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High-Dose Intravenous Immunoglobulins: An Option in the Treatment of Systemic Lupus Erythematosus

E. Toubi, A. Kessel, and Y. Shoenfeld

ABSTRACT: Despite encouraging reports on the efficacy of intravenous immunoglobulin (IVIG) therapy in systemic lupus erythematosus (SLE), the clinical value of this treatment is not well established, and most of the data are based on case reports and small series of patients. IVIG has been used successfully to treat SLE patients with a broad spectrum of clinical manifestations, such as refractory thrombocytopenia, pancytopenia, central nervous system (CNS) involvement, secondary antiphospholipid syndrome, and lupus nephritis. The beneficial effects of IVIG on overall disease activity are usually prompt, with marked improvement within a few days, but they are often of limited duration. Improvement lasts for several weeks after the last infusion, although clinical response could be maintained by continuous monthly IVIG infusions. IVIG therapy immunomodulates autoimmune diseases by interacting with various Fcγ receptors in such a way that it downregulates activating FcRIIA and FcRIIC and/or upregulates inhibitory FcRIIB. However, in SLE, additional mechanisms include inhibition of complement-mediated damage, modulation of production of cytokines and cytokine antagonists, modulation of T- and B-lymphocyte function, induction of apoptosis in lymphocytes and monocytes, downregulation of autoantibody production, manipulation of the idiotypic network, and neutralization of pathogenic autoantibodies. At present, IVIG in SLE is indicated either in severe cases that are nonresponsive to other therapeutic modalities, or when SLE can be controlled only with high-dose steroids; in such patients, IVIG thus becomes a useful steroid-sparing agent. However, this needs to be confirmed in double-blind, placebo-controlled studies. *Human Immunology 66, 395–402 (2005).*

KEYWORDS: intravenous immunoglobulin; systemic lupus erythematosus; autoimmunity; antiidiotypes; immunomodulation

ABBREVIATIONS

Ab	antibody
CNS	central nervous system
DC	dendritic cell
Id	idiotype
Ig	immunoglobulin
IVIG	intravenous immunoglobulins
IL	interleukin
SLE	systemic lupus erythematosus
Th	helper T cell
TNF-α	tumor necrosis factor alpha
WHO	World Health Organization

INTRODUCTION

Mild systemic lupus erythematosus (SLE) is treated with nonsteroidal antiinflammatory drugs, low-dose corticosteroids, and antimalarial compounds. In moderate SLE, patients are treated with cytotoxic agents, cyclophosphamide, methotrexate, and azathioprine, whereas severe cases are managed with high-dose steroids and intravenous pulse cyclophosphamide. This therapy provides broad-spectrum immunosuppression with a risk of developing secondary infections and myelosuppressive side effects. The aim of modern therapy for SLE is to regulate rather than suppress the immune response. This is achieved by manipulation of idiotypes with intravenous immunoglobulins (IVIGs), manipulation of second signal pathways in T- and B-cell interaction with anti-CD40L or anti-BLyS monoclonal antibodies (Abs), or manipulation of cytokines [1].

From the Division of Allergy and Clinical Immunology, Bnai Zion Medical Center, Haifa, Israel (E.T., A.K.); and Department of Internal Medicine B and Center of Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel (Y.S.).

Address reprint requests to: Dr. E. Toubi, Division of Allergy and Clinical Immunology, Bnai Zion Medical Center, P.O. Box 4940, Haifa, Israel; Phone: 972-4-8359253; fax: 972-4-8359659; E-mail: elias.toubi@b-zion.org.il.

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Despite encouraging reports on the use of IVIG in autoimmune disorders, the clinical efficacy and indication in SLE patients remain undetermined. It was successfully used for severe complications of SLE such as refractory thrombocytopenia, lupus nephritis, and central nervous system (CNS) involvement. Efficacy of IVIG was also demonstrated in the treatment of an experimental murine model of SLE [2, 3].

