SHORT REPORT

Treatment of chronic inflammatory demyelinating polyradiculoneuropathy with methotrexate

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We discovered many reports of other immunosuppressive drugs being used in adults with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) but none of methotrexate. As weekly low dose oral methotrexate is safe, effective, and well tolerated in other diseases, we treated 10 patients with otherwise treatment resistant CIDP. Seven showed improvement in strength by at least two points on the MRC sum score and three worsened. Only two showed an improvement in disability and both were also receiving corticosteroids. We discuss the difficulty of detecting an improvement in treatment resistant CIDP and propose methotrexate as a suitable agent for testing in a randomised trial.

Systematic reviews of randomised controlled trials endorse the general opinion that chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) usually shows an initial response to corticosteroids, intravenous immunoglobulin (IVIg) or plasma exchange.[1–3] However, the response may be incomplete and often wanes with time, so that immunosuppressive drugs are often tried despite the absence of evidence from randomised trials.[4] The drug most commonly used is azathioprine, but ciclosporin, cyclophosphamide, mycophenolate, and rituximab have all been tried.[4] In a search of MedLine and EmBase until March 2005, we only found a single report of methotrexate used in the treatment of CIDP, in which a child showed a good response, but this was not quantified or described in detail.[5] As methotrexate is an effective and well tolerated agent in other autoimmune conditions, we have begun to offer it to patients with CIDP who have had an inadequate response to their initial treatment. We report our experience with the first 10 patients.

METHODS

With permission from the local ethics committees, one author (DF) retrospectively audited the case notes of all patients treated with methotrexate for CIDP at the peripheral nerve clinics of Guy's Hospital and the National Hospital for Neurology, London. Patients fulfilled recognised clinical criteria for CIDP[6] and had neurophysiological evidence of demyelination. We did not exclude patients with paraproteinaemia. Patients received oral methotrexate 10–15 mg in divided doses once weekly under folic acid cover. Demographic data, clinical features, Medical Research Council (MRC) sum score (expanded to include the first dorsal interosseous muscles), 10 m walk time, Overall Disability Sum Score (ODSS),[6] and the opinion of the patient concerning their improvement were extracted onto a prepared form by one author (DF). The ODSS score ranges from 0 (no disability) to 12 (maximum disability); for example, the ability of a patient to walk independently with an abnormal gait compared with the requirement for unilateral support translates into a 1 point difference on the scale.

RESULTS

Clinical features

Details of the patients and their responses to treatment are given in table 1. Three patients had a serum paraprotein, including one (patient 4) with an IgM paraprotein, which developed 9 years after the onset of the neuropathy, and two others, with IgG lambda (patient 8) and IgG kappa (patient 9) paraproteins.

Six subjects fulfilled the Inflammatory Neuropathy Cause and Treatment (INCAT) electrophysiological criteria for CIDP.[6] The four patients whose electrophysiological results did not fulfil the INCAT neurophysiological criteria all had features of demyelination on biopsy. All patients had an elevated CSF protein (range 0.47–2.8 g/l; normal 0.15–0.45 g/l).

Response to treatment

Two patients had symptomatic and objective responses to methotrexate. Patient 1 reported subjective improvement in ptosis. His MRC sum score increased by 3 points, 10 m walk time did not change significantly, and ODSS remained unchanged. After discontinuing the treatment, there was a 3 point drop in the MRC score and an increase in the ODSS by 1 point. Despite this, it was considered that the benefit from methotrexate had been insufficient to justify continuing treatment. Patient 5 had been partially responsive to steroid and plasma exchange. He had not responded to immunoabsorption,[7] interferon-β 1a,[8] IVIg, azathioprine, or ciclosporin. After commencing methotrexate the patient improved by 7 points on the expanded MRC sum score and maintained this improvement for 12 months. He discontinued treatment for 10 months, worsened by 7 points, restarted, improved by 6 points, and remains on treatment 12 months later.

Another patient (patient 2) reported symptomatic improvement, but this was not accompanied by significant change in the impairment or disability measures used. Two patients improved or stabilised while receiving both methotrexate and corticosteroids. Patient 8 remained stable but IVIg dependent for several years. Following a relapse that coincided with the diagnosis of transitional cell carcinoma of the bladder, she was maintained on corticosteroids and methotrexate. On this combination, she required no IVIg for 7 months. She then had a further relapse and is now maintained on corticosteroids, IVIg, and methotrexate. Patient 9 suffered a severe relapse that was complicated by a life threatening pulmonary embolism while being treated with IVIg. He improved markedly while receiving a combination of corticosteroids, IVIg and methotrexate.

