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IM - REVIEW

Intravenous immunoglobulin therapy: a snapshot for the internist

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Abstract
Intravenous immunoglobulins are the cornerstone for the treatment of primary humoral immunodeficiencies and may be used for a great number of other autoimmune, neurological and hematological conditions as well. Given their wide application, the possibility of running across a patient who needs this kind of therapy is becoming increasingly common. Generally, intravenous immunoglobulins are well tolerated. However, numerous adverse reactions ranging from mild to severe have been reported and linked to patient- and product-related factors. For all these reasons, we present herein a comprehensive review of the on- and off-label applications of intravenous immunoglobulins and provide a guide for the internist how to minimize the risk of adverse reactions and manage them.

Keywords Immunoglobulins · IVIg · Autoimmune diseases · Immunodeficiency · Adverse drug reactions

Introduction

The history of immunoglobulins dates back the nineteenth century, when Emil Adolf von Behring and Shibasaburo Kitasato demonstrated the possibility to transfer protection against diphtheria or tetanus in animal models[1]. During the same period, Paul Ehrlich coined the term "antibody"[2].

In 1952, Ogden Carr Bruton treated the first agammaglobulinemic patient using a subcutaneous gamma-globulin preparation obtained with the technique for blood fractionation that Edwin Joseph Cohn had developed few years before[3, 4]. From this moment forward, the uses of immunoglobulins for replacement or therapeutic purposes have multiplied[5].

The aim of this review is to provide the internists with practical information on different immunoglobulin formulations and uses, with particular regards to how to manage the most common adverse reactions in an Internal Medicine setting.

When may I use intravenous immunoglobulins? On- and off-label applications

The approved indications of intravenous immunoglobulins (IVIg) according to the European Medicines Agency (EMA), can be divided in two major categories:

– Replacement therapy

- Primary immunodeficiencies (PID);
- Secondary immunodeficiencies
  - Human immunodeficiency virus (HIV);
  - Chronic lymphocytic leukemia (CLL);

– Immunomodulation

- Idiopathic thrombocytopenic purpura (ITP);
- Guillain-Barré syndrome (GBS);
- Chronic Inflammatory demyelinating polyneuropathy (CIDP);
- Kawasaki disease.

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Moreover, IVIg have been recognized as a pivotal off-label treatment for a great number of diseases, especially thanks to their immunomodulatory effect[6].

On-label therapies

Primary immunodeficiencies

PID are disorders of the immune system, mostly presenting as severe or recurrent infections often associated with autoimmunity, autoinflammation or malignancies[7]. Over 300 PID have been discovered so far. However, IVIg efficacy have been documented mainly in humoral and combined immunodeficiencies, such as agammaglobulinemic patients, hypogammaglobulinemic patients with normal or poor antibody function, patients with normal Ig levels or isolated IgG subclass deficiency but poor antibody function and recurrent infections and patients with complex PID in which a B defect has been documented[5].

The main goal of IVIg replacement therapy is the minimization of infectious events. Generally speaking, a dosage between 200 and 800 mg/kg every 3 to 4 weeks is recommended in humoral immunodeficiencies. In the past years, a trough level of 500 to 800 mg/dL IgG had been proposed as the minimum target level for replacement therapies[8]. Nowadays, the concept of "individual trough" is gaining traction. In depth, this concept highlights how the target should not be directed to reach a particular level, but to improve the clinical outcome of the single patient, according to the clinical phenotype and complications[9].

The intravenous route is preferred when a rapid increase of immunoglobulin levels is necessary within a short time. Thereafter, a shift towards the subcutaneous route can be made, according to patient- and health-centered features, such as compliance, schooling and pre-existing comorbidities[10–12].

Human immunodeficiency virus

Studies before the highly active antiretroviral treatment (HAART) demonstrated that HIV can lead to impaired specific-antibody production. Therefore, HIV-infected patients may benefit from IVIg treatment in order to reduce serious bacterial infections and hospitalizations[5].

Chronic lymphocytic leukemia

Patients suffering from CLL are at higher risk of infectious complications[13]. Therefore, IVIg should be considered in these patients, especially when an Ig deficit together with recurrent bacterial infections are present[14].

