

Intravenous Immunoglobulin

Adverse Effects and Safe Administration

Hedi Orbach,¹ Uriel Katz,² Yaniv Sherer,² and Yehuda Shoenfeld^{2,3*}

¹Department of Medicine B, Wolfson Medical Center, Holon, Israel; ²Center for Autoimmune Diseases, Department of Medicine B, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; and ³Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Tel Aviv University, Tel Aviv, Israel

Abstract

Intravenous immunoglobulin (IVIg) is administered for various indications and generally considered a safe therapy. Most of the adverse effects (AEs) associated with IVIg administration are mild and transient. The immediate AEs include headache, flushing, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnea, back pain, nausea, vomiting, diarrhea, blood pressure changes, tachycardia, and anaphylactic reactions, especially in IgA-deficient patients. Late AEs are rare and include acute renal failure, thromboembolic events, aseptic meningitis, neutropenia, and autoimmune hemolytic anemia, skin reactions, and rare events of arthritis. Pseudohyponatremia following IVIg is important to be recognized. Renal failure, usually oliguric and transient, occurs mostly on using sucrose-containing products owing to osmotic injury. Among high-risk patients who have a previous renal disease, dehydration, diabetes mellitus, advanced age, hypertension, hyperviscosity, or are treated by other nephrotoxic medications, administration of a non-sucrose-containing IVIg product after accomplishing hydration, in a low concentration and a slow infusion rate while supervising urine output and kidney function, is recommended. Thromboembolic complications occur because of hyperviscosity especially in patients having risk factors including advanced age, previous thromboembolic diseases, being bedridden, diabetes mellitus, hypertension, dyslipidemia, or those receiving high-dose IVIg in a rapid infusion rate. Immediate AEs can be treated by the slowing or temporary discontinuation of the infusion and symptomatic therapy with analgesics, non-steroidal anti-inflammatory drugs, antihistamines, and glucocorticoids in more severe reactions. Slow infusion rate of low concentration of IVIg products and hydration, especially in high-risk patients, may prevent renal failure, thromboembolic events, and aseptic meningitis.

Index Entries

Intravenous immunoglobulin; adverse effects; thromboembolism; renal failure; anaphylaxis; hemolytic anemia; aseptic meningitis.

*Author to whom all correspondence and reprint requests should be addressed. E-mail: shoenfel@post.tau.ac.il.

Introduction

Intravenous immunoglobulin (IVIg) therapy is considered a safe treatment. The reported incidence of adverse events (AEs) varies widely from 1 to 81% of patients or courses or infusions (1–13). The indication for therapy, age and comorbidity of the patients, dosage of every infusion, and rate of infusion in the studies are different because there is variation in preparations with different stabilizing sugars, protein content, pH, particle count, concentration of immunoglobulin (Ig) A, and other parameters (14). The classification of adverse effects from IVIg is either according to the mechanism by which they arise, or by dividing them into immediate and later effects.

Immediate Adverse Effects

The immediate adverse reactions following IVIg administration are usually mild and transient flu-like symptoms and include headache (the most common AE), flushing of the face, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnea, back pain, nausea, vomiting, diarrhea, change in blood pressure, and tachycardia (5,6,9,10,12,13). These reactions occur early and, in many cases, during the first 30 min of the infusion (15). The etiology of these immediate reactions remains uncertain, but IgG aggregates, IgG dimers, and complement activation appear to be involved. The standards of the World Health Organization and the US Food and Drug Administration (FDA) require the removal of the IgG aggregates from IVIg preparations. The new techniques include polyethylene glycol precipitation and pepsin treatment at pH 4.0 to remove the Fc portion of antibodies and eliminate complement consumption. IVIg preparations now are devoid of many of these contaminants. These steps reduced the rate of the immediate side effects. Other causes for immediate adverse effects to IVIg are presence of prekallikrein activator and kallikrein, and increased levels of interleukin-6, tumor necrosis factor- α , and thromboxane B₂

(9,14). The immediate reactions improve or wane following reduction of the flow rate of IVIg infusion, and in some cases, the infusion must be discontinued temporarily or permanently (3). Reduction of the infusion rate or changing to another preparation of IVIg might prevent further reactions. Pretreatment with analgesics, nonsteroidal anti-inflammatory drugs, antihistamines, or intravenous glucocorticoids may also be beneficial (12).