MECHANISMS OF ACTION OF IVIG IN SLE

Autoimmune diseases, including SLE, are the result of a dysregulation of the FcγR system where the balance between activating and inhibitory FcγR signaling is disrupted [4]. Intravenous immunoglobulin may induce a reversible blockade of the Fc receptors on phagocytic cells by saturating, altering, or downregulating the affinity of Fc receptors, a process that may render sensitized phagocytic cells unable to function, *e.g.,* in idiopathic thrombocytopenic purpura [5]. Intravenous immunoglobulin therapy immunomodulates autoimmune diseases by interacting with various FcγRs in such a way that it downregulates activating FcγRIIA and FcγRIIC and/or upregulates inhibitory FcγRIIB [6]. In Th1-mediated hypersensitivity reactions, cytokines (*e.g.,* tumor necrosis factor alpha [TNF-α]) were revealed to upregulate and activate activating FcγRs such as FcγRIIA, whereas Th2 cytokines (*e.g.,* interleukin [IL]-13) activated the inhibitory FcγRIIB [7]. High-dose IVIG treatment induced a decrease in Th1/Th2 lymphocyte ratios, suggesting that IVIGs modify peripheral Th1/Th2 balance in favor of Th2 profile [8]. Intravenous immunoglobulins accelerate autoantibody (auto-Ab) catabolism by binding to a specific Fc receptor that is found on endothelial cells and is called FcRn [9]. FcRn is a transport receptor that, by binding to intracellular immunoglobulin (Ig) G, protects it from lysosomal degradation catabolism. The saturation of FcRn receptors by IVIG treatment prevents the binding of endogenous IgG

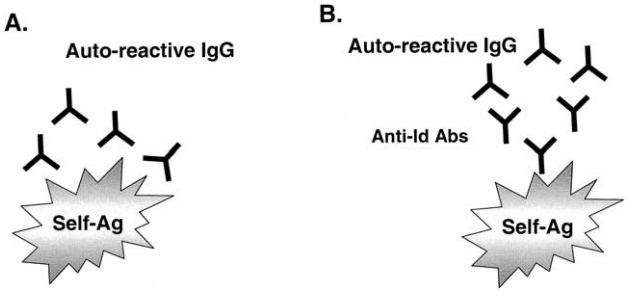

FIGURE 1 (A) Autoreactive immunoglobulin (Ig)G antibodies (Abs) recognize self-antigens inducing organ damage. (B) Anti-idiotype (Id) Abs block IgG autoreactive response and inhibit self-recognition. Ag = antigen.

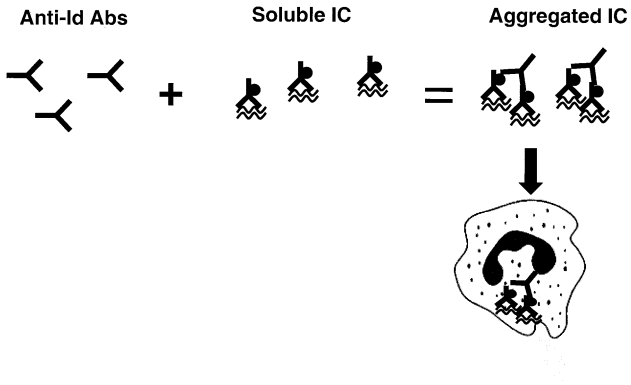

FIGURE 2 Anti-idiotype (Id) antibodies (Abs) turn soluble immune complexes into aggregated complexes, rendering them available for efficient phagocytosis.

auto-Abs, resulting in their accelerated degradation and the reduction of pathogenic auto-Ab levels.

Therapy with IVIG takes advantage of the fact that it contains a wide range of natural auto-Abs that reflect the immunologic experience of the donor population with different pathogens [10]. Natural Abs occur under physiologic conditions that are autoreactive but not autospecific, and they are believed to provide the antiinflammatory effects of IVIG preparations by the following mechanisms: IVIG contain natural auto-Abs directed against the idiotype, the hinge region, and against the constant heavy and light chain domains of Abs, suggesting that they might be able to bind pathogenic auto-Abs, thus preventing binding to autoantigens [11] (Figure 1). It is possible that antiidiotype (anti-Id) auto-Abs bind to variable regions of antigen receptors, rendering cell activation by the relevant autoantigens impossible. It was demonstrated that pooled normal polyspecific human IgG from IVIG preparations inhibited the binding of anti-DNA Abs to DNA [12]. Affinity chromatography of $F(ab)_2$ fragments or IgG containing anti-DNA auto-Ab activity on sepharose-bound $F(ab)_2$from IVIG resulted in the specific retention of Ab activity, indicating that IVIG contain anti-Id Abs against human auto-Abs. In addition, pooled human immunoglobulins were demonstrated to contain anti-Ids with reactivity against the SLE-associated 4B4 cross-reactive idiotype (a regulatory anti-Sm idiotype). Sm Ab binding by 4B4 was clearly blocked by IVIG $F(ab)_2$ fragments, illustrating the presence of Ab2 molecules in this preparation [13].

The use of isolated anti-Ids against pathogenic auto-Abs may result in more effective treatment with amounts of IgG that are hundreds of times smaller. Although the beneficial effect of monoclonal anti-Id Ab was revealed in several mice models of SLE, human SLE is characterized by the presence of numerous auto-Abs (*i.e.,* pathogenic idiotypes). Therefore, treatment with monoclonal anti-Id