

# Therapeutic plasma exchange for worsening multiple sclerosis: does it work?

*Expert Rev. Clin. Immunol.* 5(5), 491–493 (2009)



**Bhupendra O Khatri, MD**

*Medical Director  
The Regional MS Center  
and Center for  
Neurological Disorders,  
Aurora St. Luke's  
Medical Center, 2801 W.  
Kinnickinnic River Pkwy,  
Ste#630, Milwaukee,  
WI 53215, USA  
[bokhatri@aol.com](mailto:bokhatri@aol.com)*

**“...similar to relapsing-remitting MS, patients with progressive MS ... should also be considered for PLEX.”**

I first met ‘Joe’ in 1999. Over the previous 18 months, despite aggressive treatment with interferon injections and multiple courses of intravenous (IV) corticosteroids, his multiple sclerosis (MS) continued to deteriorate. He was unable to raise his arms or legs, and had difficulty with his speech, swallowing and breathing. Plasma exchange (PLEX) therapy was instituted at that time and has continued through to 2009. Improvement in his disability occurred gradually. He could stand after 1 month, walk with bilateral assistance after 5 months, walk unassisted after 3 years, and after 10 years of PLEX therapy, not only is he a proud father of a 7-year-old child, but he can climb ladders and he has resumed his job as a construction worker. If the frequency of PLEX treatments is decreased to less than once every 3 months, his MS quickly deteriorates.

Now consider the unfortunate story of ‘Jane’ who has secondary progressive MS. She, like Joe, continued to worsen despite treatment with conventional therapies. Again, similar to Joe, Jane was treated with PLEX starting in 1994. Treatment with PLEX resulted in improved gait. She initially required bilateral assistance but progressed to being able to ambulate independently. She continued to do well for the next 2 years. However, immediately (and regrettably) she promptly deteriorated when PLEX was discontinued due to an insurance denial. Ultimately, she became wheelchair bound, and remained so for 1 year, despite treatment with IV and oral corticosteroids, adrenocorticotrophin hormone (ACTH) and

cyclophosphamide. After arduous efforts, PLEX was re-approved by the insurance company and she resumed therapy. Again, PLEX resulted in significant improvements such that Jane could walk without assistance and returned to full-time work. She remained stable for 4 years on PLEX. Again, however, PLEX was stopped due to an insurance denial. Similar to the previous occasion without PLEX, she worsened to wheelchair-bound status in 6 months and remained wheelchair-bound for 1 year. PLEX was re-approved and restarted after onerous lobbying efforts. Again, similar to past treatments with PLEX, she improved and was just starting to walk unassisted when PLEX was once again discontinued due to an insurance denial. Jane became wheelchair-bound again and she remains so today.

**“MS is a leading cause of progressive neurological disability in young adults in the USA.”**

These two case histories of progressive MS are not your typical patients that one would expect to have spontaneous recovery. It is clear that MS, particularly the relapsing form, is a heterogeneous disease. We know that in the case of relapsing-remitting MS, only a certain subset of patients respond to the current drug therapies. The aforementioned case reports suggest that, similar to relapsing-remitting MS, patients with progressive MS also have heterogeneous disease traits and should also be considered for PLEX. Patients trialed on

PLEX may not improve. Yet, according to Dr Ramachandran, Director of the Center for Brain and Cognition at the University of California (CA, USA), if you can make a pig speak English by whatever means, you have made your point. You should not have to make a second pig talk to convince the skeptics [1].

Based on our experience of over 30 years and 30,000 PLEX procedures on hundreds of MS patients, as well as two double-blind, randomized, controlled studies [2,3], we can say that the response to PLEX in the two aforementioned cases is not atypical. We have learned that the most important prognostic factor for recovery with PLEX is the severity of disease progression in the previous 2 years [4]. Thus, the higher the rate of progression, the greater the response to PLEX. Based on multiple clinical characteristics of responders and nonresponders in our studies, we have published a table whereby if you know the age, duration of the disease, and severity of progression in the previous 2 years, you can predict with significant accuracy the degree of improvement you can expect with PLEX [4].

**“We have learned that the most important prognostic factor for recovery with PLEX is the severity of disease progression in the previous 2 years.”**

Rodriguez *et al.* from the Mayo Clinic (MN, USA) reported six patients who were severely affected by MS despite being treated with IV corticosteroids [5]. They were all bedridden and two were on respirators. Importantly, all of them improved dramatically with PLEX. A follow-up double-blind, randomized, controlled study of PLEX in severe steroid-refractory cases of MS by the Mayo Clinic showed a significant improvement in 42% of patients treated with true PLEX versus a 5.9% improvement in the ‘sham’ PLEX group [6]. A larger North American multicenter, double-blind, randomized, controlled study of PLEX in acute MS showed a 28-day median recovery time to pre-attack disability status in the true PLEX group versus 91 days in the ‘sham’ group, despite the fact that both groups were receiving IV ACTH and oral cyclophosphamide [2]. This clinical response is particularly important when translated into the real world. A working MS patient can expect to return to work much faster after an acute relapse when PLEX is added to the conventional therapy.