Severe anaphylactoid reactions following IVIg administration are rare. IgA-deficient patients might form macromolecular complexes with anti-IgA antibodies of the recipient of IVIg that can lead to anaphylactic reaction. The frequency of this reaction is unknown. Anti-IgA antibodies are present in 30% of patients who have selective IgA deficiency, but their presence does not necessarily predict anaphylaxis. Anaphylaxis can be prevented by using IgA-depleted IVIg, even if it is still contaminated with a small amount of IgA (14). Salama et al. (16) described a new strategy to treat a patient with recurrent anaphylactic reactions with a preparation with a very low amount of IgA. The IVIg preparation was pretreated with autologous plasma *ex vivo*, resulting in compatibility of subsequent transfusions without elevation in anti-IgA activity (16). Some authors claim that it is not justified to screen for IgA deficiency before therapy with IVIg if the patient does not have hypogammaglobulinemia or disorders associated with IgA deficiency (such as ataxia teleangiectasia) (14,17). Simple allergic reactions to foreign IgG with increased levels of IgE have also been reported. Some of the reactions wane after cessation of the infusion and some patients improve with corticosteroid or antihistamine treatment (14).

Delayed Adverse Effects

Renal Toxicity

Acute renal failure (ARF) appears to be one of the major concerns following IVIg therapy. Thirty-nine reports in the English literature

Table 1
Demographic and Clinical Data on Reported Cases of Renal Failure Following IVIg Therapy

	Published case reports (N = 87)	FDA report (N = 88)	FRPC report (N = 49)
Age—median (range)	64.2 (20–90)	62.5 (3–91)	67 (22–92)
Male/female ratio	49/38 (56%)	48/40 (55%)	30/19 (61%)
Indications for use			
Hematological	46 (53%)	39 (44%)	29 (59%)
Immunological	20 (23%)	20 (23%)	6 (12%)
Neurological	14 (16%)	17 (19%)	13 (27%)
Infectious diseases	7 (8%)	9 (11%)	0
Not reported		3 (3%)	1 (2%)
Preexisting renal disease	40/87 (46%)	14/54 (26%)	21/45 (47%)
Sucrose-containing products	64/87 (74%)	79/88 (90%)	44 (90%)
Maltose/glucose products	14/86 (16%)	7/88 (8%)	1/49 (2%)
Undetermined stabilizer	7/86 (8%)	2/88 (2%)	4/49 (8%)
Acute hemodialysis	28/87 (32%)	35/88 (40%)	17/49 (34%)
Deaths	8/87 (9%)	13/88 (15%)	4/49 (8%)

FRPC, French Regional Pharmacovigilance Center.

involving 87 patients in whom renal toxicity developed in association with IVIg have been published (3,18–24). From June 1985 to November 1996 the FDA received 120 reports worldwide on ARF related to IVIg therapy, 88 of which were from the United States (25). Between 1992 and 1998, 49 cases of ARF were reported to the French Regional Pharmacovigilance Center with marked creatinine increase following initiation of IVIg therapy (26). The demographic and clinical data of these three groups of cases are summarized in Table 1. Overall, no major differences were noted among the three groups. The median age was 62.5 to 67 (range 3–92), and 55 to 61% of the patients were male. The indication for IVIg use was a hematological disease in around half the cases (44–59%), immunological in 12 to 23%, and neurological disease in 16 to 27%. Preexisting renal failure was noted in 26 to 47% of the patients. Seventy-four to 90% of the patients who developed ARF received sucrose-containing IVIg products. ARF began 8 h to 10 d after initiation of IVIg treatment, the median being 4.5 to 5 d. In most cases, the renal failure was oliguric, and 32 to 40% of the patients required hemodialysis.

Most important, the renal failure following IVIg was usually completely reversible, with return to baseline creatinine level after 7 to 15 d. Death occurred in 8 to 15% of the patients, but most of them had severe underlying medical conditions (pneumonia, systemic lupus erythematosus, cardiac disease, and subarachnoid hemorrhage) and the contribution of the renal failure to their death was undetermined. Renal biopsy results were available in the literature in 25 patients; in 16 of the 25, the renal pathology revealed tubular injury with vacuolization consistent with osmotic injury, similar to the renal findings following treatment with intravenous sucrose as an osmotic diuretic therapy, or renal injury caused by intravenous mannitol or intravenous iodinated radiographic contrast media.

The mechanism of renal injury following IVIg treatment is thought to be the result of osmotic injury, as the pathological findings with vacuolization of proximal tubules and swelling and narrowing of tubular lamina are the same as the histology after infusion of sucrose in experimental animals. Sucrose is nonmetabolizable and pinocytosed into renal

tubular cells and incorporated into phagolysosomes. Accumulation of sucrose intracellularly causes osmotic gradient and accumulation of water that cause cellular swelling and vacuole formation, even when administered in small quantities. Igs have high molecular weight and increase the blood viscosity and might cause also ischemic renal damage.

