Review of Allergy and Clinical Immunology
2013;23 • 68-70

short communication

Key words
Anti-IgA antibodies • Common variable immunodeficiency • Subcutaneous Ig • Infusion reactions

Safety of subcutaneous immunoglobulin (Ig) replacement therapy in patients with previous anaphylactic reactions to intravenous Ig and positivity of anti-IgA antibodies

A. VULTAGGIO[1], A. FERRARO[1], R.D. COJAN[1], E. MAGGI[1 2], A. MATUCCI[1]
[1] *Department of Biomedicine, Immunoallergology Unit, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy;*
[2] *Center for Research, Transfer and High Education DENOTHE, University of Florence, Italy*

Summary
Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency. In CVID patients displaying IgA deficiency, antibodies to IgA may be present, thus leading to a greater risk of infusion reactions to intravenous Ig (IVIG) replacement therapy.
We evaluated the incidence of adverse infusion reactions in 32 CVID patients. Twelve systemic infusion-related reactions out of 3168 infusions (0.37%) were observed in 7 out of 32 patients (21.8%). IgG anti-IgA positivity was observed in 2 of 7 reactive patients and in 1 of 25 unreactive subjects (28.5% *vs.* 4%, $p < 0.01$). All patients with IgG anti-IgA antibodies had undetectable IgA serum levels. IgE anti-IgA antibodies were not detected in any patient. All 7 reactive patients were then treated with IVIG preparation with low IgA fraction (< 0.05 mg/mL), and the majority of them (6 out of 7) tolerated that therapy. The treatment was then switched to SCIG (Vivaglobin 16%® and later Hizentra 20%®, 100 mg/kg/week) that was well tolerated.
In conclusion, our results show that SCIG treatment (Vivaglobin 16%®, Hizentra 20%®) may represent a useful and safe alternative therapy in CVID patients who experienced infusion-related reactions due to high levels of anti-IgA IgG antibodies.

Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency characterized by decreased serum levels of immunoglobulins (Ig) leading to recurrent bacterial infections, usually involving upper and lower respiratory tract. Long-term administration of Ig reduces the incidence of infectious. A monthly Ig dosage of at least 400 mg/kg body weight is recommended and is most often sufficient [1]. In CVID patients displaying IgA deficiency, antibodies to IgA may be present, thus leading to a greater risk of infusion reactions to intravenous Ig (IVIG) replacement therapy [2]. In fact, it is known that IVIG can be complicated by adverse events, ranging from mild to severe reactions such as anaphylaxis.

Subcutaneous replacement therapy (SCIG) may represent an alternative route of IgG administration for CVID patients and it offers advantages not available with IVIG. SCIG allow stable serum IgG concentration thus providing good protection against infections [3] and, in contrast to IVIG, serious systemic adverse events rarely occur with SCIG infusion [4 5]. To confirm the safety profile of SCIG in comparison to IVIG in our experience, we evaluated the incidence of adverse infusion reactions in 32 CVID patients (13 male; 19 female; mean age 31 years) regularly submitted to

monthly IVIG therapy in our Institute from 2004 to 2012 Twelve systemic infusion-related reactions out of 3168 infusions (0.37 %) were observed in 7 out of 32 patients (21.8 %) during the follow-up period. According to the grading system proposed by Brown for hypersensitivity reactions [6], 9 (75 %) of them were classified as moderate and 3 (25 %) as severe.

Since adverse reactions to gamma-globulin infusions in immunodeficient patients have been associated with anti-IgA antibodies [7], and that it is estimated that 9% to 25% of CVID patients may have anti-IgA antibodies [8], we analyzed the incidence of IgE and IgG anti-IgA antibodies in the induction of adverse events in our reactive patients. The serum detection of anti-IgA antibodies was performed with fluoroenzyme-immunoassay (ImmunoCAP®, Thermofisher, Uppsala, Sweden) about 4 weeks after the reaction by using mouse monoclonal anti-human IgG or anti-IgE β-galactosidase-labelled secondary antibodies. The screening cut-off values were 0.10 kUA/L for IgE (as provided by manufacture) and 48 Unit Response (UR) for IgG, obtained from the evaluation of 20 healthy donors. As control group, 25 unreactive IVIG-treated patients were also enrolled.

