

INTRAVENOUS IMMUNOGLOBULIN THERAPY IN NEUROLOGICAL DISEASES

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Abstract

Intravenous immunoglobulin (IVIg) is used to treat a number of immune deficiencies and autoimmune diseases. The pharmacokinetic proprieties of IVIg in healthy persons are well defined. The broad range of clinical applications of IVIg shows the importance of immunoglobulins in the immune homeostasis in healthy people. Intravenous immunoglobulin (IVIg) is an immunomodulating agent that has multiple activities. IVIg can be administrated in different ways (intramuscular, subcutaneous, or intravenous) and have a half-life of 21 to 30 days. IVIg is used to treat: epilepsy and pediatric intractable Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, *miastenia gravis*, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy, multiple sclerosis. However, the therapeutical indications for IVIg use progressively expanded. The means of increased specificity of IVIg therapy should include both patient-related variables (clinical manifestations, laboratory parameters, response to other therapeutic modalities) and drug-related characteristics such as specific idiotypes' concentration within IVIg.

Rezumat

Imunoglobulinele administrate intravenos (i.v.) sunt folosite în tratamentul a numeroase deficiențe imune și boli autoimune. Proprietățile farmacocinetice ale imunoglobulinelor cu administrare pe cale intravenoasă (Ig i.v.) la persoanele sănătoase sunt foarte bine cunoscute. Utilizarea pe scară largă a Ig i.v. a demonstrat importanța Ig în homeostazia imunologică la subiecții aparent sănătoși. Imunoglobulinele cu administrare intravenoasă constituie agenți de imunomodulare cu activități multiple. Imunoglobulinele pot fi administrate pe diferite căi (intramuscular, subcutanat sau i.v.), timpul de înjumătățire este între 21-30 zile. Imunoglobulinele sunt folosite în tratamentul epilepsiei, sindromului Guillain-Barré la copii, polineuropatiei demielinizante inflamatorii cronice, *miasteniei*

gravis, sindromului miastenic Lambert-Eaton, neuropatiei motorii multifocale, sclerozei multiple. Indicațiile pentru folosirea Ig devin tot mai numeroase. Eficiența tratamentului cu Ig depinde atât de pacient (manifestările clinice și paraclinice, răspunsul la alte modalități de tratament) cât și de caracteristicile legate de tratamentul cu Ig.

Keywords: intravenous immunoglobulin (IVIg), therapy, autoimmune neurological diseases

Introduction

IVIg is a safe and useful alternative therapy for many autoimmune neurological diseases. The use of high-dose polyclonal intravenous immunoglobulin (IVIg) in the treatment of autoimmune neurological diseases has expanded over the last decade [1,2].

Several mechanisms have been proposed to explain the effects of IVIg on immune modulation, such as the anti-idiotypic modulation of pathogenic auto-antibodies. IVIg enhances immune homeostasis. Intravenous immunoglobulin (IVIg) is an immunomodulating agent that has multiple activities: modulation of complement activation, suppression of idiotypic antibodies, saturation of Fc receptors on macrophages, and suppression of various inflammatory mediators (cytokines, chemokines, and metalloproteinases) [3,4]. IVIg contains cytokines, natural antibodies [5,6]. These mechanisms may explain the effectiveness of IVIg in autoimmune neurologic disorders. IVIg treatment led to decreased production of the inflammatory cytokine TNF alpha (tumor necrosis factor alpha). IVIg treatment may exert its therapeutic effect not by inhibiting T cell recognition of self-antigens, but by inhibiting the biological consequences of T cell recognition. It has been postulated that the beneficial effect of IVIg in antibody-mediated autoimmune disorders is based on accelerated catabolism of autoantibodies. IVIg reduces autoantibodies levels through mechanisms such as down-regulation of antibody production or neutralization by anti-idiotypic antibodies [7,8]. It is used increasingly in the therapy of neurologic diseases such as inflammatory demyelinating neuropathies, multifocal motor neuropathy, inflammatory myopathies, myasthenia gravis, and the Lambert-Eaton syndrome [9].

IVIg therapy should be carefully monitored. Laboratory tests may include the following [10]:

- liver function tests,
- renal function tests,
- complete blood count (CBC) with differential,

- hepatitis screening to assess the possible disease-spread through IVIg, immunoglobulin levels to exclude IgA deficiency (if no IgA antibodies are found, then anti-IgA antibody titers should be obtained),
- rheumatoid factors and cryoglobulin levels, because IVIg can cause haematological complications [10].

IVIg treatment within the first year from the onset of the first neurological event suggestive for the demyelinating disease significantly lowers the incidence of a second attack and reduces the disease development as measured through brain magnetic resonance imaging [5,11].

The efficacy of immunoglobulin therapy has formally been proved only for the Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathies, but reports of new applications continue to be published, such as their use for treating the intractable childhood seizures (Rasmussen's encephalitis) [6,12].

IVIg is usually well tolerated. Undesirable effects from IVIg occur in less than 5% of patients and include headache, nausea or vomiting, chills, fever, hypertension or hypotension, myalgias, flushing, and tachycardia [13].

Conventional doses are 0.4 g/kg bw/day for 5 days or 1g/kg bw/day for 2 days, once a month [7]. Outcomes of controlled trials indicate that IVIg at a total dose of 2 g/kg bw is effective as first-line therapy in Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy and as secondary-line therapy in stiff-person syndrome, *myasthenia gravis*, and Lambert-Eaton myasthenic syndrome. In other clinical studies, IVIg produced a slight, variable, and temporary amelioration in patients with inclusion body myositis and paraproteinemic anti-myelin-associated glycoprotein antibody demyelinating polyneuropathy. Intravenous immunoglobulin is not effective in patients with multiple sclerosis with an established weakness or optic neuritis. In *myasthenia gravis*, it should only be indicated for complicated cases, or before thymectomy [8,14].

The IVIg mechanism of action is complex and may differ among different diseases and even patients. IVIg therapy induces a relatively long-lasting but slight, reduction of auto-antibody levels through an accelerated IgG clearance. This mechanism has clinical relevance since it can explain the gradual 20% to 40% decrease in the autoantibody levels observed in several clinical studies [15,16].

Since patients respond differently to IVIg therapy, and currently there is no reliable method to predict who should benefit from this treatment, an effort should be carried out in order to predict which patients might respond to the IVIg therapy [4].

Based on controlled clinical trials IVIg can be currently considered as the first-line treatment in Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy, and it may be used as a second-line therapy in some cases of *myasthenia gravis*. IVIg is also a second-line therapy in stiff-person syndrome and multiple sclerosis [5,7].

IVIg and interferon have been reported as successful treatments for optic neuritis in patients with pediatric multiple sclerosis. Also, IVIg therapy was reported to be successful in the treatment of acute disseminated encephalomyelitis [10,13,16].

Conclusions

The increasing number of clinical reports of IVIg use for the treatment of various autoimmune neurologic diseases indicate that IVIg is beneficial for these conditions. IVIg therapy should be carefully monitored. Investigations regarding the hepatic and renal functions should also be performed. Patients with ataxic sensory neuronopathy, Sjögren syndrome and stiff man syndrome are presently considered for IVIg therapy.

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