Adverse reactions associated with intravenous immunoglobulin therapy in patients with dermatologic diseases: An 11-year retrospective study

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Background: Intravenous immunoglobulin (IVIG) is used to treat many autoimmune and immunodeficiency disorders. The main indications of IVIG in dermatology include treatment for resistant autoimmune bullous diseases, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Although generally well-tolerated, various adverse effects can occur.

Methods: We designed a retrospective study to investigate the adverse effects of IVIG in all patients who received this drug in Razi Hospital from 2005-2016. Information was gathered from patients' medical records.

Results: During the study period, 67 patients received 94 IVIG infusions. The most common underlying dermatologic disease was pemphigus vulgaris (54 patients). The most frequent adverse effect of IVIG therapy was an increase in blood pressure for 17 patients and in 21 infusions of IVIG. Other adverse reactions included fatigue and generalized weakness, fever, chills, tachycardia, dizziness, a decrease in blood pressure, headache, flushing, chest discomfort, hemolysis, leukopenia, and deep vein thrombosis.

Conclusions: Adverse events associated with IVIG therapy are usually mild and self-limiting. The incidence of serious adverse events is low. Identification of risk factors and close monitoring of high risk patients are essential to decrease the occurrence of serious adverse events.

Keywords: intravenous immunoglobulin, adverse reaction, dermatologic disease, pemphigus vulgaris

INTRODUCTION

Intravenous immunoglobulin (IVIG) was developed more than 30 years ago. This treatment is currently approved for various conditions that include immunodeficiencies and autoimmune diseases [1-3]. IVIG is a blood product that consists of polyvalent IgG antibodies pooled from at least 1000 different human donors [1]. The main indication for IVIG in dermatology is to treat resistant autoimmune bullous diseases, especially pemphigus vulgaris. Treatment of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are other indications.

IVIG is generally considered a safe, efficacious therapeutic modality. However, it is associated with a wide range of adverse effects [4]. The reported incidence of adverse effects related to IVIG treatment in published literature varies from 2% to 81% [5]. The most common adverse reactions include headache, nausea, myalgia, fever, chills, chest discomfort, and skin and anaphylactic reactions which can arise immediately during or after the infusion. Delayed events may be more severe and include migraine

headaches, aseptic meningitis, hemolysis, renal impairment, and thrombotic events [6]. The aim of this study is to retrospectively review the frequency of adverse effects of IVIG therapy during an 11-year period at the Department of Dermatology, Razi Hospital, Tehran, Iran.

PARTICIPANTS AND METHODS

We reviewed medical records of 67 patients who received IVIG between April 2005 and March 2016. These patients received 94 IVIG infusions according to a published protocol on 3-5 consecutive days. We recorded information on sex, age, type of dermatologic disease, as well as early and delayed adverse reactions.

SPSS (version 19.0) was used for all statistical analyses. We used the t- and chi-square tests to assess the relationship between variables.

RESULTS

During this 11-year period, 67 patients received IVIG treatment. There were 40 (59.7%) male and 27 (40.3%) female patients. The patients had an average age of 38.1±14.1 years (range: 7-76 years). The patients received a total of 94 individual infusions of IVIG. Some patients received only one cycle of the IVIG infusion, whereas others received more than one cycle. Therefore, we presented the data according to IVIG infusion cycles. The average IVIG dose was 2.01±1.38 g/kg. Table 1 summarizes the patients' dermatologic diseases and dosage of IVIG for each disease.

Table 2 lists the incidence of adverse effects observed. There were adverse reactions recorded for 32 (34.04%) cycles of the IVIG infusions and in 28 (41.7%) patients. The most common adverse reaction reported was an increase in blood pressure in 17 patients (22.3% of IVIG infusions). This adverse

Table 2. Incidence of adverse events associated with intravenous immunoglobulin (IVIG) therapy.

