

## Relapse Therapy in Multiple Sclerosis – The Role of Plasma Exchange

a report by

**Ralf A Linker, Alexandra K Schröder and Ralf Gold***Department of Neurology, St Josef Hospital, Bochum, and Ruhr-University, Bochum*

DOI:10.17925/ENR.2008.03.01.104

**Glucocorticosteroid Therapy of Acute Multiple Sclerosis Relapses**

On an empirical basis, glucocorticosteroids (GS) form the basis of relapse therapy in multiple sclerosis (MS). Soon after the discovery of naturally occurring GS in the adrenal gland in 1938, synthesis of steroid hormones was achieved in 1947, thus opening the way for the development of new and more potent GS compounds, and also therapy of human autoimmune disorders with GS.<sup>1</sup> However, until the 1970s treatment with adreno- corticotrophic hormone (ACTH) as a pituitary regulator, which leads to the release of endogenous gluco- and mineralo- corticosteroid hormones, was still widely used instead of GS. Today, ACTH has been abandoned as a treatment of autoimmune diseases in clinical neuroimmunology.

Over the last seven decades, since the discovery of GS, a variety of genomic effector mechanisms have been described that are mediated by glucocorticoid receptors (GRs) acting as a transcription factor. In T cells, GS exert a distinct mode of action, ultimately resulting in T-cell apoptosis. This was shown in peripheral blood mononuclear cells from MS patients treated with GS during relapse.<sup>2</sup> Studies in experimental autoimmune encephalomyelitis (EAE) – an animal model mimicking many aspects of MS – revealed a dose–response curve for induction of T-cell apoptosis, with methylprednisolone doses up to 50mg/kg being most efficient.<sup>3</sup> In addition, recent data in GR knockout mice clearly underscore the importance of genomic mechanisms of action for EAE treatment.<sup>4</sup> In humans, short-term application of such high doses is well tolerated, as revealed in patients receiving high-dose GS (30mg/kg bodyweight [BW]) for treatment of spinal cord injury.<sup>5</sup>

The efficacy of intravenous (IV) high-dose GS in acute deterioration of MS was first described by Dowling et al.,<sup>6</sup> followed by a number of

uncontrolled trials pointing at rapid clinical improvement. In the first randomised, controlled study, by Milligan and Compston,<sup>7</sup> 50 patients received either 500mg of IV methylprednisolone or placebo over five days. The trial included patients with acute relapses and also with deterioration of progressive MS symptoms. In relapse treatment, IV GS were associated with faster remission, while chronic progressive patients displayed a benefit in motor function that lasted for the first four weeks only. The tolerability of such short-term, high-dose GS pulses in a routine clinical setting is good, while some transient mild disturbance of memory functions may occur.<sup>8</sup>

The data on efficacy of GS were corroborated by a further class I study by Beck and colleagues in optic neuritis (ON).<sup>9,10</sup> In this study, patients received 1,000mg of IV methylprednisolone for three days, followed by oral tapering at 1mg/kg BW for 11 days. Compared with oral treatment with 1mg/kg prednisone or placebo, this high-dose GS pulse resulted in a faster improvement of visual acuity. The effect disappeared after six months, yet a positive impact on the visual fields as well as contrast and colour vision persisted over time. The three groups were followed up for relapses during the study over the full disease course.<sup>10,11</sup> Surprisingly, GS pulses reduced subsequent relapses after ON: 14.7% of oral GS recipients, but only 7.5% of patients treated with high-dose GS, fulfilled the criteria for definite relapsing–remitting MS within two years. Thus, this study may be regarded as the first follow-up of patients with a first demyelinating event, which today is referred to as clinically isolated syndrome (CIS). As no other long-term immunotherapy was established at that time, the further follow-ups of this cohort over a longer time period instead reflect the natural variability of MS and therefore are not discussed here.

Further studies on GS for MS relapse therapy centred on the comparability of an oral versus IV GS application. To this end, Sellebjerg et al. conducted a randomised study with relapsing MS patients,<sup>12</sup> which included 25 patients with placebo treatment and 26 patients treated with 500mg of oral methylprednisolone for five days followed by a 10-day tapering period. Upon investigation after one, three and eight weeks, significantly more patients in the methylprednisolone group improved by one or more points on the Expanded Disability Status Scale (EDSS) score. The efficacy of oral high-dose GS was further supported in another study including 60 patients with ON,<sup>13</sup> yet significant effects of GS disappeared after three weeks. In most countries, the clinical application of oral GS is somewhat hampered by the fact that oral application of 500mg GS needs simultaneous intake of 10 tablets early in the morning. The clinical data on GS were underpinned by magnetic resonance imaging (MRI) studies revealing suppression of gadolinium-enhancement after GS therapy. In a double-blind, randomised study, Oliveri et al. compared the application of 2,000 versus 500mg methyl-prednisolone per day. Upon serial clinical



Ralf A Linker is an Attending Physician in the Department of Neurology, St Josef Hospital, Bochum, and a Group Leader in the Neuroimmunological Laboratory at the Ruhr-University, Bochum. His research interests concern experimental models of multiple sclerosis (MS), including the pathobiology of myelin and axon damage, and mechanisms of innovative MS therapies, including neuroprotective approaches.

