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# Immunoglobulin Prophylaxis in Patients with Antibody Deficiency Syndromes and Anti-IgA Antibodies

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Sera from three hundred five patients with immunoglobulin deficiencies were analyzed for the presence of anti-IgA antibodies by using indirect agglutination and enzyme-linked immunosorbent assay (ELISA). Anti-IgA antibodies were observed in 15 of 68 (22%) patients with hypogammaglobulinemia and 53 of 185 (29%) patients with selective IgA deficiency, both groups having serum IgA <0.05 g/liter. The highest frequency, 6 of 10 or 60%, was noted for patients with a combined IgA–IgG2 deficiency. No anti-IgA antibodies were detected in 25 patients with serum IgA between 0.05 and 0.27 g/liter and normal amounts of serum IgM and IgG or in 17 patients with hypogammaglobulinemia who had serum IgA of 0.05–0.7 g/liter. The anti-IgA antibodies were primarily of the IgG class, but IgD and IgM anti-IgA were occasionally found. IgE anti-IgA antibodies could not be detected with the presently used technique. The IgG anti-IgA antibodies were mainly of the IgG1 subclass but occasionally also of the subclasses IgG2, IgG3, and IgG4. Of eight patients with anti-IgA antibodies, seven tolerated Ig prophylaxis with a commercial immunoglobulin preparation low in IgA when given either intramuscularly or intravenously. The titers of anti-IgA in the sera of these patients did not rise in relation to the prophylaxis. Only one of the eight patients had a history of previous anaphylactic reactions to IgA-containing blood products. He tolerated six Ig infusions during 5 months with the IgA-depleted preparation without any adverse effects but showed increasing levels of anti-IgA antibodies and ultimately experienced a near-fatal reaction at the seventh infusion.

**KEY WORDS:** Immunodeficiency syndromes; immunoglobulin deficiency; agammaglobulinemia; IgA deficiency; IgG deficiency; immunization; adverse effects of immunoglobulins.

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## INTRODUCTION

Antibodies against IgA were first observed in patients with selective IgA deficiency (1). These antibodies can either be class specific or display subclass- or allotype-restricted specificity (2–4). The class-specific antibodies have been reported to occur in 10 to 44% of IgA-deficient individuals (5–13). Antibodies against IgA occurring in patients with IgA deficiency or hypogammaglobulinemia have been implicated as causing severe adverse reactions following injection or infusion of IgA-containing material such as blood, plasma, or immunoglobulin (Ig) (1, 2, 14–24).

Because of the risk of severe anaphylactic reactions, blood products containing IgA, including most Ig preparations, have been considered contraindicated in patients with anti-IgA antibodies. Plasma from IgA-deficient donors have been used instead of Ig preparations for prophylaxis in patients with hypogammaglobulinemia and anti-IgA antibodies (2, 3, 20).

With a commercial Ig preparation low in IgA it has been possible, however, to keep some patients with anti-IgA antibodies on continuous Ig prophylaxis without major untoward reactions according to preliminary observations (25). This study reports several such patients, with analyses of their anti-



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IgA titers of various Ig classes and subclasses before and after injections and infusions of Ig.

## MATERIALS AND METHODS

### *Patients*

Three hundred five patients with humoral immunodeficiency were investigated. Eighty-five patients with common variable immunodeficiency (CVID) (81 Scandinavian and 4 American) donated sera which were studied for the presence of anti-IgA antibodies. The diagnosis was made according to accepted criteria (26). Ten IgA-deficient patients also had decreased levels of IgG2, from <0.01 to 0.9 g/liter. In addition to the 185 patients with selective IgA deficiency and serum IgA <0.05 g/liter, 25 patients with serum IgA levels of 0.05–0.27 g/liter were also studied.

Thirty-nine patients with hypogammaglobulinemia and two with combined IgA–IgG subclass deficiency received altogether more than 1500 infusions with a commercial intravenous (iv) Ig preparation depleted of IgA. The experience of 1040 of these infusions has been reported as to the characteristics of the Ig preparation and the frequency and nature of the few side effects (27).

Eight patients had anti-IgA antibodies detectable by indirect hemagglutination and IgG subclass-specific enzyme-linked immunosorbent assay (ELISA) (12). Blood samples were obtained before and 2 to 3 weeks after Ig prophylaxis from these seven patients with CVID and one patient with combined IgA–IgG2 deficiency.

