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Corticosteroids and plasma exchange in multiple sclerosis

Abstract Corticosteroids (CS) remain a mainstay of treatment for relapses in multiple sclerosis (MS) and optic neuritis. Currently, there is not enough evidence that long-term corticosteroid treatment delays progression of long-term disability in patients with MS. Likewise, it is unclear whether there are, in fact, true differences among the various CS agents, doses, and their applications in specific pulse and tapering regimens.

In some patients suffering from severe steroid-resistant relapses, the clinical response to CS treatment may be insufficient. Such patients may obtain clinical benefit from subsequent plasma exchange (PE). PE is increasingly considered as an individual treatment decision in patients with severe relapses not properly responding to CS. Because of the lack of appropriate studies, PE is not recommended as a permanent disease-modifying strategy in MS patients.

Key words steroid, corticosteroid · plasma exchange · plasmapheresis · multiple sclerosis

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Corticosteroids

Introduction

Corticosteroids (CS) very potently prevent and suppress inflammation. Because of their potent anti-inflammatory effects, CS have been used to treat MS patients since the 1950s, and today they are considered the standard treatment for acute exacerbations [8, 10, 27]. High-dose, short-term intravenous CS therapy provides symptomatic relief, improves motor function, and shortens the recovery phase of acute disease-related attacks.

Treatment of choice of an acute relapse is a 3–5 day course of pulsed intravenous methylprednisolone (MP) at a dose between 500 and 1000 mg per day. Experiences with even higher doses (2000–5000 mg/d) indicate more effective treatment with regard to reduction of relapse severity and duration. Although cumulating scientific rationale supports application of corticosteroids for this purpose, the broad diversity of approaches with regard to route of application, dose and duration of treatment derives from expert opinion and anecdotal experience [6, 10].

Mechanism of action

The effects of CS on the immune system are thought to be threefold:

1) Very rapid, non-specific, non-genomic effects occur within seconds after exposure of a cell to high CS concentrations. It appears that these non-specific, non-genomic effects are the result of a direct interaction of CS with cell membranes.
2) Rapid, specific, non-genomic effects of CS are mediated by steroid-selective receptors on the cell surface. These receptors communicate with a second messenger system and occur within a few minutes. Alternatively, direct physicochemical interactions between CS and the cell membrane could account for these effects.
3) Delayed genomic effects are mediated by cytosolic CS receptors. Within 30 minutes of a steroid dose, engagement of these receptors leads to the activation of a signaling cascade, and ultimately decreases the transcription of numerous largely pro-inflammatory mediators [10, 11].

Despite the long history of CS research and the wide use

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of these drugs in the clinical management of MS, many open questions remain with regard to their mechanism of action, such as,

- what molecular mechanisms underlie the effects of CS in MS,
- what cell-types are the predominant targets of CS in MS therapy,
- what induces apoptosis, down-regulation of inflammatory mediators, compromised antigen presentation or effects on the BBB [26].

Studies and experiences with CS treatment to control relapse and disease progression

Several studies and a Cochrane review showed that a short-term high dose intravenous methylprednisolone (i.v. MP) course within 8 weeks of acute exacerbation of MS improved symptoms and short-term disability without significant side effects [9, 19, 25] (Table 1).

In a study two doses (2 g vs 0.5 g) of i.v. MP were compared, where the higher dose was significantly more ef-

Table 1 Summary of selected trials of corticosteroids for controlling relapses and disease progression

