Mechanisms of High-Dose Intravenous Immunoglobulins in Demyelinating Diseases

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Administration of high-dose intravenous immunoglobulins has become one of the most successful new treatment regimens for demyelinating diseases. In a decade of molecular medicine, it came as a surprise that a natural blood product would prove effective in several disorders, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and, probably, multiple sclerosis. Many experimental studies, both in vivo and in vitro, have shown that intravenous immunoglobulins can interfere with the immune system at several levels. In addition, intravenous immunoglobulins may promote remyelination in demyelinating disease associated with viral infections. At present, no single mode of action has been identified as the crucial mechanism, which leads us to suggest that multiple effects may act in concert.

Intravenous immunoglobulin (IVIg) treatment now has an established role in the therapy of immunologically mediated demyelinating disorders, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy. In multiple sclerosis, studies support a therapeutic role in inflammatory demyelination in the central nervous system. While the immunomodulating capacity of IVIgs has been studied extensively over the past 15 years, their remyelination potential has been recognized only recently.

EFFECTS OF IVIgs ON COMPONENTS OF THE IMMUNE SYSTEM

Complement

Immunoglobulins can bind complement components with their constant domain and thus prevent tissue damage caused by the complement activation cascade. This mechanism in humans has been demonstrated in an inflammatory disease of muscle (dermatomyositis) by specimens obtained from serial muscle biopsies and in vitro complement uptake studies, where C3b and the membrane attack complex disappeared under IVIg treatment. One possible mechanism may be the inactivation of C3b2-IgG complexes, which are milestones in the process of membrane-attack-complex (C5b-9) formation. Complement deposition in situ is also of prime pathogenic importance in inflammatory demyelinating disorders, eg, Guillain-Barré syndrome.

T Cells

At present, most of our knowledge of the influence of IVIgs on T cells is derived from in vitro studies. Changes in both CD8 suppressor or cytotoxic cells and CD4 helper T cells were demonstrated after IVIg treatment. Antibodies directed against several T-cell surface molecules are present in IVIgs, including the T-cell receptor, CD4, and major histocompatibility complex. Neutralizing antibodies against bacterial or viral superantigens that stimulate T cells unspecifically are also contained in IVIgs. Furthermore, soluble CD4 or CD4-like activity and soluble HLA molecules are found in trace amounts in IVIgs. The implications of these contaminations comigrat-
ing with IVIgs is uncertain because successful treatment trials have been reported with different preparations containing variable amounts of these factors.

**B Cells**

Many in vitro studies have shown the potential of IVIgs to inhibit antibody production and B-cell differentiation. This could be mediated by anti-idiotypic antibodies directed against the surface-bound idiotypes on B cells producing pathogenic antibodies (see below), or by antibodies directed against the CD5 antigen that is expressed on the subpopulation of B cells thought to produce low-affinity natural autoantibodies. Anti-idiotypes have indeed been shown to be present in IVIg preparations. Finally, IVIgs can inhibit the production of interleukin 6, a cytokine needed for the secretion of IgG by plasma cells.

**Fc Receptor**

The Fc portion of immunoglobulins interacts with many phagocytic cells expressing appropriate Fc receptors on their cell surfaces. Pathogenic antibodies can bind to the Fc receptor and thereby target macrophages. Excess amounts of immunoglobulins may compete with this binding and block the damaging effects of inflammatory effector cells. Modulation of Fc receptor-mediated functions has been shown in vitro, and administration of purified Fc fragments was indeed effective in children with idiopathic thrombocytopenic purpura. Another beneficial Fc-mediated effect is through Fc receptor neonate binding protein (FcRn), which, after excess binding to therapeutic IVIg, speeds up IgG autoantibody catabolism and elimination. For neurologic disorders, there is evidence from experimental autoimmune neuritis in rats that intact human IVIgs, but not F(ab’), fragments, can reduce disease severity, suggesting that their effect is mediated via the Fc portion.