The risk factors for the development of ARF after IVIg treatment are the same as for other nephrotoxic agents: preexisting renal disease, diabetes mellitus, hypertension, volume depletion, advanced age, sepsis, paraproteinemia, and concomitant nephrotoxic drugs usage (27). Four cases with non-Hodgkin's lymphoma and type II mixed cryoglobulinemia with IgM paraprotein and rheumatoid factor developed acute renal failure after IVIg therapy; two of them were fatal. The vasculitis and occlusion of blood vessels was the result of formation of complexes of the IgM rheumatoid factor and IgG (28). The FDA required the manufacturers of IVIg products to revise the prescriber information and include a boxed warning concerning acute renal failure. The FDA recommends initiation of IVIg infusion after assuring that the patient is not volume-depleted. For patients who have increased risk of developing ARF, the physician has to consider the benefits against the risk of sucrose-containing products. The FDA recommends not to exceed the recommended dose, reduce the dose and rate of infusion and concentration of the product for patients with high risk for nephrotoxicity, follow-up the urine output, urea, and creatinine, and if renal function deteriorates, consider discontinuation of IVIg.

Thromboembolic Events

Serious thromboembolic events following IVIg therapy have been reported. Slow infusion rates have been advocated to prevent a sudden increase in the patient's plasma viscosity that may trigger these events. Precautionary statements regarding the administration of IVIg to patients with cardiovascular disease or

previous thrombotic events who might be at higher risk for an IVIg-associated thromboembolic complication have been published and can be found at: <http://www.fda.gov/medwatch/safety/2002/safety02.htm#igiv>. In accordance with our experience, including more than 200 patients treated with IVIg (29), each daily dose should be administered over not less than 8 h to minimize risks. Therefore, in a 60-kg patient, the total course dose is 120 g over 5 d, the daily dose is 24 g (400 mg/kg), and the rate of administration should be 3 g/h (3000 mg/h or 50 mg/kg/h).

The results of a review of the literature (30) reporting cases in which thromboembolic complications related to IVIg administration occurred are presented in Table 2. In addition to these case reports, there are a few case series of thromboembolism following IVIg therapy. Wittstock et al. (6) presented the data of a prospective study including 117 patients having a neurological disease who received IVIg at doses of 400 mg/kg/d for 5 d. In that series, two immobilized patients (1.7%) developed deep venous thrombosis (DVT). In addition, infusion rates reached 10,000 mg/h, more than three times the recommended. In another series, Vucic et al. (44) reported seven cases of thromboembolic complications related to IVIg treatment over a 10-yr period: four cases of cerebrovascular accident (CVA) during the first 24 h after infusion, one case of acute myocardial infarction 14 d after infusion, one case of leg DVT, and a case of retinal artery infarction. Previously uneventful IVIg courses were given to most of the patients. Daily doses and infusion rates exceeded the recommended amount (400–600 mg/kg/d, 5000–10,000 mg/h, respectively). In addition, five of these seven patients had one or more risk factors for thromboembolism.

In the retrospective study of Brannagan et al. (3), 88 patients were given IVIg for neurological indications. These patients received IVIg 2 g/kg over 2 to 5 d, at daily doses varying between 20 and 100 g. Only one case of

Table 2
Literature Case Reports of Thromboembolic Phenomena Following IVIg Administration

Author and reference	Patient age and comorbidity	Indication for treatment	Thromboembolic phenomenon	Timing	IVIg brand	Total dose (administered or intended)	Daily dose of IVIg	Rate of infusion
Durand et al. (31)	42-yr-old woman	TTP	Suspected CVA (TTP can also be the cause)	During initial infusion	Veinoglobulin®, Merieux	ND	500 mg/kg/d	ND
Oh et al. (32)	17-yr-old man; acute lymphoblastic leukemia	Immunosuppression during chemotherapy	Central retinal vein occlusion	During IVIg infusion	Gammagard®, Baxter Healthcare	7 g/kg over 14 d (3.5 times the high-dose for autoimmune diseases)	500 mg/kg/d	ND
Rosenbaum (33)	76-yr-old woman smoker, family history of IHD, hypercholesterolemia	Uveitis	Myocardial infarction	First day of IVIg course	Baxter Healthcare	1.5 g/kg over 3 d	500 mg/kg/d	ND
Go et al. (34)	52-yr-old woman; small lymphocytic lymphoma	Evans' syndrome	Arm vein thrombosis (same arm of IVIg infusion)	At the end of IVIg infusion	ND	1 g/kg over 1 d	1000 mg/kg/d	200 mg/kg/h
Turner et al. (35)	60-yr-old woman	Guillain-Barré syndrome	CVA	2 d after IVIg infusion	ND	2 g/kg over 5 d	400 mg/kg/d	ND
Elkayam et al. (36)	60-yr-old man; HTN	Relapsing polychondritis	Myocardial infarction	10 d after IVIg	Omr-IgG-am®, Omrix	2 g/kg over 3 d	660 mg/kg/d	82.5 mg/kg/h
Elkayam et al. (36)	41-yr-old woman; family history of IHD, two previous episodes of DVT	Polymyositis	Myocardial infarction	Immediately after second day of IVIg administration	Omr-IgG-am	2 g/kg over 2 d	1000 mg/kg/d	125 mg/kg/h
Elkayam et al. (36)	67-yr-old man; hypercholesterolemia	CIDP	Myocardial infarction	Few hours after first infusion	Omr-IgG-am	2 g/kg over 5 d	400 mg/kg/d	133 mg/kg/h
Elkayam et al. (36)	67-yr-old man; systemic Castleman disease, TIA in his past, Kaposi sarcoma	Coombs positive hemolytic anemia and thrombocytopenia	CVA, myocardial infarction	CVA 1 d after second course of IVIg; myocardial infarction on d 4 of fifth course	Omr-IgG-am	2 g/kg over 5 d	400 mg/kg/d	50 mg/kg/h