E: ralf.linker@ruhr-uni-bochum.de

Alexandra K Schröder is an Attending Physician with a focus on intensive care medicine and clinical neuroimmunology in the Department of Neurology, St Josef Hospital, Bochum. She has a special interest in plasma exchange therapies for neurological disorders.

Ralf Gold is Chair of Neurology at St Josef Hospital, Ruhr-University, Bochum. Previously, he was Chair of the Multiple Sclerosis Research Institute, University of Göttingen and Gemeinnützige Hertie Stiftung. His clinical interests lie in experimental and human neuroimmunological topics, and he is a member of several international boards.

examination and high-frequency MRI studies from day seven to day 60,<sup>10</sup> the higher dose of IV methyl- prednisolone was significantly more effective. In particular, the application of 2,000mg GS resulted in a reduced number of contrast-enhancing lesions at 30 and 60 days, and decreased the rate of new lesion formation. Moreover, MRI may also provide additional information on the value of oral tapering after a GS pulse. Miller et al. observed rapid re-enhancement of lesions despite maintained clinical efficacy without tapering of GS.<sup>14</sup>

In view of expired patents, the interest in systematic modern studies with GS in MS is clearly limited. On an empirical basis, most neurologists use methylprednisolone for pulse therapy, while recent data from EAE studies point at an increased efficacy of dexamethasone (Lühder, unpublished observations) as well as liposomal formulations, which reduce side effects and even confer some long-term protection via GS targeting to sites of inflammation.<sup>15,16</sup> In clinical practice, not all patients respond well to GS, even if given repeatedly at higher dosages of up to 2,000mg/day, as recommended by guidelines.<sup>17</sup> In this situation, plasma exchange (PE) therapy should be considered.

### Plasma Exchange

The term 'plasmapheresis' was coined in 1914 when the removal of potentially pathogenic plasma factors in patients was first described. Today, more refined approaches include PE or immunoadsorption where pathogenic antibodies are selectively removed by binding to a specific matrix, e.g. coated with protein A or tryptophane. In contrast, PE is a non-selective immune therapy: 150g of plasma proteins have to be removed to eliminate about 1g of pathogenic autoantibodies. PE exerts its effects mainly via elimination of humoral factors including immunoglobulins, complement or cytokines. Although a subsequent modulation of cellular immune responses seems conceivable, this potential mechanism of action is less well characterised. PE was introduced into neurology as a therapeutic option as early as the 1980s. At this time, the efficacy of PE had already been shown for treatment of myasthenic crisis,<sup>18</sup> where passive transfer studies from man to mouse proved the pathogenic role of autoantibodies against the neuromuscular endplate.<sup>19</sup> As time progressed, the efficacy of PE was also revealed in patients suffering from Guillain Barré syndrome.<sup>20</sup>

The realisation of PE typically requires central venous access, which in some cases can lead to severe complications such as thrombosis, septic infections or pneumothorax. However, PE is otherwise usually well tolerated and easily accessible and medication costs are mainly restricted to protein replacement with albumin or fresh frozen plasma, which was used in the 1980s. At this time, PE was investigated for the first time in a study including patients suffering from severe MS courses. However, this three-armed trial focused on progressive forms of the disease and only the combination of cyclophosphamide and ACTH, which was tested in a parallel arm, had some efficacy on disease progression.<sup>21</sup> PE therapy then experienced a revival when modern molecular histopathology led to a new classification of MS lesions. Based on a large series of diagnostic brain biopsies from MS patients, the international co-operation of investigators led by Lassmann, Lucchinetti and Brück coined a four-pattern classification of the inflammatory MS lesion.<sup>22</sup> Of note, the most prevalent type II pattern reflects deposition of antibodies and complement pointing at a pathologically relevant role of B cells. In this situation, the value of GS is limited. Although GS may downregulate cellular cytotoxicity and to some degree lead to the death of activated B

cells,<sup>23</sup> GS will not modulate tissue destruction or conduction blockade by local antibody deposition. Here, the direct elimination of humoral factors via PE seems more promising. Indeed, proof of this concept was provided in a study correlating response to PE with histopathological patterns in patients who received PE therapy and also underwent diagnostic brain biopsy.<sup>24</sup> Of 19 retrospectively analysed cases, only those 10 with a pattern II lesion type exhibited moderate or substantial neurological improvement, whereas patients with other lesion types did not respond to PE. The tight correlation between PE response and histopathology underscores the concept that the efficacy of PE may result from the elimination of humoral factors, which at first lead only to conduction block but end in irreversible tissue damage after longer periods. The importance of such humoral factors in the serum of MS patients was further underpinned by the characterisation of antimyelin antibodies – e.g. antimyelin oligodendrocyte glycoprotein antibodies – which can lead to demyelination.<sup>25</sup>

