Therapeutic Plasma Exchange for Acute Inflammatory Demyelinating Syndromes of the Central Nervous System

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Idiopathic inflammatory demyelinating diseases (IIDDs) of the central nervous system, of which multiple sclerosis is the prototype, represent a family of monophasic, recurrent or progressive diseases with overlapping clinical and pathological manifestations. While most patients recover spontaneously or following a brief course of high-dose corticosteroids, occasional patients, particularly those with fulminant severe IIDDs, such as the Marburg variant, do not respond to corticosteroids and have severe, residual neurological deficits. While it is widely believed that IIDDs are mediated by T lymphocytes, as is experimental allergic encephalomyelitis, additional, possibly humoral, factors may be essential to generate the extensive demyelination seen in these conditions. Anecdotal reports over the past two decades have suggested that patients with acute, severe neurological deficits resulting from IIDDs, who fail to improve after high-dose intravenous corticosteroids, may benefit from plasma exchange. A randomized, sham-controlled, crossover study has recently been completed at the Mayo Clinic, which addresses these observations. J. Clin. Apheresis 14:144–148, 1999. © 1999 Wiley-Liss, Inc.

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INTRODUCTION

Multiple sclerosis (MS) is the prototype of a family of idiopathic inflammatory demyelinating diseases (IIDDs) of the central nervous system (CNS) [1,2]. MS is usually characterized by a relapsing-remitting course consisting of recurrent acute attacks of a neurological disability that is commonly superseded by a secondary-progressive course. Fifty percent of patients enter the progressive phase within 10 years of the onset [3,4].

Other IIDD variants have been defined based on clinical characteristics, pathological findings, or both. None can be distinguished absolutely from MS, as reviewed elsewhere [1,2]. In particular, some patients with acute fulminant forms of MS, such as the Marburg acute variant of MS, and focal demyelinating lesions that simulate brain tumors, may later develop a relapsing course consistent with MS [5]. Acute myelitis, particularly partial transverse myelitis, frequently evolves into MS [6]. While symmetrical, severe transverse myelitis is believed to evolve into a relapsing disease infrequently [7], complete, severe, transverse myelitis is a common occurrence in Devic’s neuromyelitis optica, another variant of demyelinating disease, which is typically a relapsing remitting illness [8]. Hence, it is reasonable to consider the IIDDs a spectrum of disorders, rather than entirely distinct from one another. Frequently, patients with severe deficits due to MS or IIDDs do not improve following high-dose corticosteroid treatment. The response of patients who fail corticosteroid treatment in this setting is the subject of this article.

I will consider the pathogenesis of the acute IIDDs of the CNS that provides the rationale for the use of therapeutic plasma exchange (TPE). I will also consider the experience with TPE in acute IIDDs. A recent study at the Mayo Clinic addresses the efficacy of TPE in patients with severe deficits from IIDDs of the CNS who have failed standard treatment with high-dose corticosteroids.

PATHOGENESIS

The pathogenesis of the idiopathic inflammatory demyelinating diseases has not been completely defined [9]. Given the frequency of prototypic MS, most investigators have concentrated on this entity to understand the pathogenesis of MS. However, much of the information from biopsies has been obtained from patients with rare presentations who are suspected of having brain tumors or other pathologies. Therefore, many of the insights about the pathogenesis of MS have come from the understanding of rare fulminant varieties of IIDD.

Although myelin and/or the oligodendrocytes appear to be the primary targets of the process, axons are also

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affected [10]. While remyelination is possible [11,12], axonal loss is likely irreversible. Axonal damage is widely believed to explain the permanent deficits that result following acute disability in IIDDs. Magnetic spectroscopic studies suggest that axonal loss may be progressive, as indicated by a progressive decline in levels of N-acetylaspartate, a metabolite of axons [13,14]. Axonal injury may occur early in the course of IIDD [10].

By analogy with experimental allergic encephalomyelitis (EAE), the pathogenesis of ADEM and most IIDDs including MS is suspected to involve cellular autoimmunity mediated by T lymphocytes. The evidence for T-cell autoimmunity in MS includes the following: (1) reactivity to myelin basic protein by T cells in MS patients [15], (2) the pathology of the disease, which has strong analogies with the T-cell-mediated experimental disease, EAE, and (3) major histocompatibility complex (MHC) restriction in MS.

However, the pathology of EAE better resembles that of ADEM than MS. Innumerable small cuffs of perivascular inflammation of demyelination are seen in ADEM, whereas in acute variants of multiple sclerosis, such as the Marburg variant, one to few large plaques are found with widespread demyelination, prominent astrocytosis, and less prominent perivascular inflammation. A second factor superimposed on the background of T-cell autoimmunity is thought to be essential to generate extensive demyelination. This factor is incompletely understood and there may be different factors operating in a single individual or there may be differences among individuals. The pathology of acute, active MS lesions is heterogeneous between individuals, although the pathology is remarkably homogeneous within different lesions within an individual [16]. Characteristics that distinguish between individuals include the following: (1) whether or not oligodendrocytes are preserved, (2) whether or not there is pan-necrosis of astrocytes and axons as well as oligodendrocytes, and (3) whether there is evidence for a primary oligodendrogliopathy (e.g., evidence for “dying back” oligodendrogliopathy manifest by early degeneration of the inner loops of the myelin sheath).

