been limited to a few cases and in these the regimes of treatment which were followed were somewhat arbitrary. Nevertheless, we feel that it is

worth commenting on the place of immunosuppressive therapy in this disorder in the light of our recent experience.

CASE REPORTS

There were seven patients in whom immunosuppressive agents were used; the salient clinical details are given in the Table. In six of these the polymyositis was accompanied by evidence of a multi-system disorder of connective tissue and was therefore classified as type β polymyositis (Research Group on Neuromuscular Disorders, 1968). These six cases included two of dermatomyositis, two of myositis occurring in association with progressive systemic sclerosis, one who also had rheumatoid arthritis, and another who had an unidentified connective-tissue disorder. In a single case the disorder appeared to be limited to the voluntary muscles and was classified as type α polymyositis, there being no evidence of involvement of other tissues or organs.

DERMATOMYOSITIS

CASE 1 (E.H., NGH No. N.33281) A 37 year old woman had a history of proximal weakness in the limbs, dysphagia, and a skin rash for one year when first seen by us. Tracheostomy had been performed six months after the onset of symptoms; it was needed for a period of three weeks. The patient had been unable to walk for five months. Prednisone in high doses had produced improve-

TABLE
DETAILS OF CASES TREATED AND OF DRUGS USED

Type of polymyositis*	Case no.	Duration of symptoms due to myositis at start of treatment (yr.)	Serum creatine kinase activity at time of therapy (i.u./l.)	Details of treatment	Effect of therapy
β Dermatomyositis	1. E.H.	1	26.5	Methotrexate 50 mg—single dose Azathioprine 125 mg daily for 9 mth	Moderate improvement
	2. K.P.	3.5	80.1	Methotrexate 75 mg weekly for 2 mth	?Deterioration
β Myositis with progressive systemic sclerosis	3. D.B.	1.5	393	Cyclophosphamide 100 mg daily for 1 mth	Nil
	4. V.N.	3.5	51.6	Methotrexate 100 mg weekly for 1 mth	?Slight improvement
β Myositis with rheumatoid arthritis	5. D.C.	2	59	Methotrexate 100 mg weekly for 2 mth	?Slight improvement
β Myositis with unidentified systemic disorder	6. F.W.	0.7	225	Cyclophosphamide 100 mg daily for 6 mth	Marked improvement
α 'Uncomplicated'	7. J.M.	5	633	Cyclophosphamide 600 mg daily for 12 mth	Marked improvement

* α —uncomplicated. β —with connective tissue disorder.

ment initially and after a first relapse, but had not done so at the time of a subsequent relapse. On examination, in addition to extreme muscular weakness there were marked generalized changes in the skin. Electromyography of several muscles gave findings suggestive of a severe, active myopathy. Biopsy of the left quadriceps femoris muscle showed advanced myopathic changes without inflammation (an earlier biopsy had shown perivascular lymphocytic infiltrates). The serum creatine kinase (CK) activity was 26.5 i.u./l. (normal <60 i.u./l.). A single intravenous injection of 50 mg methotrexate was followed within days by a sharp fall in the white cell and platelet counts. Thereafter, oral azathioprine was given, in a daily dose of 125 mg, and there was a gradual improvement during the next few months, the patient becoming ambulant, though remaining severely disabled.

CASE 2 (K.P., NGH No. N.41067) A 15 year old girl gave a history of weakness of proximal limb musculature, dysphagia, and dermatitis for more than three years. Prednisone in high dosage had produced some improvement when it was given a year after the onset of the disorder, but when first seen the patient showed extreme weakness despite a maintenance dose of 15 mg daily. She also showed classical skin changes of dermatomyositis, particularly in the extremities, where there was subcutaneous calcification. Biopsy of the right deltoid muscle showed marked muscle fibre necrosis, with mononuclear cell infiltration, notably perivascular. A course of intravenous methotrexate was commenced, 100 mg being given every five days, then 75 mg at the same interval after the higher dose had resulted in buccal ulceration. When methotrexate was introduced, the daily dose of prednisone was reduced from 15 mg to 10 mg. After two months of such treatment muscular weakness was evidently increasing; the immunosuppressive therapy was therefore abandoned and the daily dose of prednisone was increased to 30 mg. There has been a gradual progressive improvement since then.