Idiopathic thrombocytopenic purpura

ITP may affect all ages, but it usually requires therapy only in children at high risk for bleeding[5]. IVIg are considered to be the mainstay treatment for this disease, together with steroids and anti-D immunoglobulins[15]. According to these guidelines, a single dose of IVIg (0.8 to 1 g/kg) is comparable to a short course of corticosteroids as a first-line therapy in pediatric patients. In adults, IVIg are preferred to steroids when a more rapid increase in platelet counts is needed.

Guillain-Barré syndrome

Guillain-Barré is an immune-mediated progressive polyradiculoneuropathy, characterized by ascending weakness and sensory loss[16]. IVIg, at the dosage of 400 mg/kg/day for 5 consecutive days, may be used as an alternative to plasma exchange in non-ambulatory patients[17].

Chronic inflammatory demyelinating polyneuropathy

CIDP is an autoimmune polyneuropathy characterized by the subacute onset of upper and lower arms weakness and areflexia[18]. IVIg, plasmapheresis and steroids are considered to be effective treatment options. IVIg are preferred in case of contraindications to steroids. Standard treatment schedule consists in 500 mg/kg/day for 5 consecutive days (induction phase), then followed by a single monthly infusion for 6 months (maintenance phase). Overall, IVIg seems to have a higher relapse rate when compared to steroids. However, conclusive data is not available[19].

Kawasaki disease

Kawasaki disease is the most common vasculitis in children and the leading cause of acquired heart disease in the pediatric setting[20]. A single high dose IVIg (2 g/kg over 12 h), together with aspirin (30–50 mg/kg/day divided to every 6 h) is the recommended standard of care[21].

Off-label therapies

A great number of off-label applications of IVIg have been described in the literature. Table 1 describes all the off-label uses of IVIg which have been considered definitely beneficial, probably beneficial and/or of some benefits by three major reviews[5, 22, 23].

Table 1 All the off-label uses of IVIg which have been considered definitely beneficial, probably beneficial and/or of some benefits in the literature

Definitely beneficial	Probably beneficial	Of some benefit
Autoimmune diseases	*Autoimmune diseases*	*Autoimmune diseases*
Ocular diseases	Ocular diseases	Ocular diseases
Graves ophtalmopathy	Birdshot retinochoroidopathy	Autoimmune optic neuropathy
Neurologic diseases	Myositis	Vasculitis
Multifocal motor neuropathy	DM/PM	ANCA-associated vasculitis
	Vasculitis	Polyarteritis Nodosa
	Henoch-Schönlein purpura	Arthritis
	Neurologic diseases	JIA/Still disease
	IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathy	Severe RA/Felty Syndrome
		MAS
	MG	Connective tissue diseases
	LEMS	SLE
		APS in pregnancy & CAPS
		Liver diseases
		Autoimmune liver disease
		Hematologic diseases
		Autoimmune neutropenia
		Thrombotic thrombocytopenic purpura
		Post-trasfusion purpura
		Autoimmune hemophilia
		Autoimmune hemolytic anemia
		Evan syndrome
		Neonatal alloimmune thrombocytopenia
		Neonatal isoimmune hemolytic jaundice
		Neurologic diseases
		RR-MS
		Autoimmune encephalitides
		Acute disseminated encephalomyelitis
		Demyelinative brain stem encephalitis
Infectious diseases	*Infectious diseases*	*Infectious diseases*
Lung	Gut	Lung
CMV pneumonitis	Rotaviral enterocolitis	Cystic fibrosis with hypogammaglobulinemia
	Brain	RSV lower respiratory tract infection
	Enteroviral meningoencephalitis	Gut
	Systemic	Pseudomembranous colitis
	Neonatal sepsis	Campylobacter enteritis
	Toxic shock syndrome	Brain
	Bacterial infections in lymphoproliferative diseases	Post-infectious cerebellar ataxia
		HTLV1-associated myelopathy
		Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection
		Systemic
		Postoperative sepsis
		Chronic Parvovirus B19
		Postpolio syndrome
		Heart
		Acute myocarditis
	Neurologic diseases	*Neurologic diseases*
	Stiff-person syndrome	Intractable childhood epilepsy
		Paraneoplastic cerebellar degeneration
		Alzheimer disease
		Narcolepsy with cataplexy
		Limbic encephalitis
		Opsoclonus myoclonus syndrome
		Paraproteinemic neuropathy
		Lumbosacral or brachial plexitis
		Cerebral infarction with anti-phospholipid antibodies
		Rasmussen syndrome
		Brown-Vialetto-Van Laere syndrome