The role of humoral factors has been relatively ignored given the attention placed on T-cell immunity over the last two decades. However, at least two humoral mechanisms have been identified that may serve as a second factor in the induction of demyelination: antibodies to myelin oligodendrocyte glycoprotein (MOG), and TH1 cytokines such as TNFα [17]. Recently, Storch et al. [18] have demonstrated that a patient with MS had antibody and C9 neo-complement antigen deposition in the brain, suggesting activation of the terminal complement pathway by an antibody-mediated process. Furthermore, Genain et al. have detected antibodies that are specifically reactive to an epitope of MOG in the brains of some patients with MS as well as in a primate model of EAE [19]; these antibodies have been intimately associated with the demyelination process using ultrastructural studies.

Humoral factors may be responsible for physiological disruption of function rather than inflammatory tissue destruction. Physiological perturbations may account for some of the acute neurological deficit in demyelinating disease. Neuroelectric blocking activity has been previously described in sera from patients with MS [20]. It has recently been suggested that there may be antibody-mediated impairment of neurotransmitter release in peripheral demyelinating neuropathies [21]; perhaps, antibodies may also result in similar neurophysiological abnormalities in patients with MS.

PLASMA EXCHANGE IN ACUTE FORMS OF MS

The first report of efficacy of TPE in MS is that of Dau et al. [22]. This study included both patients with acute and progressive forms of MS. Since that time, most studies have targeted patients with progressive forms of MS, undoubtedly because most patients with acute attacks respond satisfactorily to treatment with corticosteroids in the short term, and lack of satisfactory treatment for progressive MS is a more common therapeutic dilemma. Others have reviewed the efficacy of TPE in patients with progressive forms of MS. The role of TPE in this setting remains uncertain [23,24].

Twenty-nine patients treated for acute, generally severe attacks of IIDDs, including MS, have been reported in 12 small series of between 1 to 6 patients per series [22,25–36]. These series have included patients with a variety of acute inflammatory demyelinating diseases including MS, acute transverse myelitis, acute disseminated encephalomyelitis, and neuromyelitis optica. In two patients, there was evidence of an underlying connective-tissue disease [34,35], but the neurological manifestation was acute transverse myelitis in one instance and neuromyelitis optica in another. Patients in these 12 series generally suffered from one of two types of neurological deficits. Patients with acute disseminated encephalomyelitis most commonly had confusion or coma. Patients in other categories of IIDDs had hemiplegia, paraplegia, or quadriplegia as the dominant neurological deficit. The clinical outcome in these cases has generally favored. In 21 out of 28 patients, moderate-to-marked improvement was observed in the neurological deficit usually after one to two TPE treatments. Obviously, reporting bias is a major concern when considering uncontrolled reports of this type.

At the Mayo Clinic, uncontrolled observations by Rodriguez et al. [36] suggested dramatic improvement after TPE in six consecutive patients with MS who were treated with TPE for acute severe attacks that led to severe disability. All patients in this series were hemiplegic, paraplegic, or quadriplegic. In addition, two were
aphasic, and two were ventilator-dependent at the time
that plasma exchange was initiated. All patients had
failed treatment with corticosteroids. There was marked
improvement in five out of the six, and a moderate
improvement in one patient. The median time to the onset
of clinical improvement was 4 days. The benefit was
sustained after cessation of TPE treatment.

Two randomized trials have been reported. One study
by Palm et al. [37] reported “remarkable clinical
improvements” in 19 patients treated with either TPE or
immunoabsorption, while only modest improvement was
observed in the patients who were treated with steroids
alone. However, the authors did not provide sufficient
details about the protocol or results that would permit a
reasonable critique of the paper.

Weiner et al. [38] reported the results of a randomized
sham-controlled trial in 1989. One hundred sixteen pa-
tients with relapsing remitting or progressive MS who
had experienced an acute attack sufficient to cause a one
or greater point deterioration in Disability Status Scale
(DSS) scores were randomized to 11 courses of TPE or
sham treatment over 8 weeks, as a supplement to oral
cyclophosphamide and ACTH. The primary endpoint
was improvement by 1 or 2 DSS points, depending on
baseline DSS. The overall difference between improve-
ment in patients treated with active and those treated with
sham treatment was not significant, but there was a trend
in favor of active treatment for improvement at one
month. This was particularly true for patients with re-
lapsing remitting MS with the most severe attacks. The
limitations of this study in addressing the uncontrolled
observations described above are the following: (1) pa-
tients with attacks of varying degrees of severity were
included, including patients with mild attacks, (2) pa-
tients with progressive MS were included, (3) in addition
to being randomized to receive true or sham plasma ex-
change, all patients received ACTH and cyclophos-
phamide, which makes it difficult to interpret the specific
effect of TPE, and (4) the end point was the DSS, which
is potentially insensitive to important changes, especially
those affecting cognitive function or upper-extremity
dysfunction.