MYOSITIS WITH PROGRESSIVE SYSTEMIC SCLEROSIS

CASE 3 (D.B., RVI No. 580164) A 33 year old woman presented with a history of proximal upper limb weakness for 18 months and weakness of the neck and trunk for six months. Raynaud's phenomenon had occurred for years; latterly there had been soreness of the fingers and tightness of the skin round the mouth. Examination showed the typical skin changes of systemic sclerosis. There was marked wasting and weakness of shoulder girdle musculature, with minimal weakness in the lower limbs. Electromyography of the right deltoid muscle demonstrated myopathic changes. Biopsy of the left quadriceps muscle showed large areas of necrosis with endomysial and perimysial infiltrates, mainly of mononuclear cells. The serum CK activity was 393 i.u./l. Blood lymphocytes showed cytotoxicity to muscle and epithelial cultures and stimulation by muscle antigen (Currie *et al.*, 1971). A diagnosis was made of polymyositis occurring in association with systemic sclerosis. Treatment with 60 mg prednisone per day given for eight weeks produced no improvement in muscle power and no change in the skin condition. Cyclophosphamide, 100 mg per day for four weeks, did not improve her condition either, although subsequently the blood lymphocytes showed a reduced degree of stimulation. The disorder has since remained static for two years.

CASE 4 (V.N., NGH No. N.28753) A 56 year old woman had a history of muscle weakness and skin tightness and pigmentation for more than three years. These symptoms had become marked by the time of inpatient investigation six months before treatment with immunosuppressive drugs. Electromyography of several affected muscles showed myopathic changes. Muscle biopsy was refused. Barium swallow and small bowel studies demonstrated the characteristic changes of systemic sclerosis. A diagnosis was made of polymyositis occurring in association with systemic sclerosis. Prednisone (up to 60 mg per day)

was given intermittently for eight weeks but caused intolerable gastrointestinal symptoms and no improvement in muscle power. Six months later the patient showed extreme wasting and weakness of all muscles and was confined to bed. The serum CK activity was 51.6 i.u./l. Blood lymphocytes were cytotoxic to both muscle and renal cultures and showed marked stimulation by muscle antigen (Currie *et al.*, 1971). Methotrexate was given intravenously in an initial dose of 50 mg followed by 100 mg weekly. After a total of five injections there was slight subjective and objective improvement in muscle power.

MYOSITIS WITH RHEUMATOID ARTHRITIS

CASE 5 (D.C., RVI No. 665311) A 65 year old woman presented with generalized weakness of the limbs, most marked proximally, which had been present and increasing for two years. There was a history of rheumatoid arthritis for 10 years. Electromyography of the right deltoid muscle revealed unquestionable evidence of myopathy but a biopsy from the left quadriceps femoris muscle showed no significant abnormality. She was treated with prednisone 60 mg per day with marked improvement in muscular power, and this continued as the dose was slowly reduced. However, two years later a relapse occurred which did not respond to treatment with oral prednisone 20 mg daily; this therapy induced marked hyperglycaemia requiring insulin. At this stage the patient was confined to bed with extreme wasting and weakness of the limbs and trunk and incipient cardiac failure. The serum CK activity was 59 i.u./l. The arthritis was quiescent. Blood lymphocytes showed cytotoxicity to muscle cultures and stimulation by muscle antigen (Currie *et al.*, 1971). It was not clear to what extent active myositis accounted for her muscle weakness and how much her immobility was due to rheumatoid arthritis. Intravenous methotrexate was given in an initial dose of 50 mg and then 100 mg weekly. She received a total of 750 mg over a period of two months without any side-effects. At the end of this period there was objective improvement in proximal muscle power and the patient could walk with assistance. Blood lymphocytes remained cytotoxic to muscle cells in culture but showed a reduced degree of stimulation. At this stage the daily dose of prednisone had been reduced to 5 mg per day; insulin was no longer needed and the cardiac failure remitted. However, the patient's mental state and the lack of social support made further mobilization impracticable. The therapy was therefore stopped. The patient died three months later from a cerebral vascular incident; necropsy was not performed.