### *Ig Preparations*

The Ig mainly used in Sweden for intramuscular use has an IgA content of <20 mg/liter (γ-globulin, 16.5%; KabiVitrum, Stockholm, Sweden). The Ig for iv use always has <20 mg/liter of IgA and most often has <4 mg/liter (Gammonativ, KabiVitrum). It contains 92% 7 S IgG, 6.6% IgG dimers, only traces of IgG polymers, and no detectable IgG fragments (27). The product is stabilized by the addition of 5% albumin and 2.5% glucose. One patient with CVID was also given a pH 4-treated commercial Ig containing IgA at a level of 0.7 g/liter (Sandoglobulin, Sandoz, Basel, Switzerland), and another patient a standard im preparation from an unknown source as well as maternal plasma containing IgA and IgA-deficient plasma from the American Red Cross (Bethesda, MD).

### *Ig Quantifications*

Serum IgA levels were determined by single radial diffusion with a lower limit of detection of <0.02 g/liter (28). Negative samples were analyzed with the enzyme-linked immunosorbent assay (ELISA) with a lower limit of 1 μg/liter. The anti-IgA titers were determined by agglutination of blood group 0 human erythrocytes coated with 1 g/liter of purified human serum IgA by the use of chromium chloride, according to the method of Gold and Fudenberg (29). The ELISA technique used for detection of serum anti-IgA of various Ig classes and IgG subclasses has been described previously (12). Multiwell microculture plates (Nunc, Roskilde, Denmark) were coated with polyclonal human serum IgA purified by initial separation on Sephadex G-200, followed by twofold absorption on protein A–Sepharose (Pharmacia Fine Chemicals, Uppsala, Sweden) and passage over rabbit anti-human IgG (Dako Immunoglobulins, Copenhagen, Denmark) and rabbit anti-human IgM-coupled Sepharose 4B columns. Various purified human IgG myeloma proteins (100 ng/well) in 0.1 ml of 0.05 *M* carbonate/bicarbonate buffer (pH 9.6) were also used for coating by incubation at 37°C for 3 hr, followed by overnight incubation at 4°C. Coated plates could be stored up to 1 month in the cold. After being washed four times in saline (0.154 *M* with 0.05% Tween 20), samples to be tested were added in phosphate-buffered saline (0.010 *M* $PO_4^{3-}$, 0.144 *M* NaCl, pH 7.4). IgM, IgD, and IgE were determined in sera diluted 1:10 and IgG in sera diluted 1:100, using phosphate-buffered saline with 0.05% Tween 20. The plates were incubated at room temperature overnight. After four additional washes, 1:1000 dilutions each of alkaline phosphatase-conjugated anti-human IgG, IgM, or IgD (Dako Immunoglobulins) were added, and the plates were incubated for another 4 hr.

For determination of IgE an (epsilon specific rabbit anti-human IgE, MIAB Antibodies, Uppsala, Sweden) diluted 1:200 was used as the first antibody. As the second reagent one of three different alkaline phosphatase-conjugated anti-rabbit antibodies were used: a goat antibody diluted 1:100 (Sigma Chemical Co., St. Louis, MO), a swine antibody (Dako Immunoglobulins) diluted 1:1000, or a Fab sheep anti-rabbit antibody diluted 1:200

(MIAB Antibodies). After additional washing, substrate disodium *p*-nitrophenyl phosphate, 1 g/liter (Sigma), in 10% diethanolamine buffer was added. Absorbance was measured at 405 nm after 20 min using a Titertek multiscan (Eflab Oy, Helsinki, Finland). Results were regarded as positive if the absorbance was three times the background. As positive controls for the IgE-specific ELISA, serum samples from grass pollen allergic patients were tested on timothy grass pollen extract-coated microplates, kindly provided by Prof. S. G. O. Johansson, Department of Clinical Immunology, Karolinska Hospital, Stockholm, Sweden.

