

EFNS guideline on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis relapses

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Relapses, exacerbations or attacks of multiple sclerosis are the dominating feature of relapsing-remitting multiple sclerosis (MS), but are also observed in patients with secondary progressive MS. High-dose methylprednisolone is the routine therapy for relapses at present, but other treatments are also in current use. The objective of the task force was to review the literature on treatment of MS relapses to provide evidence-based treatment recommendations. Review was carried out on the literature with classification of evidence according to the EFNS guidelines for scientific task forces. Short-term, high-dose methylprednisolone treatment should be considered for the treatment of relapses of MS (level A recommendation). The optimal glucocorticoid treatment regimen, in terms of clinical efficacy and adverse events, remains to be established. A more intense, interdisciplinary rehabilitation programme should be considered as this probably further improves recovery after treatment with methylprednisolone (level B recommendation). Plasma exchange is probably efficacious in a subgroup of patients with severe relapses not responding to methylprednisolone therapy, and should be considered in this patient subgroup (level B recommendation). There is a need for further randomized, controlled trials in order to establish the optimal treatment regimen for relapses of MS.

Background

Relapses, exacerbations or attacks of multiple sclerosis (MS) are the dominating feature of relapsing-remitting MS, but are also observed in patients with secondary progressive MS with superimposed relapses. Even patients with primary progressive MS may experience relapses (Lublin and Reingold, 1996; Confavreux *et al.*, 2000). In the McDonald criteria for the diagnosis of MS, a relapse is defined as 'an episode of neurological disturbance of the kind seen in MS, when the clinicopathological studies have established that the causative lesions are inflammatory and demyelinating in nature' (McDonald *et al.*, 2001). An attack should last for at least 24 h and, according to the McDonald criteria, there should be expert opinion that the event is not a pseudoattack as might be caused by an increase in body temperature or infec-

tion. Multiple episodes of paroxysmal symptoms, e.g. tonic spasms or trigeminal neuralgia occurring over not less than 24 h, may also constitute a relapse. Although the majority of relapses improve to some extent, incomplete recovery is an important determinant of irreversible neurological impairment in MS at least in the earlier stages of MS (Confavreux *et al.*, 2003; Lublin *et al.*, 2003).

Glucocorticoid treatment is recommended as the first-line treatment of MS relapses in North American guidelines and in the recommendations of a European consensus group on therapy in MS (Goodin *et al.*, 2002; Multiple Sclerosis Therapy Consensus Group, 2004). Other treatments for MS relapses have also been studied in clinical trials. The aim of the EFNS task force on treatment of MS relapses was to review the current literature on relapse treatment. Important issues to consider were whether treatment of MS relapses: (i) can improve the speed of recovery; (ii) can influence long-term recovery; (iii) can influence subsequent disease activity and (iv) has significant side-effects. Furthermore, the task force sought to provide guidelines on whether all relapses should be treated

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and how relapses during pregnancy should be managed.

Search strategy

We searched literature databases (Embase and PubMed) in English for papers using the search terms 'multiple sclerosis', 'attack', 'relapse', 'exacerbation' and 'treatment' in November 2004. The Cochrane Library and the reference lists of individual papers were searched for studies not identified in the Embase and PubMed searches. Studies of various treatments for patients suffering from relapses of MS were considered for the guidelines and were rated as class I to class IV studies according to the recommendations for EFNS scientific task forces (Brainin *et al.*, 2004).

Method for reaching consensus

The results of the literature searches were circulated by e-mail to the task force members for comments. The task force chairman prepared a first draft of the manuscript based on the results of the literature review and comments from the task force members. The draft and the recommendations were discussed during telephone conferences until consensus was reached within the task force. Recommendations were rated from A to C according to the EFNS guidelines for scientific task forces (Brainin *et al.*, 2004). Where there was insufficient evidence to support firm recommendations the term 'Good practice point' was used.

Results

Effect of glucocorticoid and adrenocorticotrophic hormone treatment on MS relapses

Glucocorticoid or adrenocorticotrophic hormone (ACTH) treatment of MS relapses was analysed in a Cochrane review which included results from six randomized, placebo-controlled clinical trials of either ACTH (two trials), intravenous (IV) methylprednisolone treatment (three trials) or oral methylprednisolone treatment (one trial) (Miller *et al.*, 1961; Rose *et al.*, 1970; Durelli *et al.*, 1986; Milligan *et al.*, 1987; Filipovic *et al.*, 1997; Sellebjerg *et al.*, 1998). All trials reported a benefit in terms of rate of recovery compared with placebo (Filippini *et al.*, 2000). A similar conclusion was reached in another meta-analysis, which used less stringent criteria for study inclusion than the Cochrane review (Brusaferri and Candelise, 2000).