(continued)

Table 2 (Continued)

Author and reference	Patient age and comorbidity	Indication for treatment	Thromboembolic phenomenon	Timing	IVIg brand	Total dose (administered or intended)	Daily dose of IVIg	Rate of infusion
Emerson et al. (37)	54-yr-old woman	Immune thrombocytopenic purpura	CVA	During IVIg infusion (2nd day)	Gammagard	2 g/kg over 2 d	1000 mg/kg/d	200 mg/kg/h
Emerson et al. (37)	33-yr-old woman	Evans' syndrome	DVT; 5 mo later PE	DVT, 1 wk after IVIg therapy; 5 mo later, PE 6 h after finishing IVIg course	Gammagard	2 g/kg over 5 d before DVT; 5 mo later, 1.44 g/kg over 5 d before PE	400 mg/kg/d before DVT; 5 mo later, 288 mg/kg/d before PE	80 mg/kg/h before DVT; 5 mo later, undisclosed rate before PE
Katz et al. (38)	67-yr-old woman; HTN	Dermatomyositis	CVA	During infusion in its first day	Polygam®, Baxter Healthcare	2 g/kg over 2 d	1000 mg/kg/d	3500–12,500 mg/h
Katz et al. (38)	65-yr-old woman	Pemphigus vulgaris	Arm vein thrombosis (same arm of IVIg infusion)	During infusion in its first day	ND	2 g/kg over 2 d	1000 mg/kg/d	2000–8000 mg/h
Zaidan et al. (39)	47-yr-old man; smoker, hypercholesterolemia, IHD 3 wk after acute myocardial infarction)	Guillain-Barré syndrome after rate was	New myocardial infarction	During infusion in its third day, increased	Octapharma Octagam®,	1.4 g/kg over 5 d	250–400 mg/kg/d	62.5–100 mg/kg/h (rates not clearly described)
Zaidan et al. (39)	65-yr-old woman; DM type 2, HTN	CIDP	CVA	During third day of infusion	Octagam	Probably 2 g/kg over 5 d	400 mg/kg/d	66.7 mg/kg/h
Zaidan et al. (39)	70-yr-old man; DM type 2	CIDP	CVA	4 d after finishing IVIg administration	Octagam	2 g/kg over 5 d	400 mg/kg/d	ND
Evangelou et al. (40)		IgG1 deficiency that was not permanent, therefore IVIg was not indicated	Transverse sinus thrombosis	1 d after IVIg administration	ND	21 g in 1 d	21 g	ND
Okuda et al. (41)	57-yr-old woman	ND	CVA	During IVIg infusion	Polygam	ND	ND	ND
Okuda et al. (41)	47-yr-old man; smoker	ND	Right popliteal thrombosis	At the end of third day of infusion	Polygam	ND	ND	ND

Okuda et al. (41)	61-yr-old woman; HTN, DM	ND	CVA	At the end of IVIg infusion	Polygam	ND	ND	ND
Okuda et al. (41)	63-yr-old man; hypercholesterolemia	Polymyositis	CVA	During IVIg infusion at home	Polygam	ND	ND	ND
Brown et al. (42)	70-yr-old man; IHD	CVID	CVA	During IVIg infusion	ND	0.6 mg/kg every 3 wk	600 mg/kg/d	3000–30,000 mg/h (10 times recom- mended rate).
Brown et al. (42)	91-yr-old man; IHD	CVID	TIA; after recov- ery in another hospital, CVA	During IVIg infusion in bot episodes	ND	0.6 mg/kg every 4 wk	ND	3000–30,000 mg/h (10 times recom- mended rate); after the first event (TIA), rate was increased
Brown et al. (42)	42-yr-old woman; DM, smoker, polycystic kidney, COPD/asthma, low IgG	Severe pneumonia in the context of IgG deficiency	CVA	During infusion in its first day	ND	0.6 mg/kg every 4 wk	ND	3000–30,000 mg/h (10 times recom- mended rate)
Sheehan et al. (43)	43-yr-old man	Pemphigus vulgaris	DVT	DVT 26 d after IVIg therapy and 10 d after anal fissure surgery; difficult to establish causality	ND	2 g/kg over 3 d	667 mg/kg/d	ND