IgG subclass-specific anti-IgA antibodies were measured by using commercially available monoclonal antibodies against the various human IgG subclasses (Seward Laboratories, Birmingham, England). The test samples were incubated overnight with the IgA-coated plates and the plates were washed. After 4 hr of incubation with an appropriate dilution of monoclonal antisubclass reagent at room temperature, the plates were washed again, and a 1:1000 dilution of rabbit anti-mouse Ig (Dako Immunoglobulins) was added. After another 4-hr incubation, the plates were washed, a 1:1000 dilution of an alkaline phosphatase-conjugated goat anti-rabbit Ig (Sigma Chemical Co.) was added, and the plates were incubated overnight and processed as described above. The method employed for the measurement of IgG anti-IgA of the various IgG subclasses can be described as semiquantitative, since comparison with microplates coated with various myeloma proteins may give slightly variable results (30). The concentrations of anti-IgA antibodies were estimated from a standard of four pooled myeloma proteins of the respective IgA subclasses (12, 30). The purified myeloma proteins were obtained from Prof. F. Skvaril, WHO Immunoglobulin Subcommittee, Bern, Switzerland, and Prof. S. G. O. Johansson, Stockholm, Sweden.

## RESULTS

### *The Occurrence of Anti-IgA Antibodies*

Antibodies against IgA were found in 15 of 68 patients with hypogammaglobulinemia and serum IgA <0.05 g/liter (22%), 15 of 185 patients with selective IgA deficiency (29%), and 6 of 10 patients with combined IgA–IgG2 deficiency (60%). None of the 25 patients with serum IgA levels in the range of 0.05–0.27 g/liter or of the 17 patients with CVID and serum IgA between 0.05 and 0.7 g/liter had any detectable anti-IgA (Table I). With the indirect agglutination technique, titers of 1/4–1/8,192 were found in the IgA-deficient patients, with two of them temporarily at 1/65,596. Fourteen patients with hypogammaglobulinemia had titers of 1/128–1/8192, and one up to 1/262,144.

**Table I.** The Presence of Anti-IgA Antibodies Among 85 Patients with CVID, 185 Patients with Selective IgA Deficiency, 10 Patients with Combined IgA–IgG2 Deficiency, and 25 Patients with Decreased Serum IgA

| Antibody deficiency | Serum IgA (g/liter) | No. of patients | Patients with anti-IgA | |
|---|---|---|---|---|
| | | | Number | % |
| CVID | <0.05 | 68 | 15 | 22 |
| CVID | 0.05–0.7 | 17 | 0 | 0 |
| Selective IgA deficiency | <0.05 | 185 | 53 | 29 |
| IgA–IgG2 deficiency | <0.05 | 10 | 6 | 60 |
| Low in IgA | 0.05–0.27 | 25 | 0 | 0 |
| Total | | 305 | 74 | 24 |

### *Ig Classes of Specific Anti-IgA Antibodies*

All samples positive by indirect agglutination contained detectable amounts of IgG anti-IgA by ELISA. Anti-IgA antibodies of the IgM class were found in 3 sera, and of the IgD class in 5 sera of 43, whereas IgE antibodies were not detected (Table II). In the screening method initially used for detection of IgE anti-IgA, alkaline phosphatase-conjugated goat anti-rabbit antibodies were used as the second-step reagent. With the goat antisera 10% false-positive results were observed due to the presence of antibodies to goat immunoglobulins in the positive samples (data not shown). Using swine or sheep anti-rabbit antibodies as second-step reagents, no evidence for the presence of IgE anti-IgA could be obtained.

**Table II.** The Immunoglobulin-Class Distribution of Anti-IgA in 77 Patients with Selective IgA Deficiency[a]

| Class of anti-IgA | No. of patients | |
|---|---|---|
| | With IgG anti-IgA | Without IgG anti-IgA |
| IgD | 3/34 | 0/13 |
| IgM | 5/34 | 0/43 |
| IgG | 34/34 | 0/43 |

[a]Thirty-four patients' sera with and 43 without IgG-class anti-IgA antibodies were investigated for further isotype specificities.

