CLINICAL IMPLICATIONS OF BASIC RESEARCH

The Antiinflammatory IgG

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Intravenous immune globulin is a therapeutic preparation of normal human polyclonal IgG obtained from plasma pooled from several thousand healthy blood donors. Initially used in treating primary and secondary immune deficiencies, intravenous immune globulin is increasingly used for the treatment of diverse autoimmune and systemic inflammatory diseases including immune thrombocytopenia, Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, dermatomyositis, and Kawasaki's syndrome.

Several non–mutually exclusive mechanisms have been proposed to explain the beneficial effects of intravenous immune globulin in patients.[1] One such process was proposed by Ravetch et al. in 2006[2]: that the beneficial effect of intravenous immune globulin is mediated mainly by a fraction of antibodies with terminal sialic acid at the glycan linked to asparagine at position 297 (Asn297) of the constant (Fc) chain of IgG (Fig. 1, inset). The fraction of intravenous immune globulin rich in these sialic acid–containing antibodies showed an antiinflammatory effect by enhancing the expression of the inhibitory IgG Fc receptor IIB, and the enzymatic removal of the sialic acid residues abrogated this antiinflammatory effect.

In a more recent study,[3] Anthony and Ravetch et al. have further elucidated the role of sialic acid–dependent antiinflammatory activity of intravenous immune globulin. Analysis of glycans by means of sequential mass spectrometry revealed a preferential 2,6-sialylated linkage at Asn297 in intravenous immune globulin that imparts the antiinflammatory activity. Moreover, the authors recapitulated the antiinflammatory activity of sialylated Fc fragments of intravenous immune globulin, using a homogeneous 2,6-sialylated fully recombinant human IgG1 Fc protein. This molecule showed antiinflammatory activity similar to that of IgG-derived, sialic acid–enriched Fc fragments in a mouse model of arthritis (Fig. 1).

Sialylated IgG Fc molecules (derived from either intravenous immune globulin or human recombinant IgG1) or intravenous immune globulin were administered to C57BL/6 mice 1 hour before the injection of serum (containing antibodies that induce arthritis) from the K/B×N transgenic mouse, and footpad swelling was monitored over the next 7 days to assess clinical scores of arthritis. Each sialylated IgG Fc preparation prevented swelling when administered at a low dose (33 mg per kilogram of body weight for the Fc preparations vs. 1 g per kilogram for intravenous immune globulin). These findings suggest that the 2,6-sialylated IgG Fc molecule is the biologically active component of intravenous immune globulin, at least in the context of this experimental model of rheumatoid arthritis.

What are the mechanisms of action of recombinant sialylated IgG Fc protein? These are not known. Anthony et al. describe a model (Fig. 1) wherein sialylated IgG Fc protein interacts with a currently unidentified sialic acid–specific receptor on specific regulatory macrophages in the marginal zone of the spleen. These regulatory macrophages consequently enhance the expression of the Fcγ receptor IIB on effector macrophages.[2,3] This action would, in turn, raise the threshold required for pathogenic IgG to activate signaling through Fcγ receptors and hence to trigger inflammatory processes. However, the results of some studies[4,5] are inconsistent with this proposed mechanism, and whether Fcγ receptors have a critical role in mediating the therapeutic effect of intravenous immune globulin has yet to be determined.

Will this finding by Anthony et al. change the use of intravenous immune globulin in clinical practice? Probably not for patients with immunodeficiencies such as X-linked agammaglobulinemia or common variable immunodeficiency, since these patients need the entire IgG pool found in intravenous immune globulin to com-