DM, diabetes mellitus; CVA, cerebrovascular accident; HTN, hypertension; IHD, ischemic heart disease; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CVID, common variable immunoglobulin deficiency; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; PE, pulmonary embolism; TTP, thrombotic thrombocytopenic purpura; ND, no data.

DVT in a bed-bound patient occurred. Caress et al. (45) reported a series of 16 patients (0.6%) with CVA after IVIg administration over 4 yr. Fifteen of 16 had at least one risk factor for CVA, including monoclonal gammopathy in four of them. Ten of 16 received IVIg because of neuromuscular indications. At least 10 of these patients were treated with daily doses higher than the recommended (500 mg/kg/d to 1000 mg/kg/d). The infusion rate was up to five times the recommended rate. In a prospective study that included 59 patients and 84 consecutive IVIg courses, Stangel et al. (8) reported one case of thrombosis of the jugular vein on the last day of treatment and one episode of angina pectoris. The infusion rate occasionally exceeded three times the recommended rate. Dalakas and Clark have reported that in more than 700 IVIg courses in controlled trials for neuropathy or myopathy, no events of CVA have been detected (46).

Three basic mechanisms have been cited as contributors to the potential generation of thromboembolic complications following IVIg administration. Although platelet activation and arterial vasospasm have been proposed (30), the bulk of evidence points, however, to an increase in plasma viscosity following IVIg infusion. Reinhart and Berchtold (47) reported that plasma viscosity increased from a mean of 1.26 centipoises (cp) to 1.54 cp in four patients having immune thrombocytopenic purpura receiving between 24 and 54 g/d of IVIg. Paraproteinemias are capable of inducing a hyperviscosity syndrome usually at the range of 2 to 3 cp; however, among persons with risk factors for thromboembolic events, milder increments might be dangerous (30). In another study, Dalakas (48) reported a mean increase in viscosity after IVIg administration of 0.55 cp, being strongly correlated with IgG levels. The increase in viscosity was a function of the high load of protein with a peak 24 h after the end of the IVIg course (49), and probably also a function of protein polymerization. Thromboembo-

lic events may also be triggered by a local/regional increase in viscosity leading to local thrombosis, as previously reported in a case of ipsilateral arm vein thrombosis (34,38). It may also happen as a result of a systemic increase in viscosity after the steady state has been reached, as probably illustrated by the thromboembolic complications occurring hours to days after IVIg infusion (30). Finally, it may also be a result of a gradient of viscosity occurring in a place distant from the site of infusion, before the steady state is reached, as may be illustrated by nonlocal thromboembolic events occurring during IVIg infusion (30).

According to Brown and Ballas (42), similar to other AEs, thromboembolic complications are more frequent when high-dose IVIg is used in comparison with the replacement doses (200–600 mg/kg/mo) used for immunodeficiencies, supporting the assumption that the risk for thromboembolic complications is a function of the IVIg dosage. As we have summarized from the literature (30), a significant majority of patients reported to have thromboembolic adverse events following IVIg infusion had risk factors for thromboembolism or received high doses or high infusion rates. Immobilization, which is frequent among neurological patients, is a risk factor for thromboembolism (46). In addition, traditional risk factors for thromboembolism, such as hypertension, diabetes mellitus, ischemic heart disease, previous CVA, and other conditions, such as advanced age, dyslipidemia, hypergammaglobulinemia, and hyperfibrinogenemia, should also be regarded as risk factors (30,46). In immobilized patients, ultrasound Doppler of leg veins should be performed in order to rule out preexisting flow abnormalities.

The use of schemes in which infusion rate is increased “as tolerated” should be avoided because there is no reliable sign alerting of an imminent thromboembolic event. Carefully weighting the indication for IVIg therapy and risk–benefit assessment based on the patient’s

comorbidity are key issues in the prevention of adverse effects, including thromboembolic complications. The use of IVIg in patients with risk factors for thromboembolic events should be avoided when possible. When IVIg therapy is instituted, 2 g/kg of body weight should be given over 5 d (400 mg/kg/d administered at no more than 50 mg/kg/h, in no less than 8 h) using an accurate intravenous pumping device.

