

# Immune tolerance induction in patients with IgA anaphylactoid reactions following long-term intravenous IgG treatment

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## Summary

To date, there is very little information regarding the pathomechanism of IgA anaphylactoid reactions and the management of affected patients. Five adult patients with common variable immunodeficiency (CVID) and a history of anaphylactic reactions due to the administration of immunoglobulin preparations were studied. The activity of anti-IgA was determined by the gel agglutination technique using IgA-coated beads. Antibodies to IgA were detected in the serum of all five patients. Initially, IgA 'depleted' intravenous (i.v.) IgG preparations were infused carefully into the patients until the activity of anti-IgA was decreased significantly or became undetectable. Subsequently, unselected i.v. IgG preparations were infused, and the activity of anti-IgA was abolished in all cases. Intravenous IgG long-term administration results in tolerance induction in patients with IgA anaphylactoid reactions. This tolerance appears to be related to antibody blockage in the circulation and an inhibition of antibody production. Most importantly, IgA appears to play an important role in the treatment of CVID. Patients with IgA anaphylactoid reactions can be treated safely with IgA containing i.v. IgG preparations following tolerance induction.

**Keywords:** anaphylaxis, anti-IgA, immune tolerance, intravenous immunoglobulins

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## Introduction

Anaphylaxis is a condition in which life-threatening attacks are stimulated by an immunogen. There are various immunogens which can lead to anaphylaxis, and in order to avoid further anaphylactic episodes, affected individuals must avoid re-exposure to the immunogen. Patients with common variable immunodeficiency (CVID) or selective IgA deficiency frequently build anti-IgA that may incite anaphylactoid reactions in affected patients following treatment with IgA containing blood products. IgA anaphylactoid reactions have been estimated to occur in roughly one per 50 000 transfusions [1]. During the last two decades, various strategies have been described to prevent IgA anaphylaxis. These include the use of blood from donors completely lacking IgA and/or thorough washing of the blood cells to remove all traces of donor IgA molecules [2–5]; the use of IgA 'depleted' intravenous (i.v.) IgG [6]; the subcutaneous administration of i.v. IgG in patients with immunodeficiency and a previous history of IgA anaphylaxis [7]; and lastly, the use of *ex vivo* pretreatment of i.v. IgG preparations with autologous plasma [8]. The latter strategy was implemented in the case

of a patient who subsequently developed immune tolerance to IgA. Since the commencement of treatment 3 years ago until the present, anti-IgA levels from this patient have diminished completely. In this study, we describe a simple strategy for the induction of immune tolerance in four additional patients with IgA anaphylaxis.

## Patients and methods

Five adult patients were enrolled in this study. All five patients (three females and two males, between 33 and 70 years of age) presented with common variable immunodeficiency and a previous history of anaphylaxis due to treatment with IgG preparations (Table 1).

Concentrations of IgG, IgA, IgM and circulation immune complexes were measured using rate nephelometry (Beckmann Coulter, Krefeld, Germany) and enzyme-linked immunosorbent assay (ELISA) (IMTEC Immundiagnostika, Berlin, Germany), respectively. The activity of anti-IgA was determined using IgA-coated beads and human anti-IgA gel cards (DiaMed, Cressier sur Morat, Switzerland), as has been described elsewhere [9].

**Table 1.** Patients with common variable immunodeficiency and a previous history of IgA anaphylaxis following treatment with intravenous IgG preparation.

| Patient | Age (years) | Sex | Anti-IgA | Previous anaphylactic reactions | IgG preparation†                                |
|---------|-------------|-----|----------|---------------------------------|-------------------------------------------------|
| 1       | 40          | M   | Unknown  | <i>n</i> = 1                    | IM IgG‡                                         |
| 2       | 33          | F   | 1 : 4    | <i>n</i> = 1                    | Intraglobin®                                    |
| 3       | 52          | F   | 1 : 64   | <i>n</i> = 1                    | Venimmun®                                       |
| 4       | 70          | M   | 1 : 2    | <i>n</i> = 1                    | Intratect®                                      |
| 5       | 62          | F   | 1 : 4    | <i>n</i> = 3                    | Intraglobin®, Sandoglobulin® liquid, Endobulin® |

†IgA concentration according to information provided by the manufacturer: Endobulin 30 µg/ml, Intraglobin 2.5 mg/ml, Intratect < 2 mg/ml, Sandoglobulin liquid < 15 µg/ml, Venimmun 12%. ‡Specific product is unknown.

