IMMUNOSUPPRESSION IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic progressive or relapsing neuropathy. The cause of CIDP remains unknown, but it is widely accepted that it is an autoimmune disease [1]. This has prompted the use of immune therapies in this disease, considering that over 50% of the patients may have temporary severe disability in the course of the disease and that approximately 10% of them eventually become persistently disabled or die because of the illness [2]. A few controlled studies and a number of uncontrolled or retrospective studies on large series of patients have shown the efficacy of oral steroids, plasma exchange and IVIg in CIDP as also confirmed in some recent Cochrane Reviews and in the recently updated Guidelines of the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) [3]. If the short-term efficacy of IVIg in the CIDP is well confirmed, a recent randomized double blind controlled study (ICE study) on the largest series of CIDP so far examined (117 patients) [4], confirmed that this treatment maintained its efficacy for 48 months. The necessity for long-term periodic treatments with IVIg or PE, the serious adverse events frequently associated with the chronic use of steroids, and the not so uncommon development of resistance to these therapies have led to the use of immunosuppressive agents in CIDP. Several uncontrolled studies have reported their efficacy in CIDP (reviewed in [5]), but this was not confirmed in two randomized controlled studies performed with azathioprine [6] and interferon beta-1a [7]. Similar negative results derived from two controlled studies published in the last year. In the first study, oral methotrexate, though well tolerated, was not more effective than placebo in reducing the dose of steroids or IVIg used to maintain the improvement in 60 patients with CIDP (RMC trial)[8]. In particular, 52% of the patients taking oral methotrexate, and 44% of those assuming placebo reduced by at least 20% the associated initial dose of IVIg or steroids by the end of the 40 weeks of the study. In a more recent study on 67 patients with CIDP under chronic IVIg therapy [9], treatment for 32 weeks with interferon beta-1a was not more effective than placebo in reducing the mean dose of IVIg. In particular, 47% of patients in both groups did not need to restart IVIg after their suspension after 16 weeks of interferon. Both studies showed that a consistent proportion of patients with CIDP are probably over treated with steroids or IVIg since more than 40% of them could reduce or suspend the therapy without worsening. These conclusions should be kept in mind when considering the results of open uncontrolled trials with immune suppressive agents in CIDP. Alentuzumab, a humanized monoclonal antibody targeting the CD52 antigens on lymphocytes and monocytes, was shown to reduce the dose and frequency of IVIg in 4/7 patients with CIDP. Three of these patients were however reported to develop an autoimmune disease [10]. A consistent proportion of adverse events were also reported in a study with autologous peripheral blood stem cell transplantation [11]. Some positive results on muscle strength were reported in a retrospective analysis of eight patients with CIDP treated with mycophenolate mofetil, six of whom could stop concomitant medications [12]. Similar positive results were reported in a open retrospective study on 13 patients with CIDP treated with Rituximab, eight of whom had a concomitant haematological disease [13]. Nine patients, including seven with a concomitant haematological disease, improved after Rituximab. These results are more promising than previous studies with Rituximab [14] and indicate that this therapy may be particularly effective in patients with CIDP associated with a haematological disease. In conclusion steroids, PE and IVIg remain the main treatment for CIDP also because controlled studies with immunosuppressants failed so far to identify alternative effective therapy. Several uncontrolled studies showed however that some patients with CIDP may benefit from immunosuppressant therapies whose efficacy needs to be confirmed in randomized trials.

References:

1. Hughes RAC, et al. Pathogenesis of chronic inflammatory demyelinating polyradiculoneuropathy. J Peripher Nerv Syst 2006; 11: 30-46.
2. Lunn MPT, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. J Neurol Neurosurg Psychiatry 1999: 66: 677-680
3. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/ Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First Revision. J Peripher Nerv Syst 2010; 15: 1-9.
4. Hughes RA, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomized placebo-controlled trial. Lancet Neurol 2008; 7: 136-144
5. Hughes RAC, et al.. Cytotoxic drugs and interferons for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2004; 4: CD003280.

6. Dyck PJ, et al. Combined azathioprine and prednisone in chronic inflammatory demyelinating polyneuropathy. Neurology 1995; 35: 1173-76
7. Hadden RDM, et al. Randomized trial of interferon □1a in chronic inflammatory demyelinating polyradiculoneuropathy. Neurology 1999; 53: 57-61
8. RMC Trial Group. Pilot Randomised Controlled Trial of Methotrexate for Chronic Inflammatory Demyelinating Polyradiculoneuropathy (RMC Trial). Lancet Neurol 2009; 8: 158-164 .
9. Hughes RAC, et al. Intramusculatr interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy. Neurology 2010 74: 651-657.
10. Marsh EA, et al. Alentuzumab in the treatment of IVIg-dependent chronic inflammatory demyelinating polyneuropathy. J Neurol 2010;
11. Mahdi-Rogers M, et al. Autologous peripheral blood stem cell transplantation for chronic acquired demyelinating neuropathy. J Peripher Nerv Syst 2009; 14: 118-124.
12. Bedi G, et al. Chronic inflammatory demyelinating polyneuropathy responsive to mycophenolate mofetil therapy. J Neurol Neurosurg Psychiatry. 2010; (Epub).
13. Gorson KC, et al. Efficacy of mycophenolate mofetil in patients with chronic immune demyelinating polyneuropathy. Neurology 2004; 63; 715-717.
14. Benedetti L, et al. Rituximab in patients with CIDP: A report of 13 cases and review of the literature. J Neurol Neurosurg Psychiatry 2010 (in press).