Gaining More From Gamma Globulins

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The use of intravenous immunoglobulin (IVIg), which is immunoglobulin G pooled from thousands of healthy donors, in the treatment of immunodeficient and autoimmune diseases has grown during the past 2 decades. Although its initial application was largely limited to replacement therapy in hypogammaglobulinemia, IVIg is gaining acceptance as therapy for autoimmune thrombocytopenia purpura, and a number of other autoimmune diseases such as multiple sclerosis. Although the exact mechanisms underlying the protection conferred by IVIg in these immune disorders remain undefined, several potential molecular and cellular targets have been proposed. For example, IVIg can block Fc receptors on macrophages and effector cells to reduce the phagocytic capacity of these cells. IVIg may also regulate the immune response by reacting with a number of membrane receptors on T cells, B cells, and monocytes that are pertinent to autoreactivity and induction of tolerance to self. Recent work has also revealed a beneficial effect of IVIg in systemic inflammatory disorders such as sepsis and asthma. It has been suggested that IVIg may exert its antiinflammatory effects by attenuating complement-mediated attack, inducing antiinflammatory cytokines, and reducing the production of proinflammatory cytokines such as tumor necrosis factor-α, interferon-γ and interleukin-1β (Figure). Many of these mechanistic studies of IVIg effects on the inflammatory response are based on in vitro models and in vivo data are lacking.

See p 2031

In a report published in this issue of Circulation, Gill and coworkers propose a novel target of IVIg action in the inflammatory cascade (ie, leukocyte-endothelial cell adhesion). They report that IVIg prevents leukocyte rolling on immobilized P- and E-selectin in an in vitro flow chamber system, and that this effect was mediated on the leukocyte rather than the selectin substrate. Similar antiadhesive actions of IVIg were evident on endothelial cell monolayers challenged with histamine and in feline mesenteric postcapillary venules subjected to ischemia and reperfusion (I/R), with both models involving P-selectin-dependent leukocyte rolling and β2-integrin-mediated firm adhesion. Their findings with IVIg were consistent with a mechanism that involves the downregulation of adhesion molecules (P-selectin glycoprotein ligand-1 [PSGL-1], β2-integrin) normally expressed on leukocytes (but not endothelial cells) that mediate the rolling and (to a lesser extent) firm adhesion steps of leukocyte recruitment. Another important finding of the Gill study was that IVIg mediated protection against vascular protein leakage in posts ischemic feline mesenteric venules. This protection against I/R-induced endothelial barrier dysfunction is likely to result from the attenuated leukocyte recruitment rather than a direct action of IVIg on endothelial cell function, inasmuch as numerous previous studies have demonstrated a cause-effect relationship between I/R-induced leukocyte-endothelial cell adhesion and increased vascular permeability. Nevertheless, a direct action of IVIg on endothelial barrier function cannot be ruled out because it was recently reported that IVIg treatment abrogates the gut injury and complement deposition induced by superior mesenteric artery occlusion in rats in the absence of any changes in leukocyte infiltration. Although these divergent responses to IVIg treatment in the setting of gut I/R may result from different models and end points, the benefits noted with IVIg treatment in both studies highlight the potential utility of IVIg as an inflammation-based therapeutic strategy in ischemic tissue diseases.

Although the findings of Gill and colleagues offer a novel therapeutic strategy for I/R injury and other inflammation-dependent disease processes, the feasibility and utility of IVIg therapy in the clinical setting remain uncertain and warrant further consideration. Interference with leukocyte-endothelial cell adhesion with blocking monoclonal antibodies directed against P-selectin, PSGL-1, β2-integrins, and other adhesion molecules have proven to be remarkably effective in preventing I/R injury in a number of experimental models. The clinical experience with antiadhesion strategies in ischemic tissue diseases has not yet recapitulated the animal laboratory experience. Duration of the ischemic insult, time of administration of the antibody (before or after the ischemic insult), adverse activation of cells by the antibodies, and inadequate design of the clinical trials have been offered as explanations for the different outcomes in human trials versus animal models. Whether IVIg can overcome these complications and limitations of the highly specific and more potent adhesion molecule–directed antibodies or simply offers more in the clinical setting because of its multiple sites of action in the inflammatory cascade (Figure) is unclear. Although the clinical experience to date predicts a limited potential for antiadhesion therapy for the treatment of ischemic tissue diseases, it is difficult to ignore the emerging success of antiadhesion therapies against other inflammatory conditions such as multiple sclerosis, asthma, and inflammatory bowel disease.

During I/R injury, several cell types are activated, including leukocytes and endothelial cells. Gill et al demonstrated
that IVIg does not appear to have a direct effect on endothelial cells; rather, the protective effect appears to be exerted on the neutrophil. This cellular specificity may result from the study’s focus on the immediate postischemic window, however, because there is evidence that longer exposure to IVIg induces an antiinflammatory phenotype in cultured endothelial cells. It has been reported that incubation of cytokine-activated endothelial cell monolayers with IVIg prevents the elevation of mRNA for both cytokines and chemokines. Furthermore, IVIg appears capable of preventing the upregulation of endothelial cell adhesion molecules both in vivo and in vitro. These effects of IVIg on transcription-dependent production of cytokines, chemokines, and adhesion molecules may result from an inhibitory action on the transcription factor NF-κB. Hence, there are several lines of evidence in the literature that support the possibility that endothelial cells may also be a major target for the antiinflammatory actions of IVIg, and the benefit afforded from these actions may be more evident if the microvascular dysfunction and tissue injury responses are evaluated later than the immediate postischemic window.