Study	Design	No. & subtype patients	Application route, type of steroid, dosing and duration	Outcome
Intravenous and oral application of MP for relapse recovery and tolerability				
Milligan et al., 1987	db, pc, r	50 RR, SP	i.v. MP 0.5 g/d for 5 d vs placebo	High-dose MP effective in RR-MS, less effective in SPMS
Thompson et al., 1989	db, r	61 RR	i.v. MP 1 g/d for 3 d vs i.m. ACTH for 14 d	No difference at 3, 7, 14, 28 or 90 d MP better tolerated
Oliveri et al., 1998	db, r	40 RR	i.v. MP 2 g/d for 5 d vs i.v. MP 0.50 g/d for 5 d	Dose-dependent reduction of Gd+ lesions in 2 g/d group at 30 and 60 d
Alam et al., 1993	db, r	35 RR	i.v. MP 0.5 g/d for 5 d + oral placebo vs oral MP 0.5 g/d for 5 d + i.v. Placebo	No difference after 5 or 28 days with regard to clinical effect and tolerability
Barnes et al., 1997	db, pc, r	80 RR	i.v. vs. oral MP	No clear advantage of the i.v. regime at 1, 4, 12, 24 weeks
Intravenous and oral application of MP in AON for long-term effect				
Beck et al., 1992 (ONTT)	db, pc, r	457 AON	i.v. MP 250 mg/d for 3 d oral taper over 11 d vs oral MP 1 mg/kg KG 14 d vs placebo	i.v. treatment arm superior with initial better recovery from visual disturbance; At 2 years conversion to MS 8 % (i.v.) vs 14 % (oral); At 4 years no significant difference
Chronic application of MP for long-term effect and tolerability				
Zivadinov et al., 2001	sb, r, phase 2, 5 years	88 RR	i.v. MP 1 g/d for 5 d + oral taper I: each 4 mts (3 years), each 6 mts (2 years) vs II: only for acute relapses	after 5 years good tolerability, EDSS significantly better in group I, MRI results also better in group I
Intravenous application in SPMS for preventing disease progression				
Goodkin et al., 1998	db, r, phase 2, 2 years	108 SP	i.v. MP 500 mg/d for 3 d, + oral taper over 11 d vs i.v. MP 10 mg/d for 3 d + oral taper over 11 d (every 2 mts for 2 years)	High-dose MP group showed good tolerability and tendency to less progression
Combined application of MP and DMD on long-term effect and tolerability				
Cohen et al., 2008 ACT-Study	sb, r, 1 year	313 RR	Avonex + i.v. MP vs Avonex + i.v. MP+ MTX 20 mg/week vs Avonex monotherapy	No difference between the groups, good tolerability in all groups, premature ending of study due to poor recruitment of patients
Havrdova et al., (AAN 2007) AAS-Study	pc, r, 5 years	181 RR	Avonex vs Avonex+AZA 50 mg p.o. vs Avonex+AZA+MP 10 mg p.o.	After 2 and 5 years no significant difference between all groups, good tolerability in all groups
Intrathecal application in chronic progressive MS				
Hellwig et al., 2004 and 2006	open label	161 SP, PP	i.th. TCA (Volon A) 6x (40 mg/3 d)	Significant effect of i.th. TCA – Therapy on EDSS, Barthel-Index, walking distance, SSEP (2004) i.th. TCA therapy shows more effect than mitoxantrone on EDSS and walking distance (2006)

AZA Azathioprine; *BUN* blood urea nitrogen; *CBC* complete blood count; *CP* chronic progressive; *Cr* creatine; *Cycl* cyclophosphamide; *db* double-blind; *GI* gastrointestinal; *IIDD* idiopathic inflammatory demyelinating, disease; *IOP* intraocular pressure; *i.v.* intravenous; *MP* methyl prednisolone; *MTX* methotrexate; *mts* months; *pc* placebo-controlled; *PE* plasma exchange; *sb* single-blind; *ONTT* optic neuritis treatment trial; *RR* relapse-remitting

fective than the lower dose in reducing the number of MRI contrast-enhanced lesions at 30 and 60 days after a clinical relapse, mainly by decreasing the rate of new lesion formation [21].

A small number of studies have demonstrated that high-dose oral steroid regimens appear comparable to those administered parenterally, with similar benefit and tolerability [2, 3].

In addition, these studies have shown that high-dose oral steroid treatment has no impact on gastric permeability changes, emphasizing the principle that steroid-related gastritis is not related to direct effects of these agents on gastric mucosa, but rather secondary systemic mechanisms (regardless of the route of administration) are likely. Likewise, a similar bioavailability of CS under oral and parental administration has been demonstrated [20].