**Anti-idiotypes**

Immunoglobulins that recognize and attach to the antigen-binding region of the F(ab) part of another immunoglobulin are called anti-idiotypic antibodies. These antibodies may occur naturally or may be driven by antigenic challenge with subsequent formation of autoantibodies. It is thought that a network of these various antibodies may play a role in the regulation of autoimmunity. The therapeutic relevance of this mechanism in human disease was demonstrated by the successful treatment of 2 patients with systemic lupus erythematosus with purified anti-idiotypic antibodies. This mechanism has been suggested to play a role in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy.

**Cytokines**

Clinical studies have demonstrated that the cytokine profile of patients is altered by the administration of IVIgs, and this is supported by studies showing that cytokine production can be modulated by IVIgs in cultured mononuclear cells. It has not been proved, however, that this mechanism plays a major role in the pathologic situation. Intravenous immunoglobulins contain trace amounts of interferon gamma and transforming growth factor beta. While interferon gamma is thought to activate an ongoing immune response in the peripheral nervous system, transforming growth factor beta seems to be associated with clinical recovery. On the other hand, antibodies directed against interleukin 1α, interleukin 6, and the class I and II interferons (alpha, beta, and gamma) have been found in IVIgs, which may also have a regulatory role in the cytokine network. In experimental autoimmune encephalomyelitis, human IVIgs are thought to act via down-regulation of tumor necrosis factor α secretion. Indeed a protective effect of IVIgs on tumor necrosis factor α mediated cell damage has been shown in vitro. It seems not an easy task to formulate a unifying hypothesis based on these multiple observations.

**EFFECTS OF IVIgs ON REMYELINATION**

The concept that IVIgs may have the potential to remyelinate axons originated from the observation that polyclonal immunoglobulins against spinal cord homogenate were able to increase remyelination in the inflammatory model of Theiler virus encephalitis. A monoclonal IgMκ antibody was identified that could promote remyelination, suppress inflammation, and also have some effect in a toxic model of demyelination. This monoclonal antibody was shown to be polyreactive, recognizing antigens present on oligodendrocytes and other cells. Extrapolating from these experimental observations, IVIgs may have a beneficial effect if they contain such autoantibodies. This intriguing concept challenges the traditional view of antemyelin antibodies as essentially detrimental. Besides their immunomodulatory role (see above) antemyelin antibodies may stimulate oligodendrocyte precursors or mature oligodendrocytes to proliferate or differentiate.

**CONCLUSIONS**

Treatment with IVIgs has shown a positive effect in conditions of both the peripheral and central nervous systems. As a first-line treatment for Guillain-Barré syndrome, it has demonstrated efficacy in 2 large controlled trials. Used alternatively to plasma exchange and standard immunosuppression (steroids and azathioprine), IVIgs have shown efficacy in controlled trials against chronic inflammatory demyelinating polyneuropathy. Used as a first-line treatment, either alone or in combination with cyclophosphamide to halt progression, IVIg therapy has demonstrated efficacy, again in controlled trials, for the treatment of multifocal motor neuropathy, and has shown a positive effect in single cases against neuropathy with IgM paraproteinemia (though a controlled trial failed to demonstrate efficacy). In 3 controlled trials with multiple sclerosis, IVIg therapy has shown a positive effect on relapse rate.

There is overwhelming evidence that IVIgs can manipulate the immune system at several levels. The capacity of immunoglobulins to promote remyelination has
been demonstrated in experimental models, but it remains to be shown whether this is a direct effect on myelin or is secondary to immunomodulation. A general restorative action of IVIgs is less likely, since not all demyelinating immunoneuropathies respond favorably,\(^1\) nor was there a protective effect in adrenoleukodystrophy, a peroxisomal dysmyelinating disorder. The history of IVIg treatments is a telling example of how much empirical knowledge can contribute to medical progress even in the realm of molecular medicine. Elucidation of both the pathophysiological mechanisms in the various diseases and the mode of action of IVIgs may eventually lead to more specific immunoglobulin preparations, including the generation of recombinant humanized immunoglobulin fractions.

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