IgG anti-IgA positivity was observed in 2 of 7 reactive patients and in 1 of 25 unreactive subjects (28.5% *vs.* 4%, $p<0.01$). All patients with IgG anti-IgA antobodies had undetectable IgA serum levels. IgE anti-IgA antibodies were not detected in any patient. All 7 reactive patients were then treated with IVIG preparation with low IgA fraction (< 0.05 mg/mL), and the majority of them (6 out of 7) tolerated that therapy. In contrast, 1 patient with high levels of anti-IgA IgG antibodies (1381 UR) continued to developing subsequent moderate systemic reactions, also with this kind of Ig preparation. IVIG-treated CVID patients with reactions to replacement therapy can be safely treated with SCIG [9]. The treatment was then switched to SCIG (Vivaglobin 16%® and later Hizentra 20%®, 100 mg/kg/week) that was well tolerated. The monitoring performed 2 months after the beginning of subcutaneous treatment, showed a significant reduction of IgG anti-IgA antibodies serum levels (262 UR). These observations agree with previous published data referring the induction of unresponsiveness in anti-IgA positive patients after SCIG replacement therapy, likely explained by a gradual exposure to IgA due to a slow resorption of subcutaneous preparations [10].

Concerning the pathogenic role of IgG anti-IgA antibodies in the induction of systemic adverse events to IVIG, recent data suggest that immunological mechanisms other than type I IgE-mediated hypersensitivity may be involved in anaphylactic reactions [11-13]. Indeed, IgG antibodies can directly stimulate immune cells such as basophils or activate the complement system via immune complexes, thus leading to massive degranulation of circulating basophils [14].

For the detection of Ig against IgA we used the ImmunoCAP technology, that is a robust and reproducible assay characterized by a solid phase with a high and binding capacity that enables the presence of an excess amount of antigen. However, assay validation and inclusion of relevant antibody/reference controls need to be considered and implemented appropriately. In addition, the fact that autoantibodies such as IgG anti-IgA antibodies may be administered passively with the preparation used, must be considered [15].

In conclusion, our results show that SCIG treatment (Vivaglobin 16%®, Hizentra 20%®) may represent a useful and safe alternative therapy in CVID patients who experienced infusion-related reactions due to high levels of anti-IgA IgG antibodies. Finally, SCIG treatment seems to be able to reduce the immune reactivity against Ig.

Reference

1 Kaveri SV, Maddur MS, Hegde P, et al. *Intravenous immunoglobulins in immunodeficiencies: more than mere replacement therapy*. Clin Exp Immunol 2011;164:2-5.

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

3 Gardulf A, Andersen V, Björkander J, et al. *Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs*. Lancet 1995;345:345-65.

4 Quinti I, Soresina A, Agostani C, et al. *Prospective Study on CVID patients with adverse reactions to intravenous or subcutaneous IgG administration*. J Clin Immunol 2008;28:263-8.

5 Ochs HD, Gupta S, Kiessling P, et al. *Safety and efficacy of self-admistered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases*. J Clin Immunol 2006;26:265-73.

6 Brown SG. *Clinical features and severity grading of anaphylaxis*. J Allergy Clin Immunol 2004;114:371-6.

[7] Rachid R, Bonilla FA. *The role of anti-IgA antibodies in causing adverse reactions to gamma globulin infusion in immunodeficient patients: a comprehensive review of the literature*. J Allergy Clin Immunol 2012;129:628-34.

[8] de Albuquerque Campos R, Sato MN, da Silva Duarte AJ. *IgG anti-IgA subclasses in common variable immunodeficiency and associations with severe adverse reactions to intravenous immunoglobulin therapy*. J Clin Immunol 2000;20:77-82.

[9] Eijkhout HW, van den Broek PJ, van der Meer JWM. *Substitution therapy in immunodeficient patients with anti-IgA antibodies or severe adverse reactions to previous immunoglobulin therapy.* Neth J Med 2003;61:213-7.

[10] Saudin U, Nava, Hammarstrom L. *Induction of unresponsiveness against IgA in IgA-deficient patients on subcutaneous immunoglobulin infusion therapy*. Clin Exp Immunol 1998;112:341-6.

[11] Finkelman FD. *Anaphylaxis: lessons from mouse models*. J Allergy Clin Immunol 2007;120:506-15.

[12] Oettgen HC, Martin TR, Wynshaw-Boris A, et al. *Active anaphylaxis in IgE-deficient mice*. Nature 1994;370:367-70.

[13] Ha Ty, Reed ND, Crowle PK. *Immune response potential of mast cell-deficient W/Wv mice*. Int Arch Allergy App Immunol 1986;80:85-90.

[14] Vultaggio A, Maggi E, Matucci A. *Immediate adverse reactions to biologicals: from pathogenic mechanisms to prophylactic management.* Curr Opin Allergy Clin Immunol 2012;3:262-8.

[15] Quinti I, Papetti C, Perricone R, et al. *Anaphylaxis after administration of gamma-globulin for hypogammaglobulinemia*. N Engl J Med 1986;315:519-520.

• Correspondence: Andrea Matucci, viale Morgagni 85, 50134 Florence, Italy – Tel. 0554271059 – Fax 0554271500 – E-mail: a.matucci@dmi.unifi.it