MYOSITIS WITH AN UNIDENTIFIED CONNECTIVE-TISSUE DISORDER

CASE 6 (F.W., RVI No. 695272) This case has been described more fully elsewhere (Mastaglia and Currie, 1971). A 62 year old woman presented with a history of proximal upper and lower limb weakness for nine months. Raynaud's phenomenon had occurred for many years. On examination there was severe wasting, weakness, and tenderness of proximal muscles. Biopsy of the left deltoid muscle revealed marked loss and necrosis of muscle

fibres and widespread mononuclear cell infiltration. Electromyography of several muscles showed gross myopathic changes. The serum CK activity was 225 i.u./l. Immunoassay of the serum proteins suggested a polyclonal gammopathy. The Sia water test, Rose-Waaler test (1:8), and a test for antinuclear factor were all positive. *In vitro* studies of peripheral blood lymphocytes showed cytotoxicity to muscle and to renal epithelial cultures and marked stimulation by muscle antigen (Currie *et al.*, 1971). It was suggested that a malignant reticulosis might underlie the condition and treatment was commenced with prednisone (15 mg per day) and cyclophosphamide (100 mg per day). There was a rapid improvement in muscle power. Eight months later the patient was symptom free and all treatment had been withdrawn. Her blood lymphocytes retained their cytotoxicity, but the degree of stimulation by muscle antigen had fallen, though not to a normal level. The diagnosis was considered to be one of polymyositis occurring in association with an unidentified generalized disorder of connective tissue.

'UNCOMPLICATED' TYPE α POLYMYOSITIS

CASE 7 (J.M., RVI No. 704643) A 64 year old man gave a history of weakness of proximal limb musculature for five years. Three years after the onset he was admitted for investigation. Electromyography of the right deltoid and quadriceps muscles gave findings suggestive of myopathy and a left deltoid muscle biopsy showed foci of necrosis and mononuclear cell infiltration. There was a partial response to prednisone 60 mg per day; subsequently any reduction below 20 mg per day was followed by clinical relapse with increased weakness. Congestive cardiac failure developed, persisting despite appropriate therapy including cardioversion. In August 1969 the patient had moderate weakness of deltoid, spinati, and iliopsoas muscles, with minimal weakness of other muscles. The serum CK activity was 633 i.u./l. Blood lymphocytes showed cytotoxicity for muscle cultures and stimulation by muscle antigen (Currie *et al.*, 1971). Cyclophosphamide was given in an initial dose of 100 mg per day, increasing over a period of six weeks to 600 mg per day. Within one month there was subjective improvement and objective evidence of improved muscle power became apparent after two months. The prednisone was reduced to 5 mg per day during the next four months. The patient's exercise tolerance increased as the heart failure remitted. One year after cyclophosphamide was started, he was still taking 600 mg daily of this drug, the prednisone had been stopped and clinical improvement was continuing.

DISCUSSION

The safety of immunosuppressive drugs was firmly attested by Swanson and Schwartz (1967) and compares favourably with that of steroid derivatives. They reported benefit in several disorders; side-effects such as serious leucopenia or infection were exceptional. Tests showed that there was a depression of immune responses but clinical effectiveness

did not depend upon this. Schwartz (1969) listed mercaptopurine, methotrexate, and cyclophosphamide as the most effective agents for the induction of immunological tolerance. Mercaptopurine, of which azathioprine is a derivative, can selectively block the development of delayed hypersensitivity (Borel and Schwartz, 1964). Methotrexate can not only do this but can also heal tuberculous ulcers (Friedman, 1964). In experimental work, much larger doses of these drugs have been needed to suppress established hypersensitivity than to prevent its induction (Friedman, Buckler, and Baron, 1961; Gabrielsen and Good, 1967). This fact is of relevance to the treatment of human 'autoimmune' disorders, in that the drugs may have to be given in high dosage for long periods. Nevertheless, low doses of 6-mercaptopurine were reported by Asai and Chikada (1963) to produce remissions in idiopathic thrombocytopenic purpura. The usual effectiveness of steroid therapy in these human conditions has restricted the use of immunosuppressive drugs to small numbers of cases in which steroids have been impracticable or unavailing. The potential of an individual case to respond to immunosuppressive agents may parallel its steroid-responsiveness (Goodman, Wolff, Carpenter, Anderson, and Brandiss, 1963); these drugs are unlikely to be tested if steroids are given with good effect. A point must be reached in the progression of any disorder when neither steroid nor immunosuppressive therapy can be expected to halt the disease process or to improve function (Swanson and Schwartz, 1967).