Table 1 (continued)

Definitely beneficial	Probably beneficial	Of some benefit
	Dermatologic diseases SJS/TEN	*Dermatologic/atopic diseases* Atopic dermatitis Autoimmune blistering skin diseases Chronic urticaria High-dose steroid-dependent asthma *Gynecologic diseases* Prevention of unexplained spontaneous recurrent abortions

ANCA anti-neutrophil cytoplasmic antibody, *APS* antiphospholipid syndrome, *CAPS* catastrophic antiphospholipid syndrome, *CMV* cytomegalovirus, *DM/PM* dermatomyositis/polymyositis, *HTLV1* human T-lymphotropic virus, *LEMS* Lambert-Eaton myasthenic syndrome, *JIA* juvenile idiopathic arthritis, *MAS* macrophage activation syndrome, *MG* Myasthenia Gravis, *RA* rheumatoid arthritis, *RR-MS* relapsing-remitting multiple sclerosis, *SLE* systemic lupus erythematosus, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis

Are all the immunoglobulins the same? One size does not fit all

IVIg are therapeutic preparations of normal immunoglobulins G (IgGs), usually obtained from a pool of healthy blood donors. Different methods are used for the production of IVIg, such as cryoprecipitation, chromatographic absorption, pasteurization and low pH treatments, in order to reduce viral and protein contamination (e.g. prekallikrein activators or activated coagulation factors)[24, 25]. For all these reasons, all the available products are not identical, varying in volume load, presence of stabilizers, sodium content, osmolarity/osmolality and IgA content. Therefore, the choice of certain IVIg should be tailored to the patient's clinical status, as IVIg composition may affect tolerability.

Volume load

The infused volume of IVIg differs according to the protein concentration of the single product, generally ranging between 3 and 12%, the weight of the patient and the therapeutic rationale (replacement versus immunosuppressive). In general, more than 1000 ml of solution are given at each infusion, which are well tolerated when no comorbidities are present. However, close attention should be paid in elderly and very young patients, for multiple reasons. In the first case, the presence of coexistent heart failure, renal dysfunction, frailty and elevated thromboembolic risk should be assessed before the infusions. In the latter, given the smaller plasmatic volume, the infusion might cause a volume overload[26, 27].

Stabilizers

Stabilizers are used in order to increase protein concentrations in IVIg preparations, thus avoiding formation of aggregates[24]. These substances can be divided in three categories: (1) polyols; (2) sugars; and (3) amino acids (glycine and proline).

D-Sorbitol is part of the polyol family, and should be avoided in patient suffering from hereditary fructose intolerance[28].

Among sugars, sucrose has been responsible for 88% of the cases of renal toxicity, especially in patients at risk of this complication (such as patients with diabetes mellitus) [29]. Maltose interferes with glucose meters, thus causing the report of falsely high blood glucose levels. This circumstance should be considered when giving maltose-containing products to patients with diabetes mellitus[5, 27]. Unsurprisingly, glucose-containing products should be avoided in diabetic patients or, at least, their glucose control should be carefully optimized during and after the infusions[26, 27]. Sugar content is also responsible for the final osmolality of the product (see after).

Sodium content

Sodium content varies greatly among different IVIg preparations, ranging from 1.8% to 0% in newer products. Higher sodium concentrations have been linked to thromboembolic complications and should be avoided, especially in patients suffering from heart failure or renal dysfunctions and in elderly patients[26, 27, 30].

Osmolarity/osmolality

As cited above, sugar and sodium content are the major determinants of osmolarity/osmolality of the solution. Higher concentrations of the solution have been associated to increased thrombotic risk, especially in patients with hypertension, vascular disease, heart failure, renal dysfunction and in elderly frail patients[31].