Accordingly, we designed a randomized clinical trial
primarily to confirm or refute the observations of Rod-
riquez et al. [36]. The principles underlying this study
were: (1) select patients similar to those treated by
Rodriquez et al., namely patients who have acute, severe,
demyelinating disease who had failed high-dose steroid
treatment, (2) treat with TPE only without additional im-
munosuppression, (3) use a crossover design in order to
guarantee access to the active treatment considering the
severe nature of the deficits of patients enrolled in this
study, and also to increase the power, and (4) consider
moderate-to-marked improvement in the targeted neuro-
logical deficit which is specific to the patients attack-
related disability as the primary outcome. Mild improve-
ment would not be of significant interest.

MAYO CLINIC STUDY

The study was a randomized, double-masked, sham-
controlled study of plasma exchange in 22 patients with
acute attacks of MS or other IIDDs of the CNS, including
acute disseminated encephalomyelitis, acute transverse
myelitis, Marburg’s variant, Devic’s neuromyelitis opti-
tica, or focal cerebral demyelinating disease. Accrual
continued between January 1995 and October 1998. All
patients enrolled in this study had a profound neurologi-
cal deficit consisting of quadri-, para-, or hemiplegia.
Additionally, two patients were aphasic and one was co-
matose. The spectrum of deficits was similar to that of
patients studied by Rodriguez et al. Biopsy of the brain
was performed in four patients to confirm the diagnosis,
and biopsy of the cord was performed in one patient. All
patients received high-dose intravenous methylprednis-
olone, minimum 500 mg per day for 5 days or equiva-
lent and experienced no or minimal improvement. An
exception was made for two patients who continued to
deteriorate after 5 days of intravenous methylprednis-
olone. Patients were a minimum of 3 weeks and a max-
umum of 3 months from the onset of the neurological
deficit.

Patients were randomized to receive seven treatments
of true or sham exchange every other day over 2 weeks.
Two masked neurologists evaluated the primary out-
come, which was the targeted neurological deficit indi-
vidualized to the patient’s specific attack-related disabili-
ity. The criterion for treatment success was moderate or
greater improvement in the targeted neurological deficit.
Specific rating scales were identified for each of the neu-
rological deficits that qualified for enrollment, and the
investigators reached a consensus before the trial was
initiated on the degree of improvement that would be
deemed moderate improvement. The overriding consid-
eration in determining whether improvement was mod-
erate in degree was whether there was an important
change in the functional abilities of the patient. The out-
come measure was robust and interrater agreement on the
primary outcome by the two masked neurologists was
perfect on 35 out of 36 evaluations at the end of the
2-week treatment periods.

The primary analysis was the distribution of the Z
scores. A Z score of +1, 0, and −1 was arbitrarily as-
signed to each of the following three possible outcomes
for a patient respectively: success, no crossover; failure,
crossover, failure; failure, crossover, success. If TPE
were perfectly effective, the difference between the treat-
ment-first and the sham-first group would be +2 (i.e.,
+1−[−1]). The direction and magnitude of the difference
reflect the degree of treatment benefit. The difference in
distribution of Z scores in the two treatment groups as-
sessed by a one-sided rank sum test was the primary outcome.

In general, TPE was well tolerated. The majority of adverse events were incidental or related to the patient’s underlying illness. The only common adverse effect was anemia.

The results of the study were announced on September 17, 1999, at the joint meeting of the European and America’s Committee’s for Treatment and Research in MS, in Basel, Switzerland.

CONCLUSIONS

The prospective randomized sham-controlled trial at the Mayo Clinic will prove if TPE is an effective treatment for steroid-refractory, acute attacks of IIDDs of the CNS, including MS, and will suggest whether this treatment should be included in clinical management strategies for MS. The results of the study may also give insights into other issues: (1) while we distinguish clinically and pathologically between IIDDs, is the pathogenesis of the acute inflammatory episodes in all of these variants similar and does it involve humoral mechanisms? (2) do humoral components maintain acute neurological disability in the acute inflammatory phase of inflammatory demyelinating in MS and related IIDDs?

The nature of the serum components responsible for any observed benefit is difficult to determine, as TPE is inherently nonselective. However, a planned analysis of prospectively obtained serum samples in the Mayo Clinic study may provide clues as to the nature of the humoral component that maintains the disability in IIDDs of the CNS.

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REFERENCES