IgA Content in IVIG Products

What Is the Real Concern Regarding Anaphylactic or Anaphylactoid Reactions?

By Chris Lomax, PharmD

Introduction

Human intravenous immune globulin (IVIG) products contain a range of antibodies that are purified from pooled batches of plasma from thousands to tens of thousands of donors. In addition to IgG antibodies, which constitute the largest percentage of antibodies, IVIG products also contain various amounts of IgM and IgA antibodies. Of these latter antibodies, IgA has garnered the most attention in terms of the potential for anaphylactic or anaphylactoid reactions. Some IgA deficient patients can experience anaphylactic or anaphylactoid reactions when given IVIG products that contain moderate amounts of IgA. The question is how relevant this concern is for the majority of IgA deficient patients.

Discussion

Anaphylactic or anaphylactoid reactions can occur in any patient receiving IVIG therapy, although the overall incidence is relatively low.[1] The majority of these reactions are more appropriately described as anaphylactoid in that they are slowly progressing reactions that usually begin with a patient complaining of tightness in the chest, difficulty breathing and accompanied with increases in heart rate and blood pressure. Administration of intravenous antihistamines and corticosteroids will generally reverse the reaction and, in some cases, the IVIG administration can be safely resumed.[1, 2] Unlike a true anaphylactic reaction, the administration of epinephrine is often unnecessary.

Selective IgA deficiency is the most common primary immunoglobulin deficiency and occurs in approximately one in 600 individuals in the Western world.[3] Early researchers determined that severe anaphylactoid or anaphylactic reactions to IVIG were most likely to occur only in patients who are severely deficient of IgA (<1.2 mg/dl) and who have anti-IgA antibodies of the IgE type.[4-6] More recently, Horn and co-workers[2] attempted to determine what other factors might be present in those patients who experienced anaphylactoid reactions to IVIG. They found that a correlation existed in those patients who (1) had a complete absence of serum IgA and (2) had an absence of IgA-positive B cells—although they noted that the presence of these markers was not absolute.

IgA antibodies of the IgG type can be present in up to 40 percent of patients with selective IgA deficiency and up to 10 percent of patients with common variable immune deficiency (CVID).[7] The presence of IgA antibodies of the IgG type does not predispose IgA patients to experiencing anaphylactic or anaphylactoid reactions when administered IVIG containing moderate amounts of IgA.[1, 6, 8] When Horn and co-workers reviewed the literature for CVID patients with an IgG anti-IgA-associated anaphylactoid reactions, they found only six cases.[2] Because the incidence of these reactions is so rare, there is no clear consensus as to whether or not routine screening for IgA deficiency should be performed before IVIG therapy is begun.[1] Currently available IVIG products, with the exception of Gammagard® S/D, contain moderate levels of IgA (<25-720 mcg/ml). There has never been a study that has demonstrated that IVIG-related side effects increase with increasing levels of IgA in the various brands of IVIG. Therefore, the tolerability of individual IVIG products would appear to be dependent on other factors than IgA content.

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Treatment of Patients With IgA Deficiency

Although all IVIG manufacturers' package inserts list selective IgA deficiency as a contraindication for their use, IVIG products are frequently prescribed in these patients, as many of them also have IgG subclass deficiencies. In such cases, IVIG has been safely used in a large number of IgA deficient patients. In those IgA deficient patients who experience anaphylactic or anaphylactoid reactions to IVIG products with moderate amounts of IgA, Cunningham-Rundles and co-workers demonstrated that most of those patients could be safely given an IVIG product with low levels of IgA (0.4-2.9 mcg/ml). In their study they administered Gammagard® 5% (immune globulin intravenous [human]) manufactured by Baxter Healthcare to five subjects who had IgA antibodies and had previously experienced severe infusion reactions to IVIG products with moderate levels of IgA (270–720 mcg/ml). These reactions included severe myalgias, shortness of breath and chest pain, fever, severe abdominal pain, and/or hypotension. They followed five

patients for a total of 170 infusions and found only mild to moderate infusion reactions in nine of the 170 infusions (5.3%).