IgA content

Higher IgA concentrations have been associated to an increased occurrence of adverse effects during IVIg administration[32]. Anaphylactic and anaphylactoid reactions have been attributed to anti-IgA antibodies in IgA deficient patients. Those antibodies are generally IgG or, less frequently, IgE[33]. However, there are some points to consider:

1) These reactions are exceedingly rare, and occur much less frequently than originally believed[5, 34–36],
2) Whilst it is true that 40% of IgA-deficient patients and 10% of common variable immunodeficiency (CVID) patients present anti-IgA antibodies[36], these antibodies have been also found in healthy individuals[29],

For all these reasons, it is important to remember that IVIg can be administered in IgA-deficient patients when a true IgG deficit is present[5], and that is not necessary to dose IgA levels nor anti-IgA antibodies prior to the first IVIg infusion[29]. Patient with anti-IgA antibodies who experienced a serious adverse reaction should be switched to subcutaneous infusions, which are generally well tolerated[35].

Patients with isolated IgA deficiency do not benefit from IVIg replacement therapy. In these cases, immunization with conjugate pneumoccal vaccine and antibiotic prophylaxis are considered the mainstay of therapy, even though studies of efficacy are still lacking[37].

Infusion remarks

IVIg should be administered through a peripheral venous catheter, as the introduction of permanent central venous access has been associated to thrombotic and infectious complications[7, 8]. Therefore, when the peripheral access is not available, the switch to the subcutaneous route should be encouraged[9]. Infusions usually take 2 to 6 h. Indeed, an infusion rate above 5 mg/kg/min has been associated with more side effects. For this reason, a rate between 0.5 and 1 mg/kg/min should be preferred at the beginning, then increasable up to 3–4 mg/kg/min if well tolerated[10, 11].

What to expect during infusions: how to monitor and treat the adverse reactions

IVIg are generally considered well-tolerated in general practice. However, the incidence of adverse reactions varies widely in the literature (from 1 to 81% of the infusions[33]. This variability is probably due to a selection bias. Indeed, adverse reactions are very rare if we consider immunodeficient patients who receive the same dose of a previously tolerated product; in contrast, higher rates have been reported in non-immunodeficient patients treated with high-dose IVIg for immunological, neurological or hematological conditions[29].

Adverse reactions can be divided, according to the time of occurrence in: (1) immediate, occurring during the infusion or within 6 h from the end; (2) delayed, occurring within 1 week after the infusion; and (3) late, occurring more than 1 week after the infusion (Fig. 1) (Table 2)[29].

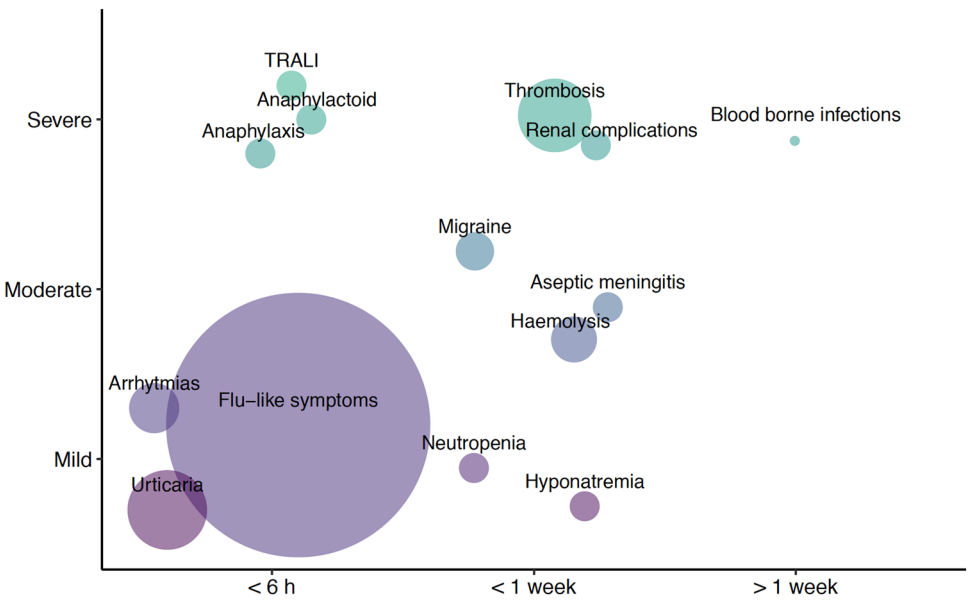

Fig. 1 Classification of IVIg adverse reactions according severity and time of onset. The diameter of the circles is directly related to the frequency of the adverse reactions (the bigger the circle, the higher the frequency)