Neurological Toxicity

Headache is a frequent complaint following IVIg administration. The rate of IVIg infusion is extremely variable in the different reports. The reported rate of headaches varies between 4.7 and 80% (14); in most of the cases, headaches are mild, but in some patients, IVIg therapy must be terminated owing to severe headaches. Aseptic meningitis is a rare complication of IVIg treatment. The rate of aseptic meningitis after IVIg treatment is low in most studies and ranges between 0 and 1% (3–5,7,8); on the contrary, Sequi et al. (50) reported occurrence of aseptic meningitis in 11% of their patients treated with IVIg. The clinical manifestations of aseptic meningitis include acute severe headache with neck rigidity, fever, lethargy, photophobia, nausea, and vomiting; cerebrospinal fluid examination demonstrates pleocytosis with high protein content and negative culture (40). The signs and symptoms commence usually within 48 h after infusion (but may occur later) and last for 3 to 5 d, mimicking the manifestations of bacterial meningitis. Sequi et al. (50) found that patients with a history of migraine were particularly prone to developing recurrent aseptic meningitis.

The exact mechanism of IVIg-induced aseptic meningitis is not clearly understood. It is probably not related to the preservatives and stabilizing agents because it occurs with all commercial preparations. The postulated mechanisms include (51): (a) activation of the complement system triggered by immunoglobulin macroaggregates; (b) IgG crossing the

blood–brain barrier and activation of local immune reaction that is demonstrated also by eosinophil pleocytosis; and (c) interaction of IgG and antigenic determinants of the endothelium of meningeal vessels with subsequent release of inflammatory cytokines. In order to prevent or reduce the incidence of aseptic meningitis (as in other side effects), it is suggested to start the initial infusion at a slow rate. Prehydration and good fluid intake throughout treatment are also recommended. In patients who experienced meningitis during previous infusions, paracetamol, with or without codeine, and antihistamines (cetirizine) can be tried as a premedication therapy. Corticosteroid treatment is not considered beneficial in IVIg-induced aseptic meningitis (52).

Hematological Toxicity

Neutropenia can occur following IVIg transfusion; it is usually transient without increased rate of infections. Matsuda et al. (53) investigated IVIg-induced neutropenia in 16 patients with neuroimmunological disorders who received 22 IVIg treatment courses. In 20 of 22 treatment courses the white blood cell and neutrophil counts decreased. The nadir of the neutrophils was after 2 d and in five cases, the neutrophil counts were less than 1500/mm³. None of the patients had any infectious complications. Prednisone treatment prevented the neutropenia. The expression of CD11b, but not of CD16, decreased after IVIg treatment in three of five patients not treated with steroids, whereas it did not decrease in the steroid-treated group. The authors suggest that the neutrophils bound to either antineutrophil antibodies or Ig aggregates with the involvement of CD11b adherence to endothelial cells, mainly in the reticuloendothelial system, resulting in apparent decrease in white blood cells and/or neutrophils and increased storage pool. Corticosteroids prevent the immune complex activity of immunoglobulins and the activation of the complement system.

Red blood cell (RBC) hemolysis after IVIg treatment is widely reported and related to RBC sequestration owing to binding of IgG directed to blood groups anti-A or anti-B or anti-Rhesus present in the product, causing a direct or indirect positive Coombs test (10). The hemolysis can be mediated by cold agglutinating anti-RBC antibodies. The erythrocytes showed the ability to bind IVIg-like moiety in vitro and in vivo (54). Usually the hemolysis is self-limited, but it is also most likely dependent on the titer of anti-A and anti-B and total dosage of IVIg. Severe autoimmune hemolytic anemia might develop and respond to corticosteroid treatment (55). Evans' syndrome (hemolytic anemia and autoimmune thrombocytopenia) has been reported in an infant with Kawasaki disease following the first IVIg therapy, IVIg-induced hypersensitivity syndrome manifested by maculopapular rash, fever, leukocytosis, eosinophilia, lymphadenopathy, and hepatosplenomegaly. Autoimmune hemolytic anemia and immune thrombocytopenia developed after the second course of IVIg, with evidence of reactivation of human herpesvirus 6. The patient was treated with plasma exchange and corticosteroids with subsequent beneficial response (56).

Dermatological Toxicity

Cutaneous adverse effects caused by the administration of IVIg occur in 0.4 to 6% of patients (3,57). The dermatological AEs after IVIg include transient urticaria or maculopapular rash, pruritus of palms, hair loss, eczema, erythema multiforme, purpuric erythema, petechiae of extremities, mucosal ulcerations of the mouth, refractory epidermolysis bulosa, and lichenoid cutaneous eruption and baboon syndrome (57). Baboon syndrome is a dermatitis characterized by erythematous, symmetrical, well-demarcated lesions on the buttocks and flexure areas, induced by medications or exposure to mercury. Immunological tests with the IVIg product were negative, but an unexpected

expression of P selectin was observed in keratinocytes (57). The etiology of the various skin side effects is not clear yet. Adverse effects that occur immediately improve with temporary termination of IVIg, or prevention with diphenylhydramine or corticosteroids in several cases.