Three trials have compared the relative efficacy of IV methylprednisolone and ACTH treatment in MS relapses (Abbruzzese *et al.*, 1983; Barnes *et al.*, 1985; Thompson *et al.*, 1989). One study including 14 patients treated with IV methylprednisolone (1 g daily for 7 days) and 11 patients treated with intramuscular (IM) ACTH (80 units, 60 units, 40 units, and 20 units daily, each for 1 week) reported more rapid improvement (after 3 and 28 days) after IV methylprednisolone treatment than after ACTH treatment, but there was no significant difference after 3 months (Barnes *et al.*, 1985). The patient blinding and the primary outcome were not clearly defined, however, for which reason this study should be considered a class III study. One class II study compared the administration of 1 g of methylprednisolone once daily for 3 days to ACTH treatment (80 units for 7 days, 40 units for 4 days, and 20 units for 3 days) in 61 patients, and found no difference in terms of rate of recovery or final outcome after 12 weeks (Thompson *et al.*, 1989). A class III study including 60 patients, treated with either IV methylprednisolone (20 mg/kg, day 1–3; 10 mg/kg, day 4–7; 5 mg/kg day, 8–10; and 1 mg/kg, day 11–15) or ACTH (1 mg IV daily for 15 days), also did not provide evidence of any difference in the efficacy of ACTH and methylprednisolone treatment (Abbruzzese *et al.*, 1983). These three studies found no major differences in adverse events between methylprednisolone and ACTH treatment. Thus there is no evidence of any major difference in the efficacy of ACTH and methylprednisolone treatment from comparative studies, but the clinical trials were too small to rule out some difference in efficacy. Indeed, in the Cochrane review it was suggested that methylprednisolone treatment could still confer greater benefit than treatment with ACTH, and the administration of methylprednisolone is simpler than the more prolonged treatment with ACTH (Filippini *et al.*, 2000).

In a separate meta-analysis (Miller *et al.*, 2000) of three double-blind, randomized, controlled trials comparing methylprednisolone treatment (500 mg or more daily) to placebo, it was concluded that treatment with IV methylprednisolone (15 mg/kg, day 1–3; 10 mg/kg, day 4–6; 5 mg/kg, day 7–9; 2.5 mg/kg, day 10–12; 1 mg/kg, day 13–15 followed by oral prednisone tapered slowly over 120 days; Durelli *et al.*, 1986), IV methylprednisolone without a tapering dose (500 mg once daily for 5 days; Milligan *et al.*, 1987), or oral methylprednisolone (500 mg once daily for 5 days followed by 400, 300, 200, 100, 64, 48, 32, 16, 8, and 8 mg once daily the subsequent 10 days; Sellebjerg *et al.*, 1998) resulted in significantly faster recovery than did treatment with placebo (Table 1). The two first trials provided follow-up data in a placebo-controlled design

Table 1 Summary of three randomized, placebo-controlled trials comparing methylprednisolone (MP) treatment to placebo in patients with relapses of MS (Durelli *et al.*, 1986; Milligan *et al.*, 1987; Sellebjerg *et al.*, 1998). Data are changes in Kurtzke EDSS scores from baseline (mean and standard deviation in brackets) or differences (mean and 95% confidence intervals in brackets) between MP and placebo reported in a meta-analysis (Miller *et al.*, 2000)

Study and treatment	Change from baseline	Difference (MP versus placebo)
Day 5–7		
Durelli; placebo (<i>n</i> = 8)	0 (0)	
IV methylprednisolone (<i>n</i> = 12)	–1.00 (0.6)	–1.00 (–1.45 to –0.55)
Milligan; placebo (<i>n</i> = 9)	–0.28 (0.51)	
IV methylprednisolone (<i>n</i> = 13)	–1.46 (1.38)	–1.18 (–2.19 to –0.17)
Sellebjerg; placebo (<i>n</i> = 25)	–0.06 (0.44)	
Oral methylprednisolone (<i>n</i> = 26)	–0.58 (0.82)	–0.52 (–0.89 to –0.14)
Pooled difference		–0.76 (SE 0.14)
Day 21–28		
Durelli; placebo (<i>n</i> = 8)	–0.38 (0.52)	
IV methylprednisolone (<i>n</i> = 12)	–2.04 (1.48)	–1.67 (–2.82 to –0.51)
Milligan; placebo (<i>n</i> = 8)	–0.25 (1.22)	
IV methylprednisolone (<i>n</i> = 13)	–2.04 (1.51)	–1.79 (–3.11 to –0.46)
Sellebjerg; placebo (<i>n</i> = 25)	–0.38 (0.81)	
Oral methylprednisolone (<i>n</i> = 26)	–0.94 (0.90)	–0.56 (–1.04 to –0.08)
Pooled difference		–0.85 (SE 0.21)