PE was first tested in a randomised, sham-controlled, double-blinded trial.<sup>26</sup> This study included patients with an acute, severe neurological deficit caused by MS or other inflammatory demyelinating diseases of the central nervous system (CNS) that did not respond to high-dose GS within the previous three months. Patients were included within a mean of six weeks after onset of symptoms, and in a cross-over design received either PE or sham-exchange treatment. Moderate or greater improvement in neurological disability occurred during eight of 19 courses (42.1%) of active PE therapy compared with only one of 17 courses (5.9%) of sham treatment. If present, the improvement took place early during treatment and was sustained over time. However, 50% of therapy responders experienced a new demyelinating event during six months of follow-up. A subsequent analysis of 59 patients from the Mayo Clinic underpinned the importance of an early PE treatment initiation – less than six weeks after onset of symptoms – as an outcome determinant.<sup>27</sup> In the next step, a prospective case series of 10 consecutive patients focused on patients with acute, severe ON who were largely unresponsive to previous high-dose IV GS.<sup>28</sup> The series also included six CIS patients with a first clinical attack. In this cohort, PE was associated with an improvement of visual acuity according to the study criteria in seven of 10 patients. On follow-up, three of the 10 patients continued to improve, two remained stable and two had worsened again, which underscores the view that PE does not confer long-term protective effects. Interestingly, treatment success was best when residual visual acuity was better than 0.05. This observation supports the notion that severe inflammation of the optic nerve may lead to swelling in the optic channel, subsequently resulting in an irreversible, secondary ischaemic damage that is no longer responsive to PE therapy. Shortly afterwards, an uncontrolled series of 16 patients with severe ON, and motor impairment or severe ataxia was reported. In this study, great emphasis was placed on a maximum time interval of six weeks between onset of symptoms and start of PE. Again, this regimen proved a significant effect of PE in about 70% of patients and defined the median time-point of improvement after the third PE.<sup>29</sup>

In view of the largely overlapping use of PE and IV immunoglobulins (IVIg) in many neurological diseases,<sup>30</sup> it may also be considered to treat GS-resistant MS relapses with IVIg instead of PE. Indeed, IVIg have been used for several aspects of MS, yet with limited success. So far, no data are available on the efficacy of IVIg versus PE. Here, a formal study is urgently needed.

Although PE is clearly ineffective in preventing chronic progression of MS, it may be of value for relapses that occur during early phases of secondary progressive MS. In those patients with an already reduced walking distance at baseline, a relapse may result in significantly impaired mobility or even loss of their ability to walk. In such situations, the decision for PE may be made on an individual basis, and again can be guided by the presence of a pattern II in brain biopsy.<sup>31</sup> In two case reports, PE therapy for superimposed relapses in secondary progressive MS patients led to improvement of mobility and a clearly ameliorated quality of life.<sup>32</sup>

Another demyelinating disease of the CNS characterised by humoral disease mechanisms is neuromyelitis optica (NMO), otherwise known as Devic disease. PE was also shown to be effective in NMO.<sup>33</sup> Histopathologically, NMO lesions are also characterised by a type II pattern with prevailing antibody and complement deposition. Recently, the pathogenic role of humoral mechanisms was further underscored by the identification of a disease-specific antibody, NMO-IgG.<sup>34</sup> Subsequently, NMO-IgG could be characterised as an antibody against aquaporin-4, which is expressed on processes of perivascular astroglia.<sup>35</sup> To date, the exact mechanism leading from the presence of anti-aquaporin-4 antibodies in serum to demyelination and tissue destruction *in situ* still remains to be elucidated.

Finally, the question of follow-up therapy after PE treatment needs attention, since long-term examination of patients in all existing PE studies consistently showed no long-term protection after PE treatment. Although no randomised studies are available, a modification of the preceding immunotherapy should be sought after PE therapy. In case of a CIS, initiation of immunotherapy is recommended. In our own experience, high-dose interferon (IFN)- $\beta$  is a well tolerated and in nearly all cases sufficiently effective follow-up therapy after PE. In view of the humoral mechanisms that obviously dominate lesion pathogenesis in patients responding to PE, B-cell-directed therapies may be considered as an alternative. Here, mitoxantrone can be taken into account; this leads to B-cell apoptosis.<sup>36</sup> A more refined and less toxic yet still off-label approach comprises B-cell depletion via the anti-CD20 antibody rituximab, which recently successfully completed two phase II studies in relapsing–remitting MS.<sup>37,38</sup>

## Conclusion

In GS-refractory MS relapses, PE is established as an important pillar of escalation therapy. While some aspects of PE treatment modalities such as the role of immunoadsorption and the number or volume of exchanges await further clarification, several studies highlight the importance of an early initiation of PE therapy within six weeks after the onset of a relapse. ■

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