Our positive double-blind, randomized, controlled study of PLEX in chronic progressive MS was heralded by George Ellison as an ‘exemplary study’ for others to match or exceed [7]. However, it was published in an era when the prevailing mantra was “a sure way to ruin your career in MS is to publish a positive study”. Publication of our subsequent long-term observational study of PLEX in chronic progressive MS [4] and a 25-year follow-up study [8] demonstrated a significant and lasting reversal of disability in over 60% of patients.

Multiple sclerosis is a leading cause of progressive neurological disability in young adults in the USA. Specifically, the total average cost of the disease burden of MS is estimated at US\$47,215 per patient per year, and more than 400,000 individuals are estimated to be diagnosed with MS in the USA. Globally, there are an estimated 2.5 million MS patients. The socioeconomic burden of this disease is significant. Since there currently is no cure for MS, and

current therapies are only partly effective in stopping the progression of disease, we can no longer ignore the therapeutic potentials of PLEX to reverse the disability in worsening MS patients.

So the question remains: why is PLEX not widely used in appropriate patients? There are multiple reasons, the foremost being that PLEX is not approved by a majority of insurance companies, despite convincing published data. In addition, vascular access is also a notable issue. While most centers use central lines for access, which can cause serious complications, this type of access is not necessary, and in most patients antecubital access is a simpler alternative. For patients who do not have veins sufficient for antecubital access, we have been successfully using temporary radial artery catheterization. We find this procedure to be safe and effective, even when used repeatedly [9]. In addition, PLEX is not backed by any pharmaceutical companies, and therefore no promotional or educational support is available to market the procedure. While the cost of PLEX had been cited as an issue in the past, second-generation MS drugs are far more expensive and this may make PLEX an economical treatment choice. Lastly, an appropriate PLEX protocol needs to be followed for a given patient. Although this protocol varies from patient to patient, we utilize an induction protocol of six to ten treatments (weekly over 6–10 weeks), followed by a gradual taper as dictated by the clinical course. Most of these patients will require ongoing maintenance therapy (~ once every 4–12 weeks).

**“...PLEX is a safe therapeutic option, which may reverse the disability and improve the socioeconomic outcomes and the patient’s quality of life.”**

The mechanism of action of PLEX is unknown and the pathophysiology of MS is complex. The role of B cells has been implicated, with evidence of antibody-mediated tissue damage in 60% of MS lesions. PLEX unequivocally removes circulating antibodies and this mechanism of action is likely to be an important factor in the response to PLEX. It also improves the function and number of circulating suppressor T cells, which have been shown to be markedly low when the disease is active [10]. The removal of circulating interferon-inhibiting factor by PLEX and the subsequent increase in endogenous protection of IFN- $\alpha$  correlated with clinical improvement in another study [11]. What is clear is that further studies are required to understand how and why PLEX works in MS.

For those patients who continue to worsen despite conventional therapies, PLEX is a safe therapeutic option that may reverse the disability and improve the socioeconomic outcomes and the patient’s quality of life.

#### **Financial & competing interests disclosure**

*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

*No writing assistance was utilized in the production of this manuscript.*

## References

- 1 Doidge N. Pain: the dark side of plasticity. In: *The Brain that Changes Itself*. Penguin Group, London, UK, 178 (2007).
- 2 Weiner HL, Dau PC, Khatri BO *et al.* Double-blind study of true vs. sham plasma exchange in patients treated with immunosuppression for acute attacks of multiple sclerosis. *Neurology* 1143–1149 (1989).
- 3 Khatri BO, McQuillen MP, Harrington GJ *et al.* Chronic progressive multiple sclerosis: double-blind controlled study of plasmapheresis in patients taking immunosuppressive drugs. *Neurology* 312–319 (1985).
- 4 Khatri BO, McQuillen MP, Hoffmann RG *et al.* Plasma exchange in chronic progressive multiple sclerosis: a long term study. *Neurology* 409–414 (1991).
- 5 Rodriguez M, Karnes WE, Bartleson JD *et al.* Plasmapheresis in acute episodes of fulminant CNS inflammatory demyelination. *Neurology* 1100–1104 (1993).
- 6 Weinshenker B, O'Brien P, Petterson T *et al.* A randomized trial of plasma exchange in acute CNS inflammatory demyelinating disease. *Ann. Neurol.* 46, 878–886 (1999).
- 7 Ellison G. Therapy aimed at slowing the rate of progression. In: *Multiple Sclerosis*. McDonald WI, Silberberg D (Eds). Butterworth & Co. Publishers, London, UK, 158 (1986).
- 8 Khatri B, McQuillen M, Tarima S *et al.* Long-term improvement in the disability of worsening MS patients with plasma exchange: results of a 25 year follow-up study. Poster P05.154. Presented at: *American Academy of Neurology 2009 Annual Meeting*. Seattle, WA, USA, 25 April–2 May 2009.
- 9 Khatri BO. Vascular access via temporary radial artery catheterization for therapeutic plasma exchange. *J. Clin. Apher.* 18, 143 (2003).
- 10 Khatri BO, Koethe SM, McQuillen MP. Plasmapheresis with immunosuppressive drug therapy in progressive multiple sclerosis. *Arch. Neurol.* 41, 734–738 (1984).
- 11 Medenica RD, Mukerjee S, Huschart T *et al.* Interferon inhibitor factor predicting success of plasmapheresis in patients with multiple sclerosis. *J. Clin. Apher.* 9, 216–221 (1994).