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment; IVIg, intravenous immunoglobulin; MRC, Medical Research Council; ODSS, Overall Disability Sum Score

Table 1 Clinical features and methotrexate treatment details

No.	Age/ Sex	Type and duration of CIDP (years)	Other illness	Previous treatment	Concurrent immuno-suppressive treatment	MTX dose and duration	Before/after MTX			Adverse effects	Reason for discontinuation and comments
							MRC sum score (out of 70)	10 m walk (seconds)	ODSS		
1	58/M	SSMCIDP, 41	–	Dexamethasone, IVIg	Prednisolone 25 mg alternate days	12.5 mg weekly for 52 weeks	56/59	4.6/5.0	4/4	None	Insufficient benefit, subjectively ptosis slightly improved, after discontinuing MTX slight deterioration
2	27/F	SSMCIDP, 19	–	Prednisolone, azathioprine, PE, IVIg, ciclosporin, IFN-β, tacrolimus, mycophenolate	IVIg 0.5 g/kg every 2 weeks; prednisolone 20 mg alternate days	10–12.5 mg weekly for 172 weeks and cont.	46/48	9.6/8.4	7/7	Transient mild hair loss	
3	57/M	MADSAM, 16	B12 deficiency; DVT; hypertension	Prednisolone, PE, IVIg, mycophenolate	None	15 mg weekly for 40 weeks	60/63	11.3/13.5	6/7	Chest infection	No benefit
4	70/M	SSMCIDP, 10	Diabetes	IVIg, PE, azathioprine, mycophenolate, cyclophosphamide, ciclosporin	Prednisolone 30 mg alternate days	10–15 mg weekly for 40 weeks	55/46	Unable/69	6/8	None	No benefit
5	44/M	SSMCIDP, 18	Depression	Azathioprine, PE, ciclosporin, IVIg, IFN-β, immunoabsorption	Prednisolone 30 mg alternate days	15 mg weekly for 64 weeks, recommenced after 1 year for 52 weeks and cont.	57/64; at re-starting 57/62	15/10.9; at re-starting 13.6/9.8	4/4	None	Stopped in between for personal reasons, response to MTX shown twice in MRC and 10 m walk time
6	70/F	SSMCIDP, 29	Hypertension; DVT	IVIg,IFN-β, PE, ciclosporin,	Prednisolone 15 mg alternate days; IVIg 1 g/kg	15 mg weekly for 45 weeks	60/64	14/10	5/6	None	No definite benefit, 4 point improvement in MRC sum score but ODSS deteriorated and no subjective improvement, fluctuating course
7	78/M	SSMCIDP, 10	Cutaneous vasculitis; hypertension; Ca prostate	prednisolone, cyclophosphamide, IVIg, methyl-prednisolone, mycophenolate	None	15 mg weekly for 32 weeks	18/6	Unable/unable	10/11	None	No benefit
8	76/F	SSMCIDP, 8	Severe pre-existing osteoporosis; chickenpox with cardiac involvement as child; bladder Ca; recurrent DVT during IVIg treatment; plasma cell dyscrasia	IVIg, PE, azathioprine	Prednisolone reducing course 50 mg once daily–4 mg once daily; IVIg 2 g/kg every 6–8 weeks, re-started 7 months after commencing MTX	15 mg weekly for 53 weeks and cont.	65/68	27 with frame/7 without aid	6/4	None	MTX and corticosteroids prevented relapses and need for IVIg for 7 months: then relapsed on MTX associated with relapse of bladder carcinoma
9	70/M	SSMCIDP, 4	L4/5 discectomy complicated by persistent foot drop post-op, DVT, pulmonary embolism	IVIg, azathioprine, prednisolone	IVIg 2 g/kg every 3 weeks; prednisolone reducing from 70 mg–12.5 mg once daily	15 mg weekly for 27 weeks and cont.	34/56	Unable/unable	11/7	None	Marked improvement while treated with high dose corticosteroids and MTX simultaneously
10	67/M	SSMCIDP,<1	Hypertension	IVIg, prednisolone	IVIg 2–3 g/kg every 1–2 weeks, plasma exchange, then mycophenolate, then ciclosporin	15 mg weekly for 20 weeks	62/	8.5/	4/	Death	Marked deterioration and death (see text)

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; SSMCIDP, symmetrical sensory motor CIDP; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; IVIg, intravenous immunoglobulin; PE, plasma exchange; IFN, interferon; DVT, deep vein thrombosis; cont., continuing; MRC, Medical Research Council.