Pseudohyponatremia

IVIg infusion increases the protein-containing nonaqueous phase of plasma and decreases the plasma water volume, and is interpreted by laboratory tests as hyponatremia, usually mild. It is important to recognize this phenomenon and to avoid treatment with fluid restriction or infusion of concentrated sodium chloride (49,58).

Arthritis

There are few case reports of patients developing arthritis after IVIg therapy. Usually the patients had severe transient pain, especially in the knees and wrists, which lasted for short duration (10 d), and could be explained by formation of antibody-antigen immune complex aggregates (13).

Pulmonary Complications

Respiratory complications of IVIg are usually attributed to fluid overload or to allergic or vasomotor reaction. A single case of transfusion-related lung injury following IVIg infusion with pulmonary edema after rapid infusion of 90 g of IVIg was reported. Granulocyte-associated IgG was detected in the patient's blood, and the batch of IVIg contained a low-titer granulocyte antibody (59).

Concluding Remarks

The safety profile of IVIg is good. Most adverse effects associated with its administration are immediate, mild, and transient. Severe late adverse effects are mainly acute renal failure and thromboembolic events. The occurrence of

these can be reduced if the therapy is given in the rate recommended and to well-hydrated patients. In patients having risk factors, the risk–benefit ratio must be considered before initiation of IVIg therapy. Upon usage of IVIg, non-sucrose-containing preparations should be given slowly, with close monitoring of kidney function and urine output.