There is also evidence that the benefits gained from IVIg treatment for inflammation extend beyond neutrophils, the major leukocyte population that is recruited into postischemic microvasculature. The same research group has recently reported the blockade of lymphocyte entry into the brain by IVIg treatment in a murine model of multiple sclerosis, which is accompanied by an improved functional recovery. Based on complimentary in vitro data, they proposed that this effect on lymphocyte recruitment was at least partially caused by inhibition of α4-integrin/vascular cell adhesion molecule-1–dependent adhesion to endothelial cells. These findings are consistent with the positive results from a clinical trial in patients with multiple sclerosis that employed the humanized monoclonal antibody natalizumab, which saturates α4β1 sites on T cells. The new findings of Gill et al suggest, however, that downregulation of PSGL-1 may also have played a role in the lymphocyte recruitment, since rolling of these cells in venules is primarily dependent on P-selectin–PSGL-1 interactions. Their experience with IVIg-mediated inhibition of lymphocyte recruitment in the brain microcirculation may also have some bearing on the protective effects of IVIg in experimental I/R injury. There are several reports that implicate lymphocytes in the pathogenesis of I/R injury. For example, T lymphocytes appear to mediate the early neutrophil recruitment to sites of I/R injury through the release of cytokines. The well-known ability of IVIg to modulate immune cell function by binding receptors on T cells may have important implications in the T cell–mediated regulation of neutrophil infiltration into the postischemic microvasculature.

Despite the many purported beneficial actions of IVIg in modulating the inflammatory cascade, some potentially deleterious actions of IVIg have been described (Figure) that may limit its application to cardiovascular disease (CVD). There are reports suggesting that predisposition to cardiovascular risk factors may be enhanced by IVIg therapy. For example, patients at risk for hypertension may experience elevated blood pressure as a side effect of IVIg treatment. Reactive oxygen species, which have been implicated in the pathogenesis of several CVDs, including I/R, are produced at an accelerated rate by neutrophils exposed to IVIg.

Many CVDs are also associated with platelet activation and aggregation. There have been several reports describing a deleterious effect of IVIg on platelet recruitment and on both venous and arterial thrombosis. Although the kinetics of platelet recruitment after vascular injury or inflammation may differ between tissues, experimental data suggests these platelets may play an important role in modulating the leukocyte recruitment and tissue injury responses observed in different experimental models. Inasmuch as P-selectin–PSGL-1 interactions are known to mediate the platelet–
leukocyte aggregation and platelet–venular wall interactions associated with several experimental models of CVD, one may expect IVIg treatment to inhibit these heterotypic adhesive interactions involving platelets. Although Gill and associates did not monitor platelet adhesion in postischemic mesenteric venules or the appearance of platelet-leukocyte aggregates in blood, the same research group has previously demonstrated that platelet and leukocyte recruitment into the postischemic cerebral microvasculature is aggravated by IVIg treatment.13 Because the recruitment of adherent platelets and leukocytes into the postischemic cerebral microvasculature is P-selectin-dependent,21 the excessive aggregation and recruitment of platelets and leukocytes induced by IVIg treatment in this model of ischemic stroke is unexpected in view of the proposal that IVIg targets PSGL-1; however, it was suggested that IVIg may bind to Fc receptors that are upregulated on platelets after stroke, thereby promoting additional leukocyte and platelet recruitment.13 These potentially detrimental actions of IVIg on platelet function in the setting of CVD raises the possibility of combining IVIg therapy with antithrombotic agents such as aspirin, which has been shown to reduce the incidence of coronary artery lesions in patients with Kawasaki syndrome.22

The apparent discrepancy between the actions of IVIg in the microcirculations of the brain13 and gut4 may simply reflect interorgan differences related to the regulation of blood cell–vessel interactions. Another notable difference was the time of IVIg administration, with a preischemic (before the induction of ischemia) and posts ischemic (after 2-hour reperfusion) treatment protocol employed in the gut and brain experiments, respectively. Indeed, the authors stated that no protection was conferred on the mesenteric microcirculation when IVIg was administered at the time of reperfusion.4 Although the need for pretreatment may limit the therapeutic potential of IVIg for myocardial infarction and stroke, this strategy may be of benefit during surgical procedures, in which the time of onset of reperfusion is known and controlled.

The article by Gill et al in this issue significantly extends our understanding of the potential mechanisms that underlie the well-documented benefits of IVIg in a variety of diseases associated with inflammation. The potency of IVIg as an antiadhesion agent may well explain its beneficial actions in diverse clinical conditions and clearly justifies additional research that is directed toward defining the molecular basis for the inhibitory action of IVIg on leukocyte-endothelial cell adhesion. The ability of IVIg to preserve the normal barrier function of microvascular endothelium has far-reaching implications of therapeutic consequence and is also worthy of additional study.

References


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