for 15 days (Durelli *et al.*, 1986) and 28 days (Milligan *et al.*, 1987). The oral methylprednisolone study found significant differences between the methylprednisolone and the placebo group after 8 weeks, but there was no significant difference in the outcome after 1 year (Sellebjerg *et al.*, 1998). In the latter trial there was no evidence that the 1-year risk of subsequent relapses was influenced by oral high-dose methylprednisolone treatment.

Specific glucocorticoids, dose, and route of administration

The clinical trials of glucocorticoid treatment in relapses of MS have mainly assessed the effect of methylprednisolone treatment. Two trials have compared the effect of methylprednisolone treatment given IV or orally. One class III study compared the effect of methylprednisolone (500 mg once daily for 5 days) given orally or IV in 35 patients with an MS relapse, and found no significant difference in recovery between the two treatment arms after 5 and 28 days (Alam *et al.*, 1993). Another study (class I) compared the effect of oral methylprednisolone (48 mg daily for 7 days, 24 mg daily for 7 days, and 12 mg daily for 7 days) to treatment with IV methylprednisolone (1 g daily for 3 days; Barnes *et al.*, 1997). In this study recovery from the relapse was similar in the 38 patients in the IV treatment group and the 42 patients in the oral treatment group at all time points for up to 24 weeks of follow-up. The relapse rate the following 2 years was also similar in the oral and IV treatment group (Sharrack *et al.*, 2000).

Oral tapering doses of glucocorticoids have been used in many trials, but none have compared the outcome of a relapse in patients treated with tapering doses of

glucocorticoids or placebo following short-term high-dose treatment.

Three studies have compared IV methylprednisolone treatment given in different doses. One class III study found that recovery was faster after treatment with IV methylprednisolone (1 g once daily for 5 days) than after a single 1 g dose of IV methylprednisolone (Bindoff *et al.*, 1988). Two other studies (both class III) have compared the effect of different doses of IV methylprednisolone in relapses of MS on a panel of different outcome measures. In the first study treatment with IV methylprednisolone at a dose of 500 mg once daily for 5 days was compared with treatment with 2000 mg once daily for 5 days in 31 patients with a relapse of MS (Oliveri *et al.*, 1998). There was no difference in the efficacy of the low dose and the high dose of methylprednisolone in terms of clinical recovery or short-term suppression of magnetic resonance imaging (MRI) disease activity, but it was suggested that the high dose resulted in more pronounced suppression of MRI disease activity after 1 and 2 months. In the second study IV methylprednisolone at a dose of 1 or 2 g once daily for 5 days was compared in 24 patients who were followed up with clinical and neurophysiologic studies for 21 days after randomization to one of the two treatment arms (Fierro *et al.*, 2002). This study showed no significant differences between the two methylprednisolone doses on the majority of diverse outcome measures, but a few favoured the higher dose over the lower dose. Two studies have compared the effect of treatment with different doses of methylprednisolone and dexamethasone in relapses of MS (Milanese *et al.*, 1989; La Mantia *et al.*, 1994). Because of the small sample sizes and the differences in the baseline characteristics of the patients randomized to

the different treatment arms, the results of these two studies are difficult to interpret.

