Intravenous Immunoglobulin in Patients With Anti-GAD Antibody-Associated Neurological Diseases and Patients With Inflammatory Myopathies

Effects on Clinicopathological Features and Immunoregulatory Genes

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Abstract

Controlled trials with intravenous immunoglobulin (IVIg) were conducted in patients with Stiff-Person Syndrome (SPS) and dermatomyositis (DM), two humorally mediated neurological disorders, and in inclusion body myositis (IBM), a T-cell-mediated inflammatory myopathy. The clinical efficacy was compared with alterations on tissue expression of complement, cytokines, chemokines, adhesion molecules, and immunoregulatory genes.

The following patients were randomized in three separate trials to receive IVIg or placebo for 3 mo: (a) 16 patients with anti-GAD antibody-positive SPS; (b) 15 patients with DM resistant to therapies; and (c) 19 patients with IBM. After a washout, they crossed to the alternative therapy for another 3 mo. Efficacy was based on the difference in the respective disease scores from baseline to the second and third month of the infusions. In patients with SPS and DM, the scores changed positively and significantly from months 1 through 3, but returned to baseline when the patients crossed to placebo. In contrast, the scores in the placebo-randomized group remained constant or worsened from months 1 to 3, but improved significantly after crossing to IVIg. The muscle scores of patients with IBM did not significantly change between IVIg or placebo. In SPS, the anti-GAD$_{65}$ antibody titers declined after IVIg but not after placebo. In DM, there was reduction of complement consumption, interception of membranolytic attack complex formation, downregulation of inflammation, fibrosis, cytokines, chemokines and adhesion molecules, and alterations in thousands of immunoregulatory genes.

We conclude that IVIg is a safe and effective therapy for patients with SPS and DM resistant to other agents. In tissues, IVIg restores tissue cytoarchitecture by suppressing the inflammatory mediators at the protein, mRNA, and gene level.

Index Entries

IVIg; anti-GAD antibodies; inflammatory myopathies; immunoregulatory proteins; genes.
Introduction

During the past decade, intravenous immunoglobulin (IVIg) has dramatically changed the way we treat autoimmune neurological disorders. Previously untreatable diseases, such as multifocal motor neuropathy, or disorders not adequately responding or resistant to available therapies, such as chronic inflammatory demyelinating neuropathy, Stiff-Person Syndrome (SPS), and inflammatory myopathies, have responded to IVIg based on controlled trials. A number of these studies have also elucidated the effects of IVIg on fundamental immunopathological pathways, such as complement consumption, idiotypic antibodies, cytokines, chemokines, and immunoregulatory genes.

In this article, the efficacy of IVIg on two groups of autoimmune neurological disorders, anti-glutamic acid decarboxylase (GAD)-positive SPS and inflammatory myopathies, is summarized based on controlled trials. A number of these studies have also elucidated the effects of IVIg on fundamental immunopathological pathways, such as complement consumption, idiotypic antibodies, cytokines, chemokines, and immunoregulatory genes.

Anti-GAD Antibodies and Neurological Diseases

Low-titer antibodies against GAD, the presynaptic enzyme responsible for the synthesis of γ-aminobutyric acid (GABA), were first described in patients with diabetes, where GAD is a major autoantigen in islet cells (1). Anti-GAD antibodies at high titers, however, have been associated only with certain autoimmune neurological disorders (2–4). The most common among them is SPS, in which more than 90% of the patients possess such antibodies (4–7). Of interest, among 40 anti-GAD-positive patients with SPS that we studied, 8% had also epilepsy and 10% cerebellar ataxia, indicating an overlap between the autoimmune phenomena of stiffness and spasms with certain forms of epilepsy and idiopathic cerebellar ataxia. Because anti-GAD antibodies can be also seen in some patients without SPS who present only with cerebellar ataxia (9), epilepsy with myoclonus, or abnormal eye movements (8), it is very likely that the disease in a subset of these patients has autoimmune pathogenesis (10). There is a challenging question whether Batten’s disease, a juvenile neuronal ceroid lipofuscinosis of autosomal recessive inheritance owing to deletions in the CLN3 gene, has also an autoimmune component because high-titer GAD antibodies also have been observed in these patients (11). Further, in CLN3 knockout mice, the animal model of Batten’s disease, high titers of anti-GAD antibodies have been observed (10,11). Although the pathogenic role of GAD antibodies in these disorders is unclear because GAD is a cytoplasmic antigen, high titers of GAD antibodies are markers of an ongoing autoimmune process within the central nervous system justifying interventions with immunomodulating drugs. Among all the GAD-positive conditions, immunotherapy has been systematically applied only in SPS. Based on anecdotal reports that patients with SPS may respond to immunotherapy with steroids, plasmapheresis, or IVIg (12–14), we conducted a control trial with IVIg (15).

Role of IVIg in SPS: Double-Blind, Placebo-Controlled Study

SPS is characterized by fluctuating muscle rigidity of truncal and proximal limb muscles with superimposed spasms (4–7,13,14). Continuous contraction of agonist and antagonist muscles caused by involuntary motor unit firing at rest are the hallmark clinical and electrophysiological signs of the disease. The autoimmune pathogenesis of SPS is suspected based on: (a) the presence of antibodies against...