Adverse effect	Infusions, number (%)	Patients, number (%)
Increase in blood pressure	21 (22.3)	17 (25.3)
Fatigue and generalized weakness	5 (5.3)	5 (7.4)
Fever	3 (3.1)	3 (4.4)
Chills	4 (4.2)	4 (5.9)
Tachycardia	3 (3.1)	3 (4.4)
Dizziness	3 (3.1)	3 (4.4)
Decrease in blood pressure	2 (2.1)	2 (2.9)
Headache	1 (1.0)	1 (1.5)
Flushing	1 (1.0)	1 (1.5)
Chest discomfort	1 (1.0)	1 (1.5)
Hemolysis	1 (1.0)	1 (1.5)
Leukopenia	2 (2.1)	2 (2.9)
Deep vein thrombosis	3 (3.1)	3 (4.4)

reaction began between 15 minutes to 4 hours after the beginning of the infusion (mean: 1 hour and 52 minutes). The increase in blood pressure had no significant relationships with sex (P=0.23), age (P=0.38), or dermatologic disease (P=0.72) of the patients. However, when compared in patients with and without underlying chronic hypertension, we observed a more frequent, statistically significant increase in blood pressure among patients with chronic hypertension (P=0.014). In most patients that experienced an increase in blood pressure, temporary cessation of the infusion for 15 to 30 minutes and restarting the infusion at a lower rate appeared to be of benefit. Some patients, especially those with chronic hypertension, received antihypertensive drugs.

There were complaints of fatigue and generalized weakness in 5 patients (5.3% of infusions). The onset of fatigue generally occurred at the end of the cycle (5 days after the beginning of the infusion). Fatigue was not severe or disabling, and resolved without specific treatment after a few days.

Fever occurred in 3 patients and was accompanied

Table 1. Type of dermatologic disease treated with intravenous immunoglobulin (IVIG) and dosage of IVIG in each disease.

Disease	Patients (N)	Cycles (N)	Mean dosage of IVIG in each cycle (g/kg)
Pemphigus vulgaris	54	81	1.96
Paraneoplastic pemphigus	3	3	2
Bullous pemphigoid	2	2	2
Mucous membrane pemphigoid	1	1	2
SJS*	4	4	2.5
TEN**	3	3	3

*SJS: Stevens-Johnson syndrome; **TEN: Toxic epidermal necrolysis

by chills in 2 patients. The average time of onset of fever was 2 hours and 20 minutes after the beginning of the infusion. The fevers responded to administration of acetaminophen in all 3 patients.

There were chills observed in 4 patients accompanied by fever in 2 patients. On average, the onset of chills was 2 hours and 7 minutes after the onset of the infusion. This adverse reaction was managed by temporary halting of the infusion and restarting at a lower rate after the resolution of chills.

Tachycardia and palpitations were reported in 3 patients and accompanied by an increase in blood pressure in 2 patients. On average, the tachycardia began approximately 45 minutes after the onset of the infusion. In these patients, the IVIG infusion was stopped and the patients received propranolol. The IVIG was restarted at a lower rate after resolution of the tachycardia.

Dizziness was observed in 3 patients, which began 3 hours and 40 minutes after the onset of the infusion on average. In one patient, the infusion was temporarily stopped and restarted after the dizziness resolved. Dizziness spontaneously resolved in 2 other patients after a few hours.

A decrease in blood pressure developed in 2 patients. The average time of onset was 1 hour and 45 minutes after the beginning of the infusion. In these patients, the IVIG infusion was stopped and the patients received intravenous infusions of normal saline. The IVIG resumed after normalization of blood pressure.

One patient developed a headache 5 days after the onset of IVIG. The headache was not severe in this patient and resolved without specific treatment.

Flushing was observed in one patient on the fifth day of the IVIG infusion. Flushing was treated with chlorpheniramine and reduction of the rate of the IVIG infusion.

One patient developed chest discomfort that was accompanied by an increase in blood pressure during the IVIG infusion. The infusion was stopped and the patient had an electrocardiography and measurement of cardiac enzymes. When a myocardial infarction was ruled out and the symptoms subsided, the IVIG infusion was restarted.