The treatment of polymyositis by immunosuppressive drugs, as described in previous reports and in this paper, illustrates many of these comments. Malaviya *et al.* (1968) obtained an improvement in four cases with intravenous methotrexate. In each case the disorder was subacute, developing over a period of weeks. One case had not responded to steroid therapy and one failed to respond after a relapse; in a third, aged 65 years, steroids were not used at all. McFarlin and Griggs (1968) treated three cases with oral azathioprine. In one there was a response to prednisone but the dose of this drug could not be reduced without deterioration and severe side-effects developed. The second case did not respond to ACTH during a relapse, while the third was not given steroid therapy. In two of these patients discontinuation of the azathioprine was followed by exacerbation.

The uniform benefit reported within weeks of commencing therapy in these seven cases previously reported prompted us to use immunosuppressive drugs in those of our patients in whom the condition was refractory to steroid therapy. Of the seven cases reported, only three (cases 4, 5, and 7) were under our

immediate care, so that no consistent therapeutic regimen was employed. The variable results which have been obtained reflect the need for careful selection of cases and for adequate therapeutic trials. The most striking improvement occurred in case 6 whose condition responded to relatively small doses of prednisone and cyclophosphamide within three weeks. The initial dose of prednisone (15 mg) was only a quarter of that which Rose and Walton (1966) recommended if the drug were to be used alone; clearly it was much less likely to produce side-effects. Equally the small dose of cyclophosphamide made the possibility of serious leucopenia a remote one. It is ironic that the drug regime in this patient was based on the erroneous assumption that the patient might be suffering from malignant disease as well as polymyositis. The rapid improvement in this case is even more noteworthy because polymyositis in association with connective-tissue disorders, type β of the Research Group on Neuromuscular Disorders (1968), is less likely to respond to steroid therapy than is uncomplicated type α polymyositis (Rose and Walton, 1966). Little or no improvement occurred in any of the other five patients with type α polymyositis (dermatomyositis, or polymyositis occurring in association with progressive systemic sclerosis or with rheumatoid arthritis). Indeed case 7, one of type α polymyositis, was the only other case in which improvement was remarkable. This man's condition differed from the subacute disorder which was present in all the seven treated cases previously reported in the literature. This patient had a chronic myopathy which was only partly responsive to a dose of prednisone which had been sufficient to induce cardiac failure. The myositis improved with cyclophosphamide and the prednisone was later stopped without relapse. In our two patients who improved, long-term immunosuppressive therapy was uncomplicated without obvious side-effects. In cases 4 and 5 the improvement was temporary and equivocal; in them the drugs were used as a last resort. In each, muscular atrophy was extreme and there were other factors which made prolonged immunosuppressive therapy impracticable. Systemic sclerosis is notably unresponsive to steroid therapy (Winkelmann, 1961) as in our case 3. In this patient, the therapeutic trial of cyclophosphamide was probably inadequate and this drug produced no improvement either; there could possibly have been a response to more prolonged treatment with higher doses. In the second case of systemic sclerosis (case 4) methotrexate produced slight and insignificant improvement.

Based upon our observations, we feel that the following tentative conclusions can be drawn:

1. If a case of acute or subacute polymyositis fails to respond to high doses of prednisone (60-80 mg daily)

within four weeks, then immunosuppressive drugs can be commenced, increased rapidly to standard dosage, and given for at least two months. During this period the prednisone can safely be reduced to a moderate dose (such as 15 mg daily) or in some instances it can be withdrawn completely. Serial estimations of the serum creatine kinase (CK) activity may help by demonstrating a response before this is clinically evident; however, we have not found the level of this enzyme to be as accurate a guide to clinical activity of the disease as have others (Pearson, 1969).