Table 2 Main adverse events and complications associated with IVIG therapy and their possible relation to the type of Ig composition and risk factors

Adverse events	Ivig composition	Risk factors
Volume overload (Hypertension, arrhythmias)	Depending on total Ig dose and protein concentration	Elderly Heart failure, renal dysfunction, frailty Pediatric Smaller plasmatic volume Faster infusion rates
Metabolic disturbances (hyperglycemia)	Maltose and glucose D-Sorbitol	Diabetes mellitus Hereditary fructose Intolerance
Thromboembolic events (stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism)	High osmolarity/osmolality (higher concentrations of sodium and sugars)	Elderly Heart failure, renal dysfunction, hypertension, vascular disease Hypercoagulable states High dose IVIG Faster infusion rates
Anaphylactic and anaphylactoid reactions	IgA content	Anti-IgA antibodies Autoimmune disease High dose IVIG
Flu-like symptoms (Flushing, chills, fever, myalgia, arthralgia, anxiety, malaise, fatigue, nausea, vomiting, diarrhea)		First time IVIG infusion or switch to new IVIG product High dose IVIG Autoimmune disease Faster infusion rates Recent infection or chronic inflammation
Neurological manifestations Migraine and tension headaches Aseptic meningitis		History of migraine Faster infusion rates
Hematological manifestations Haemolytic anemia Neutropenia	IVIg derived from non-group O blood	High dose IVIG Blood group A or AB
Renal failure		Elderly Pre-existing renal disease, Diabetes Dysproteinemias

Immediate reactions

Immediate reactions can be divided in mild and severe.

Mild immediate reactions

Mild immediate reactions may be grouped under the term "flu-like symptoms"[32]. Flushing, chills, fever, myalgia, arthralgia, anxiety, malaise, fatigue, nausea, vomiting, diarrhea are considered the most common adverse reactions, involving up to 80% of the patients[38]. Other reactions can be represented by hypotension, hypertension and tachycardia. However, it is important to highlight how the prevalence fluctuates among different categories of patients. Factors increasing this risk are: (1) first time IVIg infusion; (2) switching from one product to another; (3) higher doses (e.g. in patients with autoimmune diseases); (4) faster infusion rates; (5) presence of comorbidities; (6) recent bacterial infection and/or chronic inflammation[5, 26, 29, 32]. The treatment should be customized according to the patient's clinical condition. Generally, it is recommended to start with slower infusion rates and increase the flow as stated by the manufacturers, in order to reduce the incidence of flu-like symptoms[33]. An infusion rate of 0.5 to 1 mg/kg/min is recommended at the beginning, increasing gradually up to 3–4 mg/kg/min[39]. For these reasons, infusions usually take 2 to 6 h. Stopping the infusion usually resolves the flu-like symptoms. Thereafter, the infusion may be restarted at a lower rate. When a complete resolution of the symptomatology could not be obtained, treatment with intravenous acetaminophen (15 mg/kg), diphenhydramine (1 mg/kg) or other non-sedating antihistamine may be of help[5]. Steroids are used less frequently[40]. When a patient develops the same flu-like symptoms more than once, pre-medication with acetaminophen (15 mg/kg), non-steroid anti-inflammatory drugs and/or steroids is recommended. However, it is important to underline that there are no randomized studies in support to this practice[33]. If the patient, despite pre-medication, still present the same adverse reactions, shifting to

subcutaneous route of administration is usually safe and well tolerated[10, 41].

Arrhythmias have been reported several times, being more frequent in patients with a history of heart disease[32]. Five cases have been published so far and the condition resolved spontaneously or with antiarrhythmic therapy in all of them[42–44]. Cardiac monitoring is indicated in patients with positive history of arrhythmias[32].

Immediate skin adverse reactions such as itchy urticarial rash are uncommon[5] and usually self-limited[33].

Severe immediate reactions

True anaphylaxis is reported as exceedingly rare with IVIg, and it usually occurs in non-immunodeficient patients. IgE anti-IgA may be responsible for this clinical condition[5, 29]. Non-IgE mediated anaphylactoid reactions are also uncommon and can be mediated by IgG anti-IgA antibodies. In general, IgA deficient patients, and patients with a status of complement activation have an higher risk to develop these reactions[29, 33].