Glucocorticoid treatment of acute optic neuritis

In the North American Optic Neuritis Treatment Trial (ONTT) 457 patients were randomized to receive treatment with IV methylprednisolone (250 mg four times daily for 3 days followed by oral prednisone, 1 mg/kg for 11 days, 20 mg on day 15, and 10 mg on days 16 and 18), oral prednisone (1 mg/kg for 14 days, 20 mg on day 15, and 10 mg on days 16 and 18), or oral placebo (Beck *et al.*, 1992). Treatment allocation was not blinded in patients randomized to treatment with IV methylprednisolone, whilst prednisone treatment and placebo was given in a double-blind design. Thus, the study was regarded as a class II study investigating the efficacy of methylprednisolone treatment, but as a class I study in the comparison of oral prednisone and placebo. The study found no significant effect of IV methylprednisolone or oral prednisone treatment on the recovery of visual acuity, but the recovery of contrast sensitivity and visual fields was significantly faster in patients treated with IV methylprednisolone. After 6 months patients treated with IV methylprednisolone had still recovered slightly better than patients treated with placebo, but no significant treatment effect was seen at follow-up after 1 year (Beck *et al.*, 1993a). Oral prednisone treatment had no effect on the recovery from acute optic neuritis in neither the ONTT nor a Danish class I study of oral prednisolone versus placebo in 128 patients with acute optic neuritis (Beck *et al.*, 1992; J.L. Frederiksen, personal communication). Treatment with oral methylprednisolone (100, 80, 60, 40, 30, 20, 10, and 5 mg daily for 3 days each) was not better than treatment with oral thiamine (100 mg daily for 24 days) on any of several outcome measures in a class II study including 38 patients with acute optic neuritis (Trauzettel-Klosinski *et al.*, 1993).

Two additional studies (class I) have compared the effect of treatment with high-dose methylprednisolone in acute optic neuritis. One study included 60 patients with acute optic neuritis who were treated with oral high-dose methylprednisolone (500 mg once daily for 5 days followed by 400, 300, 200, 100, 64, 48, 32, 16, 8, and 8 mg once daily the subsequent 10 days) or oral placebo (Sellebjerg *et al.*, 1999). Oral methylprednisolone treatment resulted in significantly better recovery of spatial visual function (visual acuity and contrast sensitivity), colour vision function, and visual symptoms after 1 week, but only borderline significant effects were observed after 3 weeks, and after 8 weeks there was no evidence of an effect of oral methylprednisolone

treatment (Sellebjerg *et al.*, 1999). In a study of 66 patients with acute optic neuritis treatment with IV methylprednisolone (1 g once daily for 3 days) did not improve the outcome from acute optic neuritis after 26 weeks on neither a panel of visual function and neurophysiologic variables nor on MRI outcome measures (Kapoor *et al.*, 1998).

A controversial finding in the ONTT was that patients treated with IV methylprednisolone appeared to have a lower risk of developing MS during 2 years of follow-up than patients treated with placebo. This was not statistically significant in the original trial report (Beck *et al.*, 1992), but reached a significance level of $P = 0.03$ (not corrected for multiple comparisons) in a *post hoc* analysis where the baseline status of many patients had been reclassified (Beck *et al.*, 1993b; Goodin, 1999). It was also suggested that oral prednisone treatment was associated with an increased risk of recurrent optic neuritis, but not an increased risk of subsequently developing MS (Beck *et al.*, 1992 and 1993b). As there was no blinding to methylprednisolone treatment, and as the effect of treatment on MS risk was only observed after reanalysis and reclassification of the initial data, this part of the ONTT must be regarded as a class III study. Another class III study (a retrospective natural history study) has suggested that IV methylprednisolone treatment (1 g once daily for 3 days) could actually increase the risk of subsequently developing MS (Herishanu *et al.*, 1989). In the latter study a surprisingly low risk of conversion to MS was, however, observed in the control group of untreated patients and patients treated with oral prednisone.

Glucocorticoid treatment in MS subgroups

Whether subgroups of patients with MS relapses may benefit more from glucocorticoid treatment has been addressed only in few studies. It has been suggested that patients with more severe relapses are more likely to respond to treatment with IV methylprednisolone (class IV evidence, Nos *et al.*, 2004). Another uncontrolled (class IV) study suggested that patients with high cerebrospinal fluid (CSF) concentrations of myelin basic protein (MBP) are more likely to improve after IV methylprednisolone treatment (Whitaker *et al.*, 1993). This finding was confirmed using 1-week follow-up data in a *post hoc* analysis of patients included in two randomized, placebo-controlled trials of oral high-dose methylprednisolone treatment (Sellebjerg *et al.*, 2003). However, the additional benefit of methylprednisolone treatment in patients with high CSF concentrations of MBP was not sustained at follow-up after 8 weeks, whilst patients who had an active gadolinium-enhanced MRI at baseline appeared to benefit from treatment

even at follow-up after 8 weeks (class III evidence, Sellebjerg *et al.*, 2003).