2. Immunosuppressive drugs can be given as the sole initial therapy when for any reason prednisone is contraindicated. In chronic myositis they can be used along with moderate doses of prednisone when there is only partial responsiveness to the latter therapy alone.

3. There would seem to be little prospect that either steroid or immunosuppressive therapy will be of benefit in chronic 'burnt-out' cases, however disabled the patient may be. Nevertheless, even in such cases it may sometimes be justifiable to give a trial course of one or both forms of therapy for up to two months, accompanied by intensive efforts at rehabilitation.

4. Our preliminary evidence and the work of others suggest that it is immaterial which immunosuppressive drug is given. Cyclophosphamide is the easiest to handle but has the disadvantage that it often causes depilation. Azathioprine is an acceptable alternative but may have a greater tendency to cause leucopenia. Methotrexate should be avoided if there is impaired renal or hepatic function (Swanson and Schwartz, 1967). The effect on the blood count of a single injection of methotrexate in the first of the present cases is remarkable; it may have resulted from an idiosyncratic reaction to the drug.

5. No clear directions can be given yet concerning maintenance therapy. In only one of the seven cases previously reported had the drug been stopped. The doses which are required for such maintenance treatment are low. However, prolonged treatment may lead to infection, such as that by opportunistic viruses (Montgomerie, Becroft, Croxson, Doak, and North, 1969), and possibly to neoplasia (Burnet, 1967). In discussing the problem of relapses in polymyositis, Rose and Walton (1966) recommended that steroid therapy should be given for at least two years. If a combination of steroid and immunosuppressive therapy has been given initially, as in case 1, it would seem reasonable to phase out the immunosuppressive drug after a year, while continuing a small dose of prednisone. When immunosuppressive therapy has been given alone, gradual withdrawal could be tried at the end of a year.

6. With two types of therapy, steroid and immunosuppressive agents, both of proven efficacy and safety, the exhibition of anti-lymphocytic antiserum in polymyositis would seem to be justified only in the most exceptional circumstances.

The implications of responsiveness to either steroid or immunosuppressive therapy have been discussed by Schwartz (1969). He and his co-workers (Malaviya *et al.*, 1968) used methotrexate empirically in the absence of evidence of an immunological pathogenesis in dermatomyositis. *In vitro* studies of peripheral blood lymphocytes have been carried out in a group of patients with polymyositis (Currie *et al.*, 1971); these have included five of the patients in the present series. In polymyositis there was a raised index of transformation when lymphocytes were cultured with whole muscle homogenate. The lymphocytes were cytotoxic to cultures of foetal muscle; in addition, renal cultures were destroyed by lymphocytes from patients suffering from polymyositis in association with connective-tissue disorders (type β). Stimulation by an antigenic component of muscle may represent sensitization occurring as a secondary phenomenon. However, lymphocytes from patients with muscular wasting due to muscular dystrophy were not stimulated. It is uncertain how far the *in vitro* cytotoxicity of lymphocytes represents a corresponding action *in vivo* (Perlmann and Holm, 1970). However, the results clearly indicate that there is a disturbance of immunological processes in polymyositis and suggest that sensitized lymphocytes are possibly instrumental in producing the disorder. In four cases the *in vitro* studies were repeated after immunosuppressive therapy; there was a reduction in the degree of lymphocyte stimulation but the cytotoxic potential of the cells persisted. These findings are in some respects comparable with those of Swanson and Schwartz (1967) who found that the depression of immune responses was variable and that it was not always consistent with the clinical response to therapy. The efficacy of immunosuppressive drugs in polymyositis is further evidence that any role which viruses may have in the pathogenesis of the condition is an indirect one. The occasional finding on electron microscopy of intracellular virus-like particles in muscle biopsy specimens from patients with the condition (Chou, 1968; Mastaglia and Walton, 1970) could be taken to suggest that it is a direct viral myositis. However, it is more likely that viruses are merely one of several agents which may alter the antigenic potential of muscle cells and precipitate a hypersensitivity reaction against these (Isacson, 1967).

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