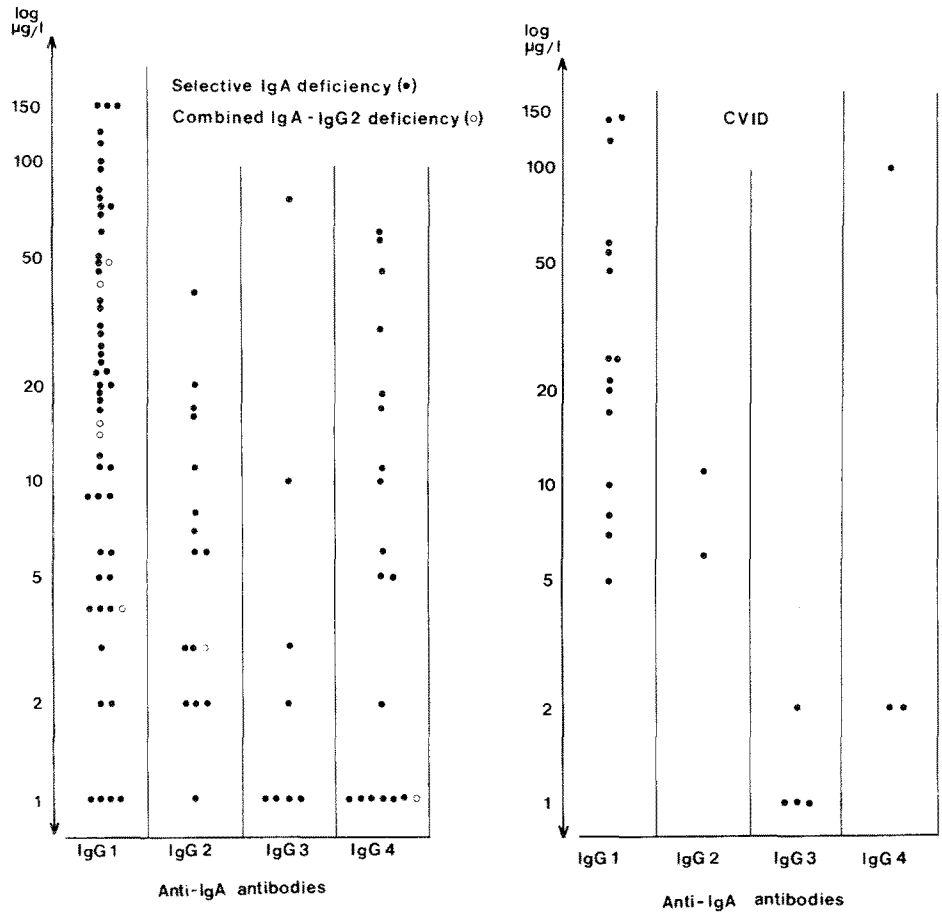


**Fig. 1.** The individual levels of anti-IgA antibodies of the various IgG subclasses in 53 of 185 patients with selective IgA deficiency and 6 of 10 patients with IgA–IgG2 deficiency (left) and 15 of 85 patients with CVID (right).

### *IgG Subclasses of Specific Anti-IgA Antibodies*

The IgG anti-IgA antibodies were consistently of the IgG1 subclass. Nineteen individuals also had anti-IgA antibodies of the IgG2 subclass, and eleven individuals had minute amounts of IgG3 anti-IgA antibodies, but a twelfth patient had as much as 77 µg/liter. Twenty-two patients had IgG4 antibodies (Fig. 1).

### *Ig Prophylaxis in Eight Patients with Anti-IgA Antibodies*

Four patients with CVID and one with IgA-IgG2 deficiency, who all had anti-IgA, were given altogether 145 infusions of the IgA-depleted Ig without any side effects. Two of the three other patients with CVID and anti-IgA had a slight headache and nausea on 24 occasions which, however, did not prevent the completion of the infusions, but the third patient with CVID had a near-fatal reaction.

These eight patients were sampled repeatedly during the course of the Ig prophylaxis and seven showed no increases in their anti-IgA antibodies. One of them had a low titer of IgG1 anti-IgA without knowingly having received Ig or other blood products previously. The anti-IgA titers showed no changes in relation to the minor reactions of the two patients mentioned above during iv Ig prophylaxis.

One of the seven CVID patients had previously had increasing agglutinin titers of anti-IgA and experienced abdominal pain when receiving Ig prophylaxis with a pH 4-treated commercial Ig for iv use containing significant amounts of IgA. She could be given the IgA-depleted iv Ig preparation without any untoward effects and showed no increases in anti-IgA while she was on prophylaxis with this preparation (Fig. 2).