A number of researchers demonstrated similar results when immune globulin was administered subcutaneously.[9-13] They found that patients who experienced anaphylactic or anaphylactoid reactions to IVIG products could tolerate subcutaneously administered immune globulins. There is even evidence to suggest that subcutaneously administered immune globulin therapy may reduce the level of IgA antibodies in the serum—a fact not seen when IgA depleted IVIG is utilized.[12] A third but more complicated option was reported by Salama and co-workers.[14] In this case report, a 40-year-old patient who experienced anaphylaxis with Octagam® (immune globulin intravenous [human]), an IVIG formulation manufactured by Octapharma and containing <100 mcg/ml of IgA, was successfully treated with the same product after it was mixed with freshly separated autologous plasma.

Conclusions

Many patients with IgA deficiency require IVIG therapy. While most patients, even those with anti-IgA antibodies, will tolerate most IVIG products, alternative options are readily available. The use of low IgA IVIG products or subcutaneously administered immune globulin products can often be safely administered to those patients who experience anaphylactic or anaphylactoid reactions to IVIG products containing moderate amounts of IgA. In fact, anaphylactic and anaphylactoid reactions can occur in any patient receiving IVIG products; clinicians need to be aware of this and be knowledgeable in the treatment of these reactions. ■

Chris Lomax is the director of pharmacy and nutrition services at Children's Hospital Los Angeles.

Reference List

1. Orbach H, Katz U, Sherer Y, Shoenfeld Y. Intravenous Immunoglobulin: Adverse Effects and Safe Administration. *Clinical Reviews in Allergy and Immunology*, 2005;29(3):173-84.
2. Horn J, Thon V, Bartonkova D et al. Anti-IgA Antibodies in Common Variable Immunodeficiency (CVID): Diagnostic Workup and Therapeutic Strategy. *Clin Immunol*, 2007 February;122(2):156-62.
3. Hammarstrom L, Vorechovsky I, Webster D. Selective IgA Deficiency (SIgAD) and Common Variable Immunodeficiency (CVID). *Clin Exp Immunol*, 2000 May; 120(2):225-31.
4. 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 February 27;314(9):560-4.
5. Ferreira A, Garcia Rodriguez MC, Lopez-Trascasa M, Pascual SD, Fontan G. Anti-IgA Antibodies in Selective IgA Deficiency and in Primary Immunodeficient Patients Treated with Gamma-Globulin. *Clin Immunol Immunopathol*, 1988 May;47(2):199-207.
6. De Albuquerque CR, 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 January;20(1):77-82.
7. Cunningham-Rundles C, Zhou Z, Mankarious S, Courter S. Long-term Use of IgA-Depleted Intravenous Immunoglobulin in Immunodeficient Subjects With Anti-IgA Antibodies. *J Clin Immunol,* 1993 July;13(4):272-8.
8. Ferreira A, Garcia Rodriguez MC, Fontan G. Follow-up of Anti-IgA Antibodies in Primary Immunodeficient Patients Treated With Gamma-Globulin. *Vox Sang*, 1989;56(4):218-22.
9. Berger M. Subcutaneous IgG Therapy in Immune Deficiency Diseases. *Immune Deficiency Foundation*, 2008 February;(13).
10. Kirmse J, Weiler CR. Subcutaneous Immunoglobulin (SCIG) Therapy: Review of 51 Patients. *J Allergy Clin Immunol* 117[2], S86. 2006. Ref Type: Abstract
11. Stiehm ER, Casillas AM, Finkelstein JZ et al. Slow Subcutaneous Human Intravenous Immunoglobulin in the Treatment of Antibody Immunodeficiency: Use of an Old Method With a New Product. *J Allergy Clin Immunol,* 1998 June;101(6 Pt 1):848-9.
12. Sundin U, Nava S, Hammarstrom L. Induction of Unresponsiveness Against IgA in IgA-Deficient Patients on Subcutaneous Immunoglobulin Infusion Therapy. *Clin Exp Immunol*, 1998 May;112(2):341-6.
13. Misbah S. Intravenous Immunoglobulin in the Guillain-Barre Syndrome. Products With Low IgA Content May Be Used in Patients With Total IgA Deficiency. *BMJ*, 1996 November 30;313(7069):1400.
14. Salama A, Temmesfeld B, Hippenstiel S, Kalus U, Suttorp N, Kiesewetter H. A New Strategy for the Prevention of IgA Anaphylactic Transfusion Reactions. *Transfusion*, 2004 April;44(4):509-11.