IVIg for RRMS

A recently published paper summarizes four double-blind IVIg trials in RRMS. Sorensen, Intravenous Polyclonal Human Immunoglobulins in Multiple Sclerosis. *Neurodegenerative Dis* 2008;5:8-15. This review demonstrates that IVIg reduces the relapse rate and, possibly, disease progression in RRMS. This is consistent with prior publications.

IVIg has several effects on the immune system that could be beneficial to RRMS. It may help treat acute relapses, prevent new relapses, and promote remyelination. Sorenson PS. The role of intravenous immunoglobulin in the treatment of multiple sclerosis. *J. Neuor. Scien* 2003 Feb 15;206(2): 123-130. That article goes on to state that IVIg also has been proven to be beneficial in treating secondary progressive MS. Thus, "IVIG is a valuable alternative for treatment of relapsing-remitting MS . . . ." The same author found, too, that IVIg "exerts a number of effects that may be beneficial in multiple sclerosis: reduction of inflammation, inhibition of macrophages, and promotion of remyelination." Sorenson PS. Treatment of multiple sclerosis with intravenous immunoglobulin: review of clinical trials. *J Neurol Sci*, 2003 Oct; 24 Suppl 4:S227-30.

IVIg is "thought to exert a twofold effect: an immunomodulating action and a positive action on remyelization." Valiat, JM, et al., "Inflammation and demyelinization: IgIV mode of action," *Rev Neurol* (Paris), 2006 Jun; 162 Spec. No. 1: 3S12-3S16. This result is not achieved with Betaseron alone.

There is much additional support in the literature for the use of IVIg in treating RRMS. In the first study to test the assumption that IVIg might be effective for the interval treatment of MS, beneficial effects were seen within 6 months of treatment and did not appear to depend on the severity of baseline disability. "IVIG treatment also had a positive effect on daily and social living according to patient self rating on the Incapacity Status and Environmental Status Scales and was associated with a lower, though not significantly different number of hospital admissions and days spent in hospital. These data support IVIG as an alternative treatment option for relapsing-remitting MS . . . ." Strasser-Fuchs, S., et al., "The Autstrian Immunoglobulin in MS (AIMS) study: Final analysis. " *Multiple Sclerosis* 2000; 6(Suppl 2): S9-S13.

In 2004, a randomized, placebo-controlled double-blind study in 91 patients were studied after rthe first neurological event suggestive of demyelinative disease. Achiron, A., et al., "Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial." Arch Neurol. 2004 Oct; 61(10):1515-20. That study showed that IVIg treatment for the first year from onset of the first neurological event suggestive of demyelinative disease significantly lowers the incidence of a second attack and reduces disease activity as measure by brain MRI.

In another double-blind placebo-controlled study of 40 patients with RRMS found that IVIg "may be safe and effective in reducing the frequency of exacerbations in RR-MS." Achiron, A., et al., "Intravenous Immunoglobulin treatment in multiple sclerosis. Effect on relapses," *Neurology* 1998 Feb; 50(2); 398-402. See also Achiron, A., et al., "Intravenous gammaglobulin treatment in multiple sclerosis and experimental autoimmune encephalomyelitis: delineation of usage and mode of action," *J. Neurol. Neurosurg Psychiatry*, 1994 Nov; 57 Suppl: 57-61 ("IVIg treatment significantly reduced the number and severity of acute exacerbations and resulted in a lesser neurological disability.").

In addition, IVIg's use was heralded in Fazekas, F., "Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis," *Lancet* 1997 Mar 1; 349 (9052): 589-93. The EDSS score decreased in the IVIg-treated patients and increased in the placebo group in significant numbers. The authors conclude that "[m]onthly IVIg is an effective and well-tolerated treatment for patients with relapsing-remitting multiple sclerosis." That same year, a study was published that showed that "IVIg treatment was associated with a significant reduction in relapses. . . ." Fazekas, F., et al., "Treatment effects of monthly intravenous immunoglobulin on patients with relapsing-remitting multiple sclerosis," *Mult Scler*, 1997 Apr; 3(2); 137-141.