References

1. Weisman, L. E. (1994), *Isr J Med Sci* **30**, 459–463.
2. Bertorini, T. E., Nance, A. M., Horner, L. A., et al. (1996), *Muscle Nerve* **19**, 388–391.
3. Brannagan, T. H., Nagle, K. J., Lange, D. J., et al. (1996), *Neurology* **47**, 674–677.
4. Al Wahadneh, A. M., Khriesat, I.A., and Kuda, E. H. (2000), *Saudi Med J* **21**, 953–956.
5. Sherer, Y., Levy, Y., Langevitz, P., et al. (2001), *Pharmacology* **62**, 133–137.
6. Wittstock, M., Benecke, R., and Zettl, U. K. (2003), *Eur Neurol* **50**, 172–175.
7. Colovic, M., Dimitrijevic, M., Sonnenberg, C., et al. (2003), *Hematol J* **4**, 358–362.
8. Stangel, M., Kiefer, R., Pette, M., et al. (2003), *J Neurol* **250**, 818–821.
9. Knezevic-Marmarica, I., and Kruskall, M. S. (2003), *Transfusion* **43**, 1460–1480.
10. Pierce, L. R. and Jain, N. (2003), *Transfus Med Rev* **17**, 241–251.
11. Aghamohammadi, A., Farhoudi, A., Nikzad, M., et al. (2004), *Ann Allergy Asthma Immunol* **92**, 60–64.
12. Reutter, A. and Luger, T. A. (2004), *Am J Clin Dermatol* **5**, 153–160.
13. Marinos, C. and Dalakas, M. C. (2004), *Pharmacol Therapeut* **102**, 177–193.
14. Nydegger, U. E. and Sturzenegger, M. (1999), *Drug Safety* **21**, 171–185.
15. Kazatchkine, M. D. and Kaveri, S. V. (2001), *N Engl J Med* **345**, 747–755.
16. Salama, A., Temmesfeld, B., Hippenstiel, S., et al. (2004), *Transfusion* **44**, 509–511.
17. NIH Consensus Conference. (1990), *JAMA* **264**, 3189–3193.
18. Orbach, H., Tishler, M., and Shoenfeld, Y. (2004), *Semin Arthritis Rheum* **34**, 593–601.
19. Windrum, P., Bharucha, C., and Desai, Z. R. (1998), *Br J Haematol* **101**, 592.
20. McColl, M. D., Omran, A., Walker, I. D., et al. (1999), *Haemophilia* **5**, 124–126.
21. Khalil, M., Shin, H. J., Tan, A., et al. (2000), *Acta Cytol* **44**, 86–90.
22. Bassilios, N., Mercadal, L., and Deray, G. (2001), *Nephrol Dial Transplant* **16**, 1513–1514.
23. Akhtar, I. and Bastani, B. (2003), *Ann Intern Med* **139**, W65.
24. Chapman, S., Glikerson, K. L., Davin, T. D., et al. (2004), *Ann Pharmacother* **38**, 2059–2067.
25. Renal insufficiency and failure associated with immune globulin intravenous therapy—United States, 1985–1998. (1999), *MMWR Morb Mortal Wkly Rep* **48**, 518–522.
26. Gras, V., Andrejak, M., and Decocq, G. (1999), *Pharmacoepidemiol Drug Safety* **8**, S73–S78.
27. Epstein, J. S., Gaines, A., Kapit, R., et al. (summer 1999), *FDA Med Bull*.
28. Yerba, M., Barrios, Y., Rincon, J., et al. (2002), *Clin Exp Rheumatol* **20**, 225–227.
29. Shoenfeld, Y. and Krause, I. (2004), *J Clin Immunol* **24**, 107–114.
30. Katz, U. and Shoenfeld, Y. (2005), *Lupus* in press.
31. Durand, J. M., Lefevre, P., Kaplanski, G., Retornaz, F., Cretel, E. and Soubeyrand, J. (1993), *Am J Hematol* **44**, 214–215.
32. Oh, K. T., Boldt, H. C., and Danis, R. P. (1997), *Am J Ophthalmol* **124**, 416–418.
33. Rosenbaum, J.T. (1997), *Arthritis Rheum* **40**, 1732–1733.
34. Go, R.S. and Call, T. G. (2000), *Mayo Clin Proc* **75**, 83–85.
35. Turner, B. and Wills, A. J. (2000), *J Neurol Neurosurg Psychiatry* **68**, 790–791.
36. Elkayam, O., Paran, D., Milo, R., et al. (2000), *Ann Rheum Dis* **59**, 77–80.
37. Emerson, G. G., Herndon, C. N., and Sreih, A.G. (2002), *Pharmacotherapy* **22**, 1638–1641.
38. Katz, K. A., Hivnor, C. M., Geist, D. E., et al. (2003), *Arch Dermatol* **139**, 991–993.
39. Zaidan, R., Al Moallem, M., Wani, B. A., et al. (2003), *Eur J Neurol* **10**, 367–372.
40. Evangelou, N., Littlewood, T., Ansow, P., and Chapel, H. (2003), *J Clin Pathol* **56**, 308–309.
41. Okuda, D., Flaster, M., Frey, J., and Sivakumar, K. (2003), *Neurology* **60**, 1825–1826.
42. Brown, H. C. and Ballas, Z. K. (2003), *J Allergy Clin Immunol* **112**, 797–799.
43. Sheehan, D. J. and Leshner, J. L. Jr. (2004), *Cutis* **73**, 403–406.
44. Vucic, S., Chong, P. S., Dawson, K. T., et al. (2004), *Eur Neurol* **52**, 141–144.
45. Caress, J. B., Cartwright, M. S., Donofrio, P. D., et al. (2003), *Neurology* **60**, 1822–1824.
46. Dalakas, M. C. and Clark, W. M. (2003), *Neurology* **60**, 1736–1737.
47. Reinhart, W.H. and Berchtold, P. E. (1992), *Lancet* **339**, 662–664.
48. Dalakas, M. C. (1994), *Neurology* **44**, 223–226.
49. Steinberger, B A., Ford, S. M., and Coleman, T.A. (2003), *Am J Hematol* **73**, 97–100.
50. Sequi, E. A., Cupler, E. J., and Dalakas, M. C. (1994), *Ann Intern Med* **121**, 259–262.

51. Nettis, E., Calogiuri, G., Colandari, M. C., et al. (2003), *Curr Drug Targets Immune Endocr Metabol Disord* **3**, 143–149.
52. Jolles, S., Sewell, W. A., and Leighton, C. (2000) *Drug Safety* **22**, 215–226.
53. Matsuda, M., Hosoda, W., Sekijima, Y., et al. (2003), *Clin Neuropharmacol* **6**, 306–311.
54. Kessary-Shoham, H., Levy, Y., Shoenfeld, Y., et al. (1999), *J Autoimmun* **13**, 129–135.
55. Nakagawa, M., Watanabe, N., Okuno, M., et al. (2000), *Am J Hematol* **63**, 160–161.
56. Miyamae, T., Kurosawa, R., Mori, M., et al. (2004), *Med Rheumatol* **14**, 314–319.
57. Barbaud, A., Trechot, P., Granel, F., et al. (1999), *Dermatology* **199**, 258–260.
58. Lawn, N., Wijdicks, E. F. M., and Buritt, M. F. (1998), *N Engl J Med* **339**, 632.
59. Rizk, A., Gorson, K. C., Kenney, L., et al. (2001), *Transfusion* **41**, 264–268.