Of the other five patients, two showed improvements in MRC sum score and three worsened.

Adverse events

Methotrexate was generally well tolerated and no patient had to discontinue treatment because of abnormal blood parameters. In patient 2, the dose of methotrexate was transiently reduced to 10 mg weekly due to a possible relationship with mild hair loss. The dose was later increased with no further hair loss. Patient 3 developed a severe chest infection after 8 months of treatment without neurological improvement and then discontinued methotrexate without any further change in his condition. Despite transient responses to IVIg and plasma exchange, patient 10 had an inexorable downhill course despite the addition of first mycophenolate and then ciclosporin to the methotrexate regimen, and died suddenly with hypotension and fever of undiagnosed cause.

DISCUSSION

In this, apparently the first,series of adult patients with CIDP treated with methotrexate, seven of 10 patients had improvements in their MRC sum scores and five improved symptomatically. Four showed measurable improvements in impairment or reduction in concomitant treatment, although in two of these, simultaneous treatment with corticosteroids confounds interpretation of the response. Although the proportion of responders was low and the extent of the response was limited, it was considered worthwhile by the patients themselves, and four continue on methotrexate.

Several factors militated against detecting a treatment effect. The patients were known to have an inadequate or no response to other immunomodulatory treatments, consistent with a heterogeneous underlying pathogenesis, which might be responsive to immunosuppressive drugs only in a proportion of cases. Most patients had advanced disease, so that much of the impairment and disability was probably due to axonal degeneration that may have been irreparable. Our impairment and disability measures were not sufficiently responsive to capture the symptomatic improvement reported by one of the patients. The doses used by us were in the lower range of those used in randomised trials showing efficacy in rheumatoid arthritis, which have varied from 7.5 to 25 mg weekly.[9]

Methotrexate inhibits the dihydrofolate reductase enzyme, leading to the inhibition of de novo purine and pyrimidine synthesis. The resulting inhibition of DNA synthesis in proliferating cells is the dominant effect at high doses used in oncological practice. Although methotrexate has some antiproliferative effect even at low doses of 7.5–20 mg per week, other mechanisms, including induction of apoptosis in cells involved in immune and inflammatory reactions, inhibition of both monocytic and lymphocytic proinflammatory cytokine secretion, and indirect inhibition of cyclooxygenases and lipooxygenases, may account for its anti-inflammatory properties.[10] A Cochrane review concluded that low dose methotrexate may be efficacious in secondary progressive multiple sclerosis[11] in addition to rheumatoid arthritis and psoriasis. Observational studies suggest that it is efficacious in dermatomyositis, polymyositis and inflammatory bowel disease.[12 13] The apparent broad spectrum anti-inflammatory action of methotrexate is appropriate for a disease such as CIDP in which the pathogenesis is uncertain, probably involving macrophages and both B and T cells.[14]

For a chronic condition such as CIDP, low toxicity is especially important. Methotrexate commends itself from this point of view. Although one of our patients developed a chest infection and another died while also receiving corticosteroids, plasma exchange, and ciclosporin, such occurrences are exceptional. In a series of 248 patients with rheumatoid arthritis, 79% of patients were continuing on treatment after 5 years.[15] Monitoring of haematological and liver function rarely detected significant abnormalities, and only 26 patients discontinued the treatment due to side effects.

Our experience with methotrexate is difficult to compare with other series treated with other agents. The most commonly used drug is probably azathioprine, but there are no case series describing its use and the single randomised trial reported did not demonstrate efficacy.[16] Both cyclophosphamide[17] and ciclosporin[18] have been reported to have high rates of success but also serious side effects. The treatment responses reported with these drugs have sometimes been greater than ours, but comparison is difficult because of differences in disease duration, severity, and previous and concomitant treatment. Published experience with mycophenolate, rituximab, etanercept, and other agents is extremely limited.[4]

In our series, five of seven patients who had shown a previous response to IVIg or corticosteroids improved with methotrexate, whereas all three patients who had not shown such response did not. This suggests that patients with secondary treatment resistance are more likely to respond to a second line immunosuppressive agent than those who show primary treatment failure.

The retrospective, unblinded nature of this study limits the conclusions that can be drawn but the findings are sufficient to prompt testing the efficacy of methotrexate in a randomised controlled trial.

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