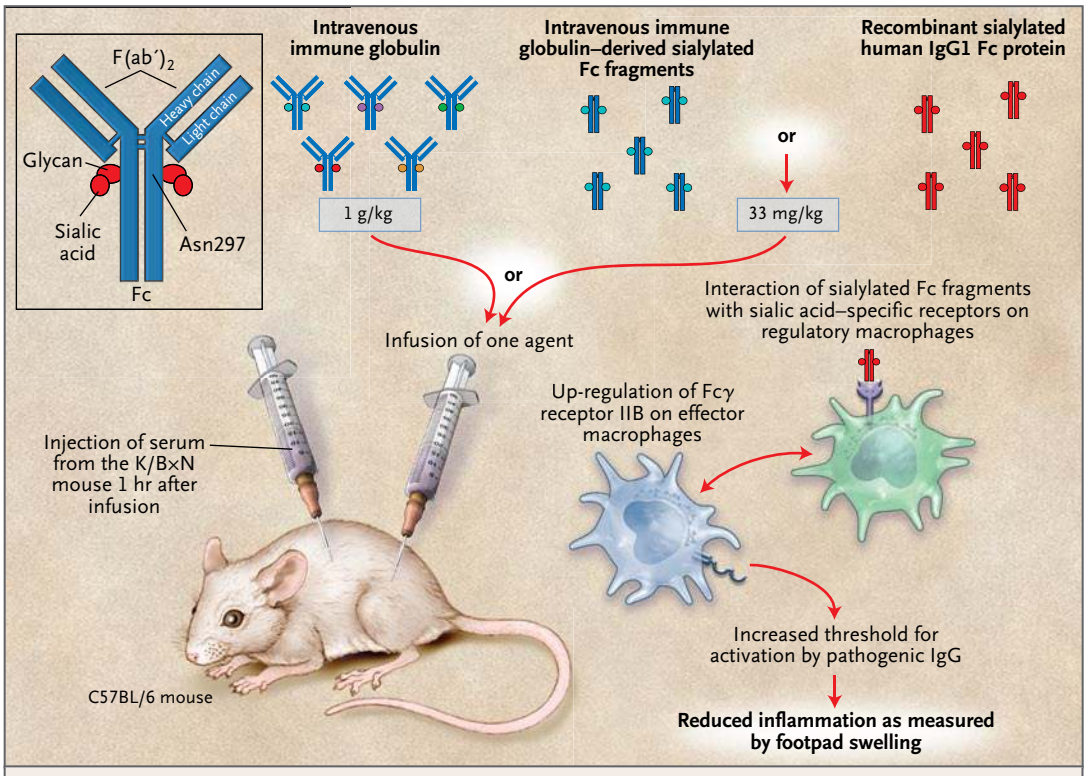

Figure 1. Effects of Recombinant Sialylated Human IgG1 Fc Protein and Intravenous Immune Globulin.

By using the K/B×N mouse model of serum-transfer arthritis, Anthony et al.[3] recently found that both 2,6-sialylated recombinant human IgG1 Fc protein and Fc fragments derived from intravenous immune globulin and enriched with sialic acid have an antiinflammatory effect that is similar to that of intact intravenous immune globulin. The IgG molecule (inset) is the principal component of intravenous immune globulin — and the Asn297 residue can be glycosylated. The authors suggest that recombinant sialylated IgG1 Fc protein interacts with regulatory macrophages. These macrophages then enhance the expression of Fcγ receptor IIB on the surface of effector macrophages that, in turn, raises the threshold required for pathogenic IgG to engage activating Fcγ receptors and to trigger the inflammatory process.

bat repeated infections. In contrast, the study by Anthony et al. may affect the treatment of patients with certain autoimmune diseases — in particular, immune thrombocytopenia. Results from both experimental models and clinical trials have shown the antiinflammatory effect of Fc fragments of intravenous immune globulin, suggesting a role for Fcγ receptors in the pathogenesis of this disease.[6] If recombinant sialylated IgG Fc protein shows a benefit in patients with immune thrombocytopenia similar to that shown in rodents by Anthony et al., it may become possible to avoid the infusion of huge amounts of intravenous immune globulin. Another benefit of recombinant intravenous immune globulin would be the elimination of variation among batches of a given preparation and also among preparations. The likelihood of contamination by emerging and reemerging infectious agents would also be minimized.

Despite the promising results in experimental models, recombinant protein therapies can cause adverse reactions in patients. Because immune responses against repeatedly infused recombinant proteins have been reported in patients, the therapeutic use of sialylated recombinant IgG Fc protein should be considered with caution. Given the heterogeneous pathogenesis and presentation of autoimmune and inflammatory diseases and the beneficial effect of intravenous immune globulin in patients with these diseases, despite the heterogeneity, recombinant sialylated IgG Fc protein alone seems unlikely to be consistently effective in all groups of patients currently known to ben-

efit from intravenous immune globulin. That said, phase 1 clinical trials may now be considered in autoimmune diseases for which Fcγ receptors have a clear role in the pathogenesis and Fc fragments of intravenous immune globulin are shown to be beneficial.

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