Other studies have found IVIg to be beneficial in treating RRMS. For example, Sorensen, P.S., et al., "Intravenous Immunoglobulin G reduces MRI activity in relapsing multiple sclerosis," *Neurology*, 1998 May; 50(5): 1273-81. In that study, 26 patients in a randomized, double-blind, crossover study were studied, and the results showed that, with IVIg therapy, there were fewer lesions on MRI than in the placebo treatment. In another study, IVIg was found to be "beneficial for prevention of exacerbations in patients with relapsing MS." Sorensen, PS, et al., "A double-blind cross-over trial of intravenous immunoglobulin G in multiple sclerosis," *Mult Scler*, 1997 Apr; 3(2): 145-8. "The ability of intravenous immunoglobulin (IVIg) to restore visual acuity and/or muscle strength is also being investigated." "Multiple Sclerosis: Hope Through Research," National Institute of Neurological Disorders and Stroke, p. 9 (last updated February 2007). Both clinical evidence and MRI show that IVIg has beneficial effects on relapse rate and neurological disability, decreasing both the "disease burden" and the appearance of new lesions. Achiron, A., et al. Use of intravenous immunoglobulin in multiple sclerosis. BioDrugs. 1998 Jun;9(6): 465-75.

Although we have been unable to locate a published report of this study, we enclose a Science Daily report of a Chicago study that found that IVIg reduces the risk of a second attack of MS, and that IVIg may, in fact, reduce the number of lesions on MRI. IVIg not only improves the course of the disease, but also repairs "the damage to the myelin sheath by enhancing remyelination." Advances in Multiple Sclerosis, <http://www.msadvances.com.faq.php3> (last accessed on 3/14/2007). The National Multiple Sclerosis Society reports on these studies, stating that studies show that IVIg both decreases the rate of relapse and decreases the number of lesions shown on MRI.

Nor is there reason to worry about the safety of IVIg. A group in Israel administered more than 10,000 infusions for more than 200 patients for various autoimmune disease, including MS. Katz, U., et al., "Safety of intravenous immunoglobulin therapy," *Autoimmune Rev*. 2007 Mar; 6(4): 257-9. See also Katz, U., et al., "Long term safety of IVIg therapy in multiple sclerosis: 10 years experience," *Autoimmunity*, 2006 Sep; 39(6): 513-7 (showing that IVIg has a beneficial effect in patients with RRMS and that it is safe); Poehlau D. Treatment of chronic progressive multiple sclerosis with intravenous immunoglobulins – interim results on drug safety of an ongoing study. IVIG study group. *Mult. Scler*, 2000; 6 Suppl 2:S21-3 (IVIG is safe therapy even for severely disabled multiple sclerosis patients).

Some detractors cite to the American Academy of Neurology Report of the Therapeutics and Technology Assessment Subcommittee from 2001, which states that the studies of IVIg to date "have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIg reduces the attack rate in RRMS." *Neurology* 2002; 58(2): 169-78. However, there are several aspects in which this report is lacking. First, it is nearly six years old. We cite studies here that post-date that 2001

review. Second, the published article does not contain any of the analysis of IVIg studies; that analysis is found in a far longer document that contains the full report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. The entire consideration of IVIg is reduced to less than one page and considers only three studies from 1997 to 1999, the abstracts of some of which are enclosed herein. The authors of the report state that the first of these studies "reported that treatment with IVIg reduced the clinical attack rate," and the "difference in final unconfirmed proportion with 1- point EDSS progression was also reduced although this outcome was not significant." The second study generated "mixed" results. "For patients who completed both treatment arms . . . the total number of enhancing lesions seen on MRI . . . and the number of new lesions . . . were reduced in patients treated with IVIg." The third study also reported significant reductions in the clinical attack rate. Thus, reliance on this Report, which considers only three studies conducted in the late 1990s, is entirely misplaced.

In fact, the majority of insurance companies are covering IVIg for RRMS. We enclose policies from CIGNA, United Healthcare, Aetna, and Blue Cross Blue Shield of Texas, all of which indicate that IVIg would be covered for patients with RRMS.

In sum, IVIg is not experimental or without significant support in the literature. The fact that it is covered by insurance companies quite widely shows that this is the standard of care.