Hemolytic anemia was reported in one patient. Hemolysis developed 3 days after the end of the IVIG infusion. The patient's hemoglobin level reduced to 9 g/dL. A serial complete blood count was performed to check hemoglobin levels, which

gradually increased after a few days.

Leukopenia developed in 2 patients who received IVIG for the treatment of TEN on the third day of the IVIG infusion. The white blood cell count returned to normal after 3 days in both patients and no infection developed.

Thromboembolic events were reported in 3 patients in the form of deep vein thrombosis of the lower leg. Deep vein thrombosis developed 3.6 days after the onset of infusion on average. Two of these patients had risk factors for thromboembolic events (one patient had internal malignancy and the other one had a history of a pulmonary embolism). These patients received heparin and warfarin.

Serum IgA levels were measured in 43 patients before the IVIG administration. Among these 43 patients, 3 were IgA deficient. None of these 3 patients had any anaphylactic reactions after the IVIG infusion.

Nausea, vomiting, diarrhea, myalgia, arthralgia, eczema, urticaria, aseptic meningitis, renal failure, anaphylaxis, and death related to IVIG infusion were not observed in our patients.

DISCUSSION

The incidence of adverse effects with IVIG therapy varies widely. The adverse events most commonly reported are minor and include headache, nausea, malaise, myalgia, arthralgia, chills, fever, and chest discomfort. Less commonly reported minor adverse effects include fatigue, dyspnea, back pain, diarrhea, urticaria, leukopenia, hemolytic anemia, changes in blood pressure, and tachycardia [7]. Reducing the infusion rate or temporarily stopping the infusion generally relieves these symptoms [8]. Serious adverse events that include aseptic meningitis, thromboembolism, acute renal failure, and anaphylaxis have been less frequently reported.

The most common adverse reaction in our study was an increase in blood pressure observed in 22% of the infusions and 25% of the patients. This adverse reaction was significantly more frequent in patients with underlying chronic hypertension. Interestingly, the increase in blood pressure during the IVIG infusion was not reported as a common adverse reaction in any of the previous literature; its incidence was much lower in other studies compared to the current study [5,7-11]. The reasons for the high frequency of this adverse event in our

study were not clear. The increase in blood pressure in the current study patients was easily treated by reducing the infusion rate in most patients. Antihypertensive drugs were administered to a few patients. All could complete the IVIG therapy.

The second most frequent adverse effect in our patients was fatigue and generalized weakness, seen in 5.3% of the infusions. Its incidence in the current study was comparable with the results of a number of previous studies [5,7,10]. The occurrence of other minor adverse effects that included fever, chills, chest discomfort, tachycardia, dizziness, and flushing were low in this and other studies [5,7-10].

Headache was the most common adverse event in previous studies with an incidence that ranged from 10.7% to 48% [5,12-16]. We observed this effect in one patient. Gastrointestinal problems (nausea, vomiting, and diarrhea) and skin reactions (urticaria and eczema) were reported in other studies at different frequencies [1,5,7-11], but we did not observe these complications in our patients.

An uncommon adverse effect of IVIG is hemolysis. Risk factors for IVIG-related hemolysis include a high dose of IVIG given to non-O blood group recipients [17]. IVIG is typically pooled from approximately 1000 individuals of all blood types. Donors with type O blood can contribute blood group antibodies towards type A and B antigens, and these antibodies in rare cases lead to hemolysis [4]. Leukopenia, neutropenia, and monocytopenia are also rarely associated with IVIG therapy [4]. We have observed one case of hemolysis and 2 cases of leukopenia in our series.

The major concerns with IVIG therapy include serious adverse reactions such as aseptic meningitis, acute renal failure, thromboembolic events, and anaphylaxis. Aseptic meningitis was observed at a low frequency in some studies [5,16,18], but not in our study. Risk factors for the development of aseptic meningitis include high immunoglobulin concentration, fast infusion rate, and a history of migraines [16].