Since oral CS regimens are often the most simple, convenient, and cost-effective regimens, oral application may be recommended for the treatment of MS exacerbations if i.v. application poses practical problems.

Beyond the effects on controlling acute relapses, several phase II studies showed that corticosteroids might prevent new exacerbations, reduce long-term disability, and therefore modify the natural history of MS.

The initial results of the Optic Neuritis Treatment Trial suggested that treatment of a first episode of optic neuritis with a single course of i.v. MP followed by a tapering course of oral prednisone reduced the 2 year rate of development of clinically definite MS, although this effect was lost on further follow-up extending to 4 years [4, 5].

A phase II randomized controlled trial (RCT) in relapsing-remitting (RR) MS, comparing the efficacy of repeated pulsed i.v. MP with i.v. MP at the same dosage regimen but administered only for relapses, showed that pulsed i.v. MP slowed the development of destructive lesions (T1 black holes), the rate of whole-brain atrophy progression and the development of sustained physical disability [30].

Another phase II RCT of bimonthly i.v. MP pulses in patients with secondary progressive (SP) MS showed a beneficial effect on time to onset of sustained progression of disability with the high-dose regimen [12].

Combination studies

Several ongoing studies investigate the combination of CS and immune modulatory drugs such as IFNn-1a (Avonex, ACT study) [7]. The ASSERT study is investigating the effect of high-dose oral prednisone plus glatiramer acetate (Copaxone) *versus* Copaxone alone on brain atrophy in RRMS patients. Another study is investigating the effects of IFN-1b (Betaseron) alone or in combination with monthly IVMP in SPMS patients. Several other studies are investigating the combination of pulse IVMP with subcutaneous IFN-1a (Rebif 22 and 44 mg).

Intrathecal application of CS

An open label study analyzed the application of the steroid triamcinolone acetonide (TCA) administered intrathecally six times within three weeks on a regular basis every third day in 161 hospitalized primary and predominant SPMS patients with spinal symptoms. It was reported that following intrathecal application of TCA clinical and electrophysiologic outcome parameters improved significantly with only rare side effects such as post lumbar puncture syndrome. More effect on EDSS was observed in the intrathecal TCA group than in the mitoxantrone group [13, 14].

Side effects of CS

The adverse-event profile is mostly associated with the chronic utilization of CS. Some patients, however, can exhibit highly conspicuous and intolerable side effects even with very short courses of CS. The more commonly encountered problems are listed in Table 2.

Recommendation to minimize or prevent side effects includes regular lab assessments, and supplementation with vitamin D and calcium (500 mg, 2–3 times daily, as tolerated). In patients with evidence of osteopenia or osteoporosis, antiresorptive agents such as bisphosphonates and calcitonin are used.

Conclusions

Use of high-dose, short-term intravenous CS therapy for acute disease-related attacks in MS is an established standard, as they are reported to be well-tolerated and safe, with only minor and dose-related side effects. However, there is not enough evidence that long-term corticosteroid treatment delays progression of long-term disability in patients with MS. An adequately powered, high quality RCT is needed to confirm that the administration of pulsed high-dose i.v. MP is associated with a significant reduction in the risk of long-term disability progression in patients with RRMS [10].

Moreover, the above mentioned studies mainly consisting of class II evidence show that the current data do not provide sufficient evidence for the many relevant practices:

1) use of a specific steroid for exacerbations, with the exception of a first event of optic neuritis (in which case the standard of care is high-dose i.v. MP, 1 g/day for 3 days, followed by a prednisone taper);

