Chronic Inflammatory Demyelinating Polyradiculoneuropathy: Revisiting the Role of Intravenous Immmunoglobulins

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Chronic inflammatory demyelinating polyradiculoneuropathy is the most common treatable chronic autoimmune neuropathy. It is an acquired heterogeneous condition of sensory and motor peripheral nerve malfunction. Two inflammatory neuropathies, Guillain-Barré syndrome and multifocal motor neuropathy, share major features with CIDP [1]. Patients with any disorder of the subset may manifest proximal and distal weakness of sub-acute to chronic onset, with areflexia and characteristic electrodiagnostic findings. All three have been shown to respond to intravenous immunoglobulin [2]. The precise molecular understanding of how IVIg mediates recovery in inflammatory neuropathies has yet to be elucidated, and countless theories have been put forward. Among them, the biochemically plausible interaction of IVIg with B cells, specifically inhibition of antibody production and plasma cell differentiation [3-8]. IVIg also modulates cell-mediated immunity. It inhibits production of interleukin-2 and interferon-gamma by T cells, induces degradation of complement factors, and upregulates/downregulates expression of the FcγRII macrophage receptor [9-11].

An elegant experiment by Zhang et al. [12] revealed additional protective mechanisms of IVIg. The binding of mice anti-ganglioside antibodies to serum gangliosides, a presumed key player in the pathogenesis of Guillain-Barré syndrome, was inhibited by IVIg and, as a result, neuromuscular transmission was restored [12]. The authors implicated IVIg's anti-idiotypic neutralization of anti-ganglioside antibodies with the favorable response. In the same study, suppression of complement activation by IVIg, via interference with the assembly of C5-convertase, was postulated to alleviate cumulative injury to nerve fibers [12].

Moving from mice to humans, several randomized clinical trials have attempted to determine the efficacy of IVIg as induction therapy for CIDP. The administration of IVIg (0.4 g/kg for 5 consecutive days) to CIDP patients resulted in improvement in the Neurologic Disability Score and grip strength [13]. More recently, IVIg (1 g/kg on days 1, 2 and 21) was shown to increase the average muscle score and improve the functional disability grade at 42 days [14]. In view of the presumed autoimmune nature of CIDP, prednisone has also been assessed. The results showed a small but significant improvement in neurological disability scores following treatment with prednisone for 3 months, particularly in patients with a progressive course [15]. A groundbreaking study, the Immune Globulin Intravenous CIDP Efficacy (ICE) trial, was a randomized, double-blind, placebo-controlled, crossover trial of IVIg in 117 patients with CIDP of whom about 10% were recruited in Israel [16]. The short- and long-term benefits gained with immunoglobulins in this landmark trial reinforced the results of previous studies. A clinical response was demonstrated as early as 10 days and continued to the full length of the trial [16]. The ICE trial also demonstrated lower rates of relapse in patients treated with IVIg [16]. The U.S. Food and Drug Administration subsequently approved IVIg for use in CIDP. Further analysis confirmed the safety and tolerability of IVIg for the same indication [17].

It is currently speculated that a "hybrid strategy" to treat CIDP, incorporating induction with IVIg and maintenance with corticosteroids, yields synergistic effects. Such an approach takes advantage of IVIg's greater short-term effectiveness and corticosteroids' more long-lasting immunosuppression. Interestingly, the degree of immune response aberration varies between individuals, and suboptimal clinical response to IVIg remains a challenge. Pharmacogenomic studies have been successful in defining one SNP polymorphism (transient axonal glycoprotein 1, TAG-1) as a surrogate marker of positive clinical response to IVIg [18]. Future genomic insights would facilitate

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy

IVIg = intravenous immunoglobulin

immunotherapy in CIDP, simplifying drug selection and dose optimization.

IVIg is underutilized as a treatment for CIDP. The reasons for this are diverse and include high cost and short supply. Large randomized clinical trials are scarce and small due to the low incidence and prevalence of CIDP. Trial interpretation is further confounded by the variety of clinical courses (monophasic or subacute progression versus the classical multiphasic and chronic nature) and lack of accepted surrogate endpoints. Moreover, most studies administered IVIg to patients who had not been naïve to immunomodulatory drugs. That has fostered skepticism among some neurologists regarding IVIg's role as the initial treatment. That state of uncertainty prompted a more meticulous scrutiny of IVIg in drug-naïve patients, with the results lending further support to its absolute efficacy in CIDP patients [19]. This does not imply that IVIg should be the only first-choice treatment in every patient with CIDP, or that it should be used exclusively. Prednisone is a viable and less costly option, though prolonged treatment is associated with extensive side effects [19]. Plasmapheresis is another therapeutic tool, but it is limited by availability and catheter complications and is thus typically reserved for refractory cases.

The data provided highlight the rigorous scientific basis for utilizing IVIg in patients with CIDP. Its remarkable effectiveness justifies its application in immune-mediated neuropathies, CIDP among them. Administration of IVIg, with a loading dose of 2 g/kg over 2–4 days followed by a maintenance infusion of 1 g/kg over 1–2 days every 3 days for a total of 24 weeks, is the current recommendation. Some uncertainties persist, though, and should be addressed in the future, including those that are trial-related (e.g., optimizing neurological functional scales as reliable response criteria) and others that are clinically based (e.g., appropriate dose of IVIg). The lessons of past investigations of inflammatory neuropathies, from experimental mice to the clinical (trial) ICE, should continue to inform our decisions and push us towards a more refined understanding of IVIg and its application.

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"True compassion is more than flinging a coin to a beggar; it is not haphazard and superficial. It comes to see that an edifice that produces beggars needs restructuring"

Martin Luther King, Jr (1929-1968), American Civil Rights leader who promoted the use of non-violent civil disobedience. King has become a national icon in the history of American progressivism

"In the face of suffering, one has no right to turn away, not to see"

Elie Wiesel (b. 1928), Romanian-born Jewish-American writer, professor and political activist. When Wiesel was awarded the Nobel Peace Prize in 1986, the Norwegian Nobel Committee called him a "messenger to mankind," adding that he had delivered a powerful message "of peace, atonement and human dignity" to humanity