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Novel therapeutic strategies for multiple sclerosis: potential of intravenous immunoglobulin

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In a recent article (Novel therapeutic strategies for multiple sclerosis — a multifaceted adversary. *Nature Rev. Drug Discov.* **7**, 909–925; 2008)[1], Lopez-Diego and Weiner discuss a number of novel potential therapies to treat multiple sclerosis (MS) that target leukocyte trafficking, T cells and B cells. However, the authors do not discuss an important immunotherapeutic option for relapsing–remitting MS (RRMS): intravenous immunoglobulin (IVIg) — a therapeutic preparation of normal human polyclonal immunoglobulin G obtained from pools of plasma from several thousand healthy blood donors.

IVIg has been extensively used to treat a wide range of autoimmune and inflammatory disorders of neuromuscular and systemic origin[2,3]. Several randomized, double-blind studies in RRMS have shown a beneficial effect of IVIg on disease with respect to reductions in relapse rates and lesion activity detected with magnetic resonance imaging[4–9]. Although a recent study did not find a beneficial effect of IVIg in RRMS[10], for several reasons (discussed below), we believe that IVIg remains a reasonable therapeutic candidate for RRMS and could yet prove its therapeutic utility, provided some unresolved issues on its clinical use can be addressed.

The therapeutic dose of IVIg is empirically set at 2 g per kg, which is infused either in five daily doses of 400 mg per kg each, or divided into two or three daily doses[2,3]. The studies with IVIg in RRMS have involved different dosages, and patients with different stages of disease and previous treatment history[4–7], indicating that the treatment regimen for IVIg for RRMS has yet to be optimized. Indeed, a recent European Federation of Neurological Societies task force recommended IVIg as a second- or third-line therapy for RRMS, but did not include it among first-line therapies owing to the limited evidence for clinical efficacy and optimum dosage[11]. Therefore, the first challenge would be to establish the minimum effective dose and the precise dosing interval of IVIg for induction and maintenance of immune tolerance in RRMS.

Therapy of MS with monoclonal antibodies (mAbs) is associated with several adverse effects and the immune tolerance is not long lasting. In addition, the pathogenesis of MS cannot be attributed to a single cell type or cytokine. In this context, the multiple and overlapping mechanisms of action of IVIg and its proven safety could provide a new option for a combination therapy with mAbs[2,3]. Indeed, the combination of the anti-CD20 mAb rituximab (Rituxan/MabThera; Biogen Idec/Genentech/Roche) and IVIg has been found to be effective in refractory pemphigus vulgaris and transplantation[12,13]. Such a combination therapy might not only reduce the dose of both mAbs and IVIg, thereby reducing the potential for adverse effects, but could also impart a more long-lasting therapeutic effect compared with monotherapy[14].

In conclusion, we consider that the available data indicate that IVIg is not a lost cause for the therapy of MS[15,16], and that clinical trials are therefore warranted to determine if a combination of mAbs with IVIg could lead to a more effective therapy for RRMS.

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