Table 2 Recommendation for treatment of MS with corticosteroids

evidence	Dosing and tapering regimens	Lab assessment	Safety, adverse effects
for controlling relapses			
Class I and II evidence for accelerating recovery from relapses	1) i.v. MP, 0.5 g–2 g /d for 3–5 d 2) Oral prednisone, 250–1000 mg/d, for 3–5 d 3) Various schemes for tapering regimens over 10–14 d	Acute monitoring for 1) diabetes patients; 2) anticoagulation patients; 3) glaucoma patients (intraocular pressure) CBC with differentials; BUN–Cr, electrolytes, glucose, lipid profile, bone density, Chest X-ray, urine analysis	Behavioral effects a) Depression b) Euphoria c) Agitation d) Anxiety e) Psychosis, Sleep derangements, Hypertension, Diabetes, Lipid derangements, Gastritis and reflux, Edema
for controlling disease progression			
Some class II evidence for pulse steroid treatment controlling relapses and progression	1. i.v. MP, 1 g/d (1–5 d)-monthly/quarterly for maintenance 2. Oral MP: 500–1000 mg daily (1–5 d)-monthly, every other month, or quarterly for maintenance	CBC with differentials; BUN–Cr, electrolytes, glucose, lipid profile, Ophthalmologic examination (IOP), bone density, urine analysis	GI side effects Mania, insomnia, headache, anxiety hyperglycemia, diabetes, lipid derangements, bone loss, cataracts, skin changes, vascular necrosis, myopathy, cushingoid features, glaucoma

See Table 1 for abbreviations

2) use of a specific steroid for relapse reduction;
3) a particular route of administration for steroids (i.v. or oral);
4) use of a particular dose of steroid for treatment of relapses.

Evidence class I studies are needed to determine whether there are, in fact, true differences among the various agents, doses, and their applications in specific pulse and tapering regimens. Unfortunately, a challenge to conduct such studies is the absence of any patent rights on these agents, and the long-existing perception that the use of these agents does not alter the ultimate course of the MS disease process.

Plasma exchange

Introduction

Plasma exchange (PE) made its way into neuroimmunology in the 1980s, via myasthenia gravis to autoimmune neuropathies, and finally into long-term MS treatment, mostly in combination with cytotoxic immunosuppressive therapy (Table 3). Therapeutic PE constitutes an extracorporeal blood purification technique designed to remove large molecular weight particles from plasma. The removal of circulating autoantibodies, immune complexes, cytokines, and other inflammatory mediators is thought to be the principal mechanism of action [18].

Therapeutic plasma exchange is based on the separation of plasma from the blood's cellular elements. This can be achieved with centrifugation devices or with permeable blood filters. During continuous or intermittent centrifugation, blood components separate because of differences in density. In membrane ultrafiltration, the separation is according to molecular size [17].

Studies with PE to control relapse and disease progression

Acute relapses and optic neuritis

The largest study investigating the effectiveness of plasma exchange in acute relapses in MS was a randomized, controlled, double-blind trial, where 116 patients were assigned to receive 11 treatment cycles of plasma exchange or sham exchange during 8 weeks [28]. Corticotropin (ACTH) and cyclophosphamide were given to patients in both groups as indicated. During the treatment period, a greater clinical improvement was observed in the plasma exchange group at 2 and 4 weeks. However, the long-term effect at 12 months was less clear.

In a placebo-controlled, cross-over study, Weinshenker and colleagues observed substantial improvement in 42 % of patients receiving seven treatment sessions of PE, whereas only 6 % in the sham treatment group. Importantly, PE had to be given within 6 weeks after onset of symptoms [29].

The usefulness of PE has also been shown in an open label study with improvement of optic neuritis symptoms in patients with MS or clinically isolated syndromes [23, 24].

Table 3 Summary of selected trials of plasma exchange in MS

Study	Design	No. & subtype patients	application route, type of steroid, dosing and duration	Outcome
Acute relapses				
Weiner et al., 1989	db	116 RR	PE (11x) + ACTH + p.o. Cycl vs. Placebo + ACTH + p.o. Cycl	PE patients had moderate improvement at 2 weeks. PE patients with relapsing or remitting disease had significantly marked improvement at 4 weeks. No clear long-term benefits.
Weinshenker et al., 1999	db	22 MS (12) IIDD (10)	PE vs sham treatment, crossover to alternative treatment in case of no improvement	Significant better improvement in primary outcome in 42 % of PE population vs 5.9 % of sham group.
Ruprecht et al., 2004	Open label	10 AON	PE	Improvement of visual acuity.
Chronic progressive				
Khatri et al., 1985	db	54 SP	PE + MP + Cycl vs. sham treatment + MP + Cyc	Better clinical improvement (EDSS) in PE group after 5 months.
Canadian Cooperative Multiple Sclerosis Study Group, 1991	sb	168 CP	i.v. Cycl + p.o. MP vs. p.o. Cycl+MP+PE vs. Placebo + sham treatment	No significant differences in EDSS at 6 and 12 months examinations.