## Results

All patients were observed to be suffering from recurrent infections which included abdominal discomfort, and could not be treated further with i.v. IgG due to preceding anaphylactic reactions (Table 1). On admission to this hospital, anti-IgA was detectable in the serum of all five patients. Patient 1 received i.v. IgG that was pretreated *in vitro* with autologous plasma, as has been described elsewhere [8]. The activity of anti-IgA was diminished completely during treatment, and

the patient subsequently received different i.v. IgG preparations containing varying amounts of IgA without any further complications (Table 2). Patients 2, 3 and 4 developed delayed reactions (4–8 h) following i.v. IgG readministration, as long as anti-IgA was detectable. However, these reactions were generally mild, and did not occur during i.v. IgG administration. Patient 5 initially received 10 g of an 'IgA-depleted' preparation that was infused slowly over an 8-h period. Her anti-IgA became undetectable, and all additional preparations were infused under standard conditions (10 g

**Table 2.** Results following re-exposure to intravenous (i.v.) IgG preparations.

| Patient | Re-exposure | After     | Anti-IgA titre | g       | i.v. IgG preparation          | Adverse reactions |
|---------|-------------|-----------|----------------|---------|-------------------------------|-------------------|
| 1       | 1           | 20 years  | 1 : 32         | 0.1–0.2 | Octa                          | Shock             |
|         | 2           | 1 day     | 1 : 16         | 1.25    | Octa in autologous pl         | –                 |
|         | 3           | 2 days    | 1 : 8          | 10      | Octa in autologous pl         | –                 |
|         | 4           | 3 days    | –              | 10      | Octa in autologous pl         | –                 |
|         | 5           | 4 weeks   | 1 : 8          | 30      | Octa in autologous pl         | –                 |
|         | 6–8         | 4 weeks   | –              | 30      | 1 × Octa, 1 × Intra, 1 × Ven  | –                 |
|         | Further     | 6–8 weeks | –              | 30      | 11 × Intratect                | –                 |
| 2       | 1           | 4 days    | 1 : 1          | 30†     | Fleb†                         | mp                |
|         | 2           | 3 weeks   | 1 : 2          | 30      | Fleb†                         | mp, v             |
|         | 3           | 2 weeks   | 1 : 1          | 30      | Fleb†                         | mp, v             |
|         | 4           | 3 weeks   | 1 : 1          | 10      | Intra                         | ch, mp, v, f      |
|         | Further     | 2–3 weeks | –              | 20      | 4 × Fleb, 1 × Sand, 8 × Intra | –                 |
| 3       | 1           | 2 weeks   | 1 : 8          | 30†     | Octa                          | ch, arth          |
|         | 2           | 4 weeks   | 1 : 8          | 30      | Gam                           | ch, arth, f       |
|         | 3           | 4 weeks   | 1 : 16         | 30      | Gam                           | ap, arth          |
|         | 4           | 10 months | 1 : 32         | 20      | Fleb                          | –                 |
|         | 5–7         | 4 weeks   | 1 : 8          | 30      | 3 × Fleb                      | –                 |
|         | 8–14        | 2 weeks   | –              | 20      | 7 × Intra                     | –                 |
|         | 15–24       | 2 weeks   | 1 : 8          | 20      | 10 × Sand                     | ap                |
|         | 25–27       | 2 weeks   | –              | 20      | 3 × Intra                     | arth              |
| 4       | 1           | 2 weeks   | 1 : 1          | 20†     | Fleb                          | mp                |
|         | 2           | 1 weeks   | –              | 20      | Fleb                          | –                 |
|         | Further     | 4 weeks   | –              | 20      | 17 × Fleb                     | –                 |
| 5       | 1           | 8 years   | 1 : 4          | 10†     | Fleb                          | –                 |
|         | 2           | 1 day     | 1 : 2          | 20      | Fleb                          | –                 |
|         | Further     | 1–3 weeks | –              | 20      | 3 × Fleb, 20 × Intra          | –                 |

Octa = Octagam (IgA < 100 µg/ml); Flebo = Flebogamma (IgA < 50 µg/ml); Gam = Gammagard (IgA 2.2 µg/ml); Sand = Sandoglobulin liquid (IgA < 15 µg/ml); mp = muscle pain, v = vomiting, ch = chill, ap = abdominal pain, arth = arthritis, f = fever pl = plasma. †The first 10 g were infused carefully (4–6 h).