Side-effects of glucocorticoid treatment

In the placebo-controlled trials serious adverse events were not observed after high-dose methylprednisolone treatment. (Durelli *et al.*, 1986; Milligan *et al.*, 1987; Sellebjerg *et al.*, 1998). Milligan *et al.* (1987) did not report the precise frequency of adverse events, but noted that treatment was surprisingly free from serious adverse events. Those most frequently reported were a slight reddening of the face, transient ankle swelling, and a metallic taste in the mouth during infusion. In the Cochrane review it was concluded that the oral administration of methylprednisolone is associated with a higher frequency of side-effects (mainly gastrointestinal and psychic disorders), and that oral administration should be avoided for this reason (Filippini *et al.*, 2000). In the study of Durelli *et al.* (1986) the incidence of elevated mood and insomnia increased during the study from two of 11 patients (18%) treated with intravenous high-dose methylprednisolone at day 5 to 5 out of 11 patients (45%) at day 15. In the study of oral high-dose treatment with an oral tapering dose and a total treatment duration of 15 days, disturbed sleep was observed in 65% and slight mood changes in 23% (Sellebjerg *et al.*, 1998), which is not significantly different from the frequency observed by Durelli and coworkers. In the study by Durelli *et al.* (1986) gastrointestinal side-effects were not reported, but all patients received prophylactic antacid treatment. In the study of oral high-dose methylprednisolone treatment gastrointestinal side-effects (mainly heartburn not requiring symptomatic treatment) was observed in 38% of patients treated with oral methylprednisolone and 8% in the placebo group (Sellebjerg *et al.*, 1998). The only randomized comparison of IV and oral treatment with methylprednisolone at equivalent doses did not report the exact frequency of side-effects, but found that the side-effects (including gastrointestinal side-effects) of oral and IV methylprednisolone treatment were similar (Alam *et al.*, 1993). This is supported by the results of a smaller, non-randomized class III study comparing treatment with IV methylprednisolone and oral prednisone at equivalent doses, which also failed to detect any difference in the side-effects of oral and IV treatment (Metz *et al.*, 1999).

In a review of 240 patients who had been treated with one or more courses of IV methylprednisolone (1 g daily for 5 days followed by 10 days of oral prednisone treatment), minor infections were observed in four patients, one patient had a single seizure within 12 h of treatment, 11 patients were noted to have glucosuria

during treatment, five had gastrointestinal symptoms that required antacid or H₂ antagonist treatment, three patients had an exacerbation of acne, ankle oedema was recorded in two patients, and one patient was hypertensive during treatment. A feeling of well being was common (frequency not given), and four patients had episodes of euphoria whereas two patients were depressive. Transient facial flushing, a transient disturbance of taste, distal paraesthesia, insomnia, and mild weight gain occurred in a significant proportion of patients, but the exact frequency was not stated (Lyons *et al.*, 1988).

Severe side-effects of methylprednisolone treatment are rare, but psychosis, acute pancreatitis, and anaphylactoid reactions to IV treatment have been reported (Pryse-Phillips *et al.*, 1984; Chrousos *et al.*, 1993; van den Berg *et al.*, 1997). Short-term methylprednisolone treatment in patients with MS appears to be safe in terms of long-term effects on bone mineralization, but pulsed methylprednisolone treatment has marked short-term effects on bone metabolism, and the available studies do not entirely rule out adverse effects on bone structure (Dovio *et al.*, 2004).

Other treatments

A single class I crossover study of 22 patients with severe relapses of inflammatory demyelination (including 12 with MS) who were refractory to treatment with high-dose methylprednisolone suggested a beneficial effect of treatment with plasma exchange (Weinshenker *et al.*, 1999). In this study there was 'moderate' or 'marked' improvement during plasma exchange treatment in eight of 19 patients (42%), whereas such improvement was observed only after one of 17 courses (6%) of sham treatment ($P = 0.01$). An effect of plasma exchange on 10 patients with acute optic neuritis who had not improved after high-dose IV methylprednisolone treatment has also been reported in an open (class IV) study (Ruprecht *et al.*, 2004).

A Cochrane review and studies of treatment with intravenous immunoglobulin (IVIG) have shown that prophylactic treatment may result in a decrease in the number of relapses in patients with relapsing-remitting MS (Gray *et al.*, 2003; Sørensen *et al.*, 2004). A single class IV study of IVIG treatment in relapses of MS suggested that as many as 68% of patients improved within 24 h of treatment (Soukop and Tschabitscher, 1986). Two recent studies have investigated if IVIG treatment as add-on to therapy with high-dose IV methylprednisolone is superior to add-on placebo treatment (Sørensen *et al.*, 2004: class I study; Visser *et al.*, 2004: class II study). Both studies were negative on primary and secondary end-

points. In addition, a randomized class I trial of treatment with IVIG or placebo in 68 patients with acute optic neuritis failed to detect any treatment effect (Roed *et al.*, 2005). Similarly, whereas treatment with natalizumab appears to lower the frequency of relapses in MS, natalizumab was not efficacious in the treatment of relapses in a randomized, placebo-controlled class I study of 180 patients with an MS relapse (O'Connor *et al.*, 2004).