See Table 1 for abbreviations

Chronic progressive MS

Khatri and co-workers were the first to report a randomized, controlled, double-blind trial of PE among 54 patients with a progressive form of MS [16]. In this study, a clinical benefit was shown after 5 months in the PE group compared with the sham treatment group. The larger 3-armed trial from the Canadian Cooperative Multiple Sclerosis Study Group randomized 168 patients with chronic progressive MS to receive daily cyclophosphamide and oral prednisone (n = 55), daily cyclophosphamide and prednisone every other day for 22 weeks and weekly plasma exchange for 20 weeks (n = 57), or placebo medications and sham plasma exchange (n = 56) [1]. The study showed no efficacy in the EDSS progression at 6 and 12 months of follow-up. Therefore the long-term benefit of PE in the treatment of chronic progressive forms of MS remains elusive, and plasma exchange cannot be recommended.

In a retrospective analysis of patients with fulminant attacks of MS who had had brain biopsy because of tumefactive lesions on MRI Keegan and colleagues studied histopathological patterns and treatment response to PE [15]. Primary treatment response was assessed independently from and without knowledge of the immunopathological classification. Finally, of the 19 patients, three patients had pattern I, ten patients had pattern II, and six patients had pattern III (distal oligodendrogliopathy). All patients of pattern II responded to PE with a median interval of 3 days, whereas none of the other individuals improved according to an established grading scale. Although the treatment groups were small, this study was the first to correlate histopathological changes in MS with treatment success.

Adverse events

Possible complications related to the use of central venous access, anticoagulation, or replacement fluids have to be considered, especially when treatment alternatives exist. Citrate infused for anticoagulation or as part of fresh-frozen plasma may lead to hypocalcemia or alterations in acid-base homeostasis (a metabolic acidosis resulting from the breakdown of bicarbonate). Symptoms of hypocalcemia include paresthesia, muscle cramps, and, in severe cases, cardiac arrhythmias. The incidence of hypocalcemia-related symptoms ranges from 1.5 % to 9 % [17]. Repeated apheresis treatments with albumin replacement may lead to depletion of coagulation factors and immunoglobulins, increasing the risk of bleeding and infections. Adverse effects that are related to the central venous access are infection and septicemia, thrombosis, and pneumothorax. If filtration techniques are used, hemolysis and hypotension may occur. Although extremely rare, there is a risk of viral transmission by replacement of fresh-frozen plasma [17].

Summary

PE treatment of relapses, with albumin-electrolyte solute as a replacement, has been evaluated in some studies for severe RRMS and optic neuritis refractory to conventional pulsed CS therapy. Based on these studies best effects can be expected when therapy is administered within 4–6 weeks after onset of symptoms. Therapeutic effects typically occur after a minimum of three sessions of PE. However, the evidence on its efficacy is still limited. Therefore this treatment modality is still to be considered as an individual treatment decision in patients with severe relapses not properly responding to CS. Currently, PE is not recommended as a permanent disease-modifying strategy in MS patients, because it was not tested appropriately [22].

Conflict of interest The author has participated in meetings sponsored by, and received honoraria from pharmaceutical companies marketing treatments for MS. His institution received financial support for participation in randomized controlled trials of IFNβ-1b (Betaferon, Schering), IFNβ-1a (Avonex, Biogen Idec; Rebif, Serono), glatiramer acetate (Copaxone, Teva), and Natalizumab (Tysabri, Biogen/Elan) in MS. He received honoraria for acting as advisor to various pharmaceutical companies that have drug development programmes for MS.

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