**Table 3.** Immunoglobulin concentration prior to and following treatment with intravenous (i.v.) IgG.

| Patient             | IgG†     | IgM†    | IgA†    |
|---------------------|----------|---------|---------|
| 1                   | 70/493   | 18/97   | < 5/< 5 |
| 2                   | 389/559  | 15/13   | < 5/10  |
| 3                   | 204/1455 | 29/29   | < 5/< 5 |
| 4                   | 108/592  | 13/15   | < 5/< 5 |
| 5                   | < 40/893 | < 3/< 3 | < 5/< 5 |
| Reference intervals | 700–1600 | 40–230  | 70–400  |

†Measured prior to the final administration of i.v. IgG.

in 1 h). IgG concentration increased adequately in all five patients, IgM only in patient 1, and IgA only in patient 2 (Table 3).

From a clinical perspective, all symptoms that were related to immunodeficiency disappeared in patient 1 following a small series of infusions. Interestingly, all symptoms in patients 2, 3 and 4 were observed to be improved post-treatment as opposed to pretreatment although abdominal discomfort, including diarrhoea, ceased following the administration of 'IgA undepleted' preparations. This was repeatedly obvious in patient 3. Her abdominal symptoms became significant only during treatment with 'IgA-depleted' preparations, i.e. Flebogamma or Sandoglobulin liquid. To date, patient 5 still suffers from mild abdominal discomfort, presumably because this patient is still receiving an 'IgA undepleted' preparation. Fear of further anaphylactic episodes is the reason given for the patient's refusal to alter the method of preparation.

## Discussion

The phenomenon of IgA anaphylaxis is well known, but the true pathomechanism of the reaction is still poorly understood. It is unknown what factors stimulate the production of anti-IgA, which anti-IgA type is clinically relevant, whether affected patients would tolerate long-term treatment with i.v. IgG and whether these patients indeed require 'IgA depleted' blood products [1,4,6,10–12].

In this study, we have described our findings in five patients with both CVID and a previous history of IgA anaphylaxis. These results help to provide further insight and understanding of the pathomechanism of IgA anaphylaxis. On admission to hospital, the patients were carefully re-exposed to i.v. IgG until anti-IgA was abolished. Subsequently, all five patients developed a complete tolerance to i.v. IgG preparations. It appears that IgA anaphylaxis is dependent upon the IgA concentration present in the preparation, anti-IgA activity, infusion speed and the interval between each treatment. Interestingly, all shocks observed in our patients (Table 1) were provoked by the standard administration of IgA undepleted i.v. IgG preparations. In contrast, the careful administration of IgA depleted preparations resulted in either a delayed and relatively mild reaction or the

absence of a reaction (Table 2). This finding is supported by previous studies using IgA depleted preparations [6,13]. In agreement with previous studies [10], the titre of anti-IgA seems to play a key role in IgA anaphylaxis. Based on our findings, patients with weak anti-IgA appear to develop tolerance much easier than patients with strong anti-IgA titres (Table 2). This may explain the impact of infusion rate (speed) on the reaction, as has been discussed in previous studies [14–16].

The phenomenon of tolerance induction and reduction of anti-IgA activity has been observed previously in few patients treated with preparations containing significant amounts of IgA [17]. The most probable explanation for the elimination of IgA activity is that the infused residual IgA molecules in i.v. IgG preparations block anti-IgA, and the high-dose i.v. IgG inhibits anti-IgA production. It has been demonstrated previously that infused IgA molecules form *in vivo* complexes with anti-IgA [17]. Anti-IgA activity is then diminished completely following treatment with IgG containing IgA. The question as to why the concentration of immune complexes does not increase significantly in the circulation of the remaining four patients and does not result in the development of immunocomplex diseases (vasculitis) is obscure. A possible explanation for this phenomenon might be that the concentration of the formed complexes is too low to result in the development of clinically relevant symptoms.

The impact of high-dose i.v. IgG on anti-IgA production is an attractive prospect, as high-dose i.v. IgG appears to inhibit the production of antibodies both *in vivo* and *in vitro* [18–20]. However, further studies are required in order to draw a final conclusion.

Of further interest is the observation that anti-IgA does not seem to result from allogenic stimulation in almost all cases. In our experience, anti-IgA was not developed following long-term treatment with i.v. IgG in a single case with CVID. In addition, anti-IgA appears not only to be boosted by IgA, but its activity is decreased or even eliminated following IgA administration. The only exception might be as a result of IgE anti-IgA that has been described in isolated cases [4]. The possibility of controlling such patients with IgA containing i.v. IgG preparations remains unclear.

Although none of the patients described in this study, who developed tolerance to IgA, received other blood products containing IgA, i.e. human plasma or platelet concentrates, we believe that these patients will tolerate blood transfusion of any kind. However, further studies are required in order to provide a definitive answer to this question.

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