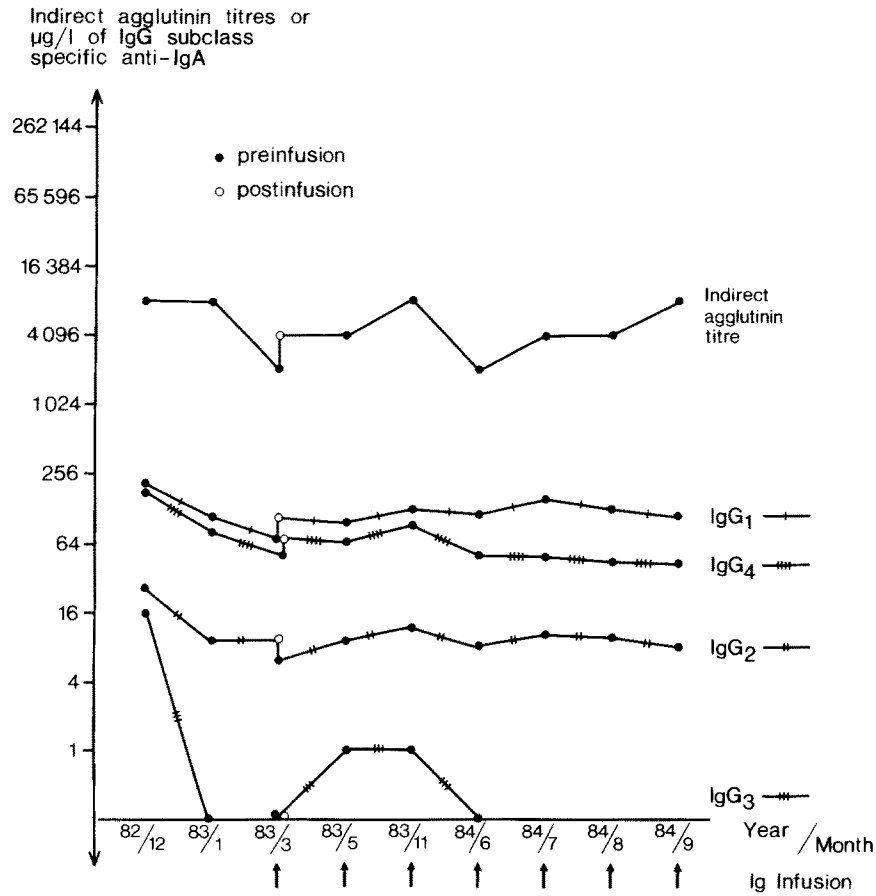


**Fig. 2.** The levels of anti-IgA antibodies determined with indirect agglutination and subclass-specific ELISA for IgG1, IgG2, IgG3, and IgG4, in relation to prophylaxis with IgA-depleted iv Ig. This patient had previously (during 1982) reacted to pH 4-treated iv Ig.

The eighth patient with anti-IgA antibodies had had a near-fatal reaction after receiving an injection of a standard commercial im Ig of unknown source. His prophylaxis was then changed to infusions of maternal plasma containing IgA and he subsequently experienced another almost fatal reaction. He was found to have a high titer of anti-IgA antibodies and was therefore switched to IgA-deficient donor plasma for several years, with minimal untoward reactions except on one occasion in May 1983 with a moderate reaction and on one occasion in July 1983 when he received units containing IgA (Fig. 3). However, in February 1984 he had a non-A, non-B hepatitis after one such infusion and this prophylaxis was discontinued. Six infusions of the IgA-depleted iv Ig were then given uneventfully over a 5-month period. Concomitantly his anti-IgA titers measured by indirect agglutination and the levels of IgG2, IgG3, and IgG4 anti-IgA progressively increased. He then again experienced an anaphylactic reaction in connection with the seventh infusion from the same lot (Fig. 3). There was no marked fall in IgG1 anti-IgA immediately after this reaction, as he had shown after the one in July 1983. The changes in IgG2–4 subclass-specific anti-IgA were also minimal, but his agglutinating titer diminished 128-fold.

## DISCUSSION

The present study demonstrates antibodies against IgA in 29% of IgA-deficient patients, 22% of hypogammaglobulinemic patients, and as many as 60% of patients with combined IgA–IgG2 subclass deficiency. In previous studies the incidence of anti-IgA has varied from 9–46% in IgA deficiency (8, 10, 12, 13) and has been reported in only a few patients with hypogammaglobulinemia (2, 17–20, 22, 31).