The incidence of acute renal failure, as an adverse effect of IVIG, is estimated to be lower than 1% [5]. We have not observed this complication in the current study. Acute renal failure has been predominantly reported with products that contain saccharose, maltose, and glucose. The risk factors for development of acute renal failure include preexisting renal insufficiency, diabetes, advanced age, hypovolemia, concomitant use of other nephrotoxic drugs, and paraproteinemia [19]. Acute renal failure is related to acute tubulointerstitial nephropathy due to the occurrence of osmotic nephrosis. In most patients, acute renal failure is reversible but progression to chronic renal failure has been reported [20-23].

We did not observe any anaphylactic reactions to IVIG. These have been rarely reported in the literature. Anaphylactic reactions usually occur in IgA deficient patients who have detectable serum anti-IgA antibodies [24-27]. We had 3 IgA deficient patients in our series but they received IVIG without any anaphylactic reactions.

Arterial and venous thrombotic events that include stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolism have been reported with an incidence of 0.6%-3% per patient and 0.15%-1.2% per treatment course [7,28-30]. The exact mechanism of thromboembolic events associated with IVIG is unclear. Serum hyperviscosity caused by the IVIG infusion has been suggested to contribute to the occurrence of thromboembolic events [31,32]. In addition, rapid infusion and hyperosmolarity of IVIG have been associated with increased serum viscosity [31]. Three patients in our study developed deep vein thrombosis during the IVIG infusion, of which two had risk factors for thrombosis. It was reasonable that patients with a higher risk of thromboembolic events were infused with a low osmolarity product at a slow rate to reduce the likelihood of thromboembolic events [5].

The results of our study have shown that IVIG is safe with a few easily manageable minor adverse effects and a very low incidence of serious adverse effects, which is similar to those observed in previous studies. However, knowledge of the adverse effect profile is important. Before considering the use of IVIG in any patient, it is advisable that physicians thoroughly evaluate the patients for possible risk factors for serious adverse effects of the IVIG. Consideration and close monitoring of patients with identified risk factors during the infusion is critical.

REFERENCES

1. Gerstenblith MR, Antony AK, Junkins-Hopkins JM, Abuav R. Pompholyx and eczematous reactions associated with intravenous immunoglobulin therapy. J Am Acad Dermatol. 2012;66(2):312-6.

2. Shoenfeld Y. Fifth international symposium on IVIG: IVIG in the third millennium, 25-27 September 2003, Interlaken, Switzerland: a meeting review. Autoimmun Rev. 2004;3(3):234-41.

3. Shoenfeld Y, Katz U. IVIG therapy in autoimmunity and related disorders: our experience with a large cohort of patients. Autoimmunity. 2005;38(2):123-37.

4. Baxley A, Akhtari M. Hematologic toxicities associated with intravenous immunoglobulin therapy. Int Immunopharmacol. 2011;11(11):1663-7.

5. Souayab N, Hasan A, Khan HM, et al. The safety profile of home infusion of intravenous immunoglobulin in patients with neuroimmunologic disorders. J Clin Neuromuscul Dis. 2011;12(Suppl 4):S1-10.

6. Cherin P, Marie I, Michallet M, et al. Management of adverse events in the treatment of patients with immunoglobulin therapy: A review of evidence. Autoimmun Rev. 2016;15(1):71-81.

7. Gurcan HM, Ahmed AR. Frequency of adverse events associated with intravenous immunoglobulin therapy in patients with pemphigus or pemphigoid. Ann Pharmacother 2007;41(10):1604-10.

8. Tufan F, Kamali S, Erer B, et al. Safety of high-dose intravenous immunoglobulin in systemic autoimmune disases. Clin Rheumatol. 2007;26(11):1913-5.

9. Katz U, Achiron A, Sherer Y, Shoenfeld Y. Safety of intravenous immunoglobulin (IVIG) therapy. Autoimmune Rev. 2007;6(4):257-9.

10. Stangel M, Kiefer R, Pette M, et al. Side effects of intravenous immunoglobulins in neurological autoimmune disorders-a prospective study. J Neurol. 2003;250(7):818-21.