Transfusion-Related Acute Lung Injury is a rare, but potentially fatal complication secondary to the infusion of blood and plasma derived products, including IVIg[32, 33]. The necessity and the response to supplemental oxygen therapy defines the severity of this complication[45].

Delayed reactions

Delayed adverse reactions can be divided in mild, moderate and severe as well.

Mild delayed reactions

Transient neutropenia is a rare complication that usually resolves without any treatment within 2 weeks[33]. Hyponatremia (true or pseudo) was reported twice, but another study failed to confirm this evidence[46].

The overall incidence of dermatological adverse reactions is 6%, the majority of whom is mild and characterized by pompholyx and eczematous reactions. Spontaneous resolution happens in 25% of the patients and topical steroids are usually administered in persistent cases[47].

Moderate delayed reactions

Migraine headaches are rare if compared to tension headaches. They are more common in patients with history of migraine, independently of preparation or infusion rate[48]. The onset is often delayed and it usually last less than 72 h[49]. Analgesics are generally sufficient to control the symptoms[29]. Pre-hydration and prophylactic anti-migraine medications might help preventing the occurrence of migraine[33].

Persistent severe headaches, especially when coupled with neck stiffness, photo- and phono-phobia, fever and myalgia, might hide aseptic meningitis[29]. Analgesics, anti-migraine therapy and anti-emetics have been used to treat this condition, whereas corticosteroids seem not to be beneficial[33]. Pre-hydration and slower infusion rates in patients at risk are recommended[48].

Haemolysis is a rare but overlooked complication and can present with anemia, increased non-conjugated bilirubin, decreased haptoglobin and, in severe cases, renal failure[29]. IVIg derived from non-group O blood, A or AB-type patients' blood, and higher doses are the major risk factors[50]. In self-limiting cases, switching to another IVIg product or slowing the infusion rate are usually sufficient to control the reaction. In severe cases, blood transfusion and dialysis might be needed[50].

Severe delayed reactions

Thrombosis is a serious event that occurs in 1% up to 16.9% of the IVIg-treated patients[51, 52]. The variability of the incidence depends on patient-related risk factors. Indeed, elderly patients with previous thrombotic events, preexisting atherosclerotic disease and other hypercoagulable states, larger doses together with higher infusion rates are major risk factors for this complication[53, 54]. Thrombosis site is arterial in 76% of the cases, including mainly stroke and myocardial infarction, and occurs usually within 24 h from infusion. The remaining cases are characterized by deep venous thrombosis and pulmonary embolism, and tend to occur later[55]. Careful physical examination, search for underlying clinical conditions favoring thrombotic events and close monitoring of the at-risk-patients are the main recommended preventive measures[29]. The infusion rate should be slow (0.5 ml/kg/hour), with a maximum daily dose of 400 mg/kg. Movable pumps are encouraged in order to leave the patient walk around during the infusions[33]. In higher-risk patients, antiplatelet agents (e.g. aspirin 100 mg/day), low-molecular-weight heparin (e.g. 1000 IU heparin calcium) and pre- and post-infusion hydration (500 mL of normal saline in total) are recommended[29, 32, 33, 56].

Renal complications are not uncommon in patients with pre-existing conditions, such as renal disease, diabetes, older age and dysproteinemias, especially when higher IVIg doses are administered[29]. Slowing infusion rate and reducing the daily dose are useful to avoid IVIg overload. Adequate pre-hydration is also usually needed[57].

Late reactions

As with any other blood product, IVIg carry an intrinsic risk for the transmission of pathogens. However, infectious events are exceedingly rare nowadays after the adoption of anti-viral strategies during IVIg preparation[24].

Conclusive remarks

IVIg therapy has demonstrated its efficacy in a wide range of diseases, both in their on- and off-label applications. Despite the high rate of adverse reactions, these are usually mild and reversible, and may be avoided by appropriate premedication. More severe reactions are rarer and depends primarily on product-related and patient-related factors. The clinicians should be aware of the important differences among different IVIg products and the risk of switching from one product to another without professional consultation by expert immunologists. A tailored approach is advocated in patients with multiple comorbidities or when disease-related factors are known risks of adverse reactions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals preformed by any of the authors.

Informed consent Not required for this type of article.

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