A single class II study compared the effect of multidisciplinary rehabilitation to the effect of 'standard therapy' in a randomized clinical trial design, where both treatment arms received IV methylprednisolone treatment. The study suggested that a multidisciplinary team rehabilitation programme results in better functional recovery after 3 months than does treatment with IV methylprednisolone in a 'standard' setting (Craig *et al.*, 2003).

Treatment of relapses during pregnancy

There are no specific studies on relapse treatment in pregnant patients with MS, but short-term treatment with glucocorticoids is generally considered safe in pregnant women, and treatment may be considered in patients with a relapse of sufficient severity to warrant treatment, although treatment during the first trimester should probably be avoided (class IV evidence: Ferrero *et al.*, 2004).

Recommendations

There is consistent evidence from several class I studies and meta-analyses for a beneficial effect of glucocorticoid treatment in relapses of MS. Hence, treatment with intravenous or oral methylprednisolone in a dose of at least 500 mg daily for 5 days should be considered for treatment of relapses (level A recommendation). Treatment with IV methylprednisolone (1 g once daily for 3 days) should be considered as an alternative treatment (good practice point; Multiple Sclerosis Therapy Consensus Group, 2004). Treatment with IV methylprednisolone (1 g once daily for 3 days with an oral tapering dose) may be considered for treatment of acute optic neuritis (level B recommendation).

There is no evidence of major differences in the efficacy of methylprednisolone treatment given IV or orally in terms of clinical efficacy or side-effects, but prolonged, oral treatment may possibly be associated with a higher prevalence of side-effects. Furthermore, because of the low number of patients included in the available clinical trials, some efficacy differences between the IV and oral route of administration cannot be excluded. The optimal dosage, the specific gluco-

corticoid to be used, and whether to use a taper after initial pulse therapy, has not been adequately addressed in randomized, controlled trials. This implies a need for new, randomized studies assessing risk/benefit ratios and adverse effects of specific glucocorticoids, dose, and route of administration for treatment of MS relapses.

There is insufficient data to clearly define patient subgroups who are more likely to respond to methylprednisolone treatment, but treatment may be more efficacious in patients with clinical, MRI, or CSF evidence (increased MBP concentration in CSF) indicating higher disease activity (level C recommendation). Administration of treatment in an inpatient or outpatient setting has not been addressed in clinical trials, but consideration could be given to administering the first course of methylprednisolone as an inpatient (good practice point).

In patients who fail to respond to therapy with methylprednisolone in the dose range used in the randomized, placebo-controlled trials (Durelli *et al.*, 1986; Milligan *et al.*, 1987; Filipovic *et al.*, 1997; Sellebjerg *et al.*, 1998), treatment with higher doses (up to 2 g daily for 5 days) should be considered (level C recommendation; Multiple Sclerosis Therapy Consensus Group, 2004).

Patients with inflammatory demyelination, including patients with MS, who have not responded to treatment with methylprednisolone may benefit from plasma exchange treatment, but only about one-third of treated patients are likely to respond. This treatment regimen should probably be restricted to a subgroup of patients with severe relapses (level B recommendation). A randomized, controlled study specifically addressing the effect of plasma exchange in patients with severe relapses of MS not responding to methylprednisolone treatment would be desirable.

A more intense, interdisciplinary rehabilitation programme should be considered after treatment with IV methylprednisolone as evidence from a single trial suggests that this probably further improves recovery (level B recommendation).

There is insufficient data to support the use of IVIG therapy as monotherapy for relapses of MS. Treatment with IVIG as an add-on to treatment of MS relapses with methylprednisolone or as monotherapy for acute optic neuritis is not efficacious (level A recommendation). Neither is natalizumab as monotherapy efficacious in MS relapses.

Update

These guidelines will be updated when substantial new data pertaining to the treatment of MS relapses become available.

Conflicts of interest

Finn Sellebjerg has received a travel grant and an unrestricted research grant from Pharmacia.

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