11. Aghamohammadi A, Farhoudi A, Nikzad M, et al. Adverse reactions of prophylactic intravenous immunoglobulin in Iranian patients with immunodeficiency. Ann Allergy Asthma Immunol. 2004;92(1):60-4.

12. Rigas M, Tandan R, Sterling RJ. Safety of liquid intravenous immunoglobulin for neuroimmunologic disorders in the home setting: a retrospective analysis of 1085 infusions. J Clin Neuromuscul Dis. 2008;10(2):52-5.

13. Stangel M, Muller M, Marx P. Adverse events during treatment with high-doseintravenous immunoglobulins for neurological disorders. Eur Neurol. 1998;40(3):173-4.

14. Brannagan TH III, Nagle KJ, Lange DJ, et al. Complications of intravenous immunoglobulin treatment in neurologic disease. Neurology. 1996;47(3):674-7.

15. Bertorini TE, Nance AM, Horner LH, et al. Complications of intravenous immunoglobulin in neuromuscular and other diseases. Muscle Nerve. 1996;19(3):388-91.

16. Sekul EA, Kupler EJ, Dalakas MC. Aseptic meningitis associated with high dose intravenous immunoglobulin therapy: frequency and risk factors. Ann Intern Med. 1994;121(4);259-62.

17. Padmore RF. Hemolysis upon intravenous immunoglobulin transfusion. Transfus Apher Sci. 2012;46(1): 93-6.

18. Orbach H, Katz U, Sherer Y, et al. Intravenous immunoglobulin: adverse effects and safe administration. Clin Rev Allergy Immunol. 2005;29(3):173-84.

19. Haskin JA, Warner DJ, Blank DU. Acute renal failure after large doses of intravenous immunoglobulin. Ann Pharmacother. 1999;33(7-8):800-3.

20. Itkin YM, Trujillo TC. Intravenous immunoglobulin associated acute renal failure: case series and literature review. Pharmacotherapy. 2005;25(6):886-92.

21. Ashan N, Wiegand LA, Abendroth CS, et al. Acute renal failure following immunoglobulin therapy. Am J Nephrol. 1996;16(6):532-6.

22. Cantu TG, Hoehn-Saric EW, Burgess KM, et al. Acute renal failure associated with immunoglobulin therapy. Am J Kidney Dis. 1995;25(2):228-34.

23. Hansen-Schmidt S, Silomon J, Keller F. Osmotic nephrosis due to high-dose immunoglobulin therapy containing sucrose (but not with glycine) in a patient with immunoglobulin A nephritis. Am J Kidney Dis. 1996;28(3):451-3.

24. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. N Engl J Med. 1986;314(9):560-4.

25. De Albuquerque Campos R, Sato MN, da Silva Duarte AJ. IgG anti-IgA subclasses in common variable immunodeficiency and association with severe adverse reactions to intravenous immunoglobulin therapy. J Clin Immunol. 2000;20(1):77-82.

26. Bjorkander J, Hammarstorm L, Smith CI, et al. Immunoglobulin prophylaxis in patient with antibody deficiency syndromes and anti-IgA antibodies. J Clin Immunol. 1987;7(1):8-15.

27. McCluskey DR, Boyd NA. Anaphlaxis with intravenous gammaglobulin. Lancet. 1990;336(8719):874.

28. Paran D, Herishanu Y, Elkayam O, Shopin L, Ben-Ami R. Venous and arterial thrombosis following administration of intravenous immunoglobulin. Blood Coagul Fibrinolysis. 2005(5);16:313-8.

29. Marie I, Maurey G, Herve F, et al. Intravenous immunoglobulin-associated arterial and venous thrombosis: report of a series and review of the literature. Br J Dermatol. 2006;155(4):714-21.

30. Katz U, Shoenfeld Y. Review: intravenous immunoglobulin therapy and thromboembolic complications. Lupus. 2005;14(10):802-8.

31. Nydegger UE, Sturzenegger M. Adverse effects of intravenous immunoblobulin therapy. Drug Saf. 1999;21(3):171:85.

32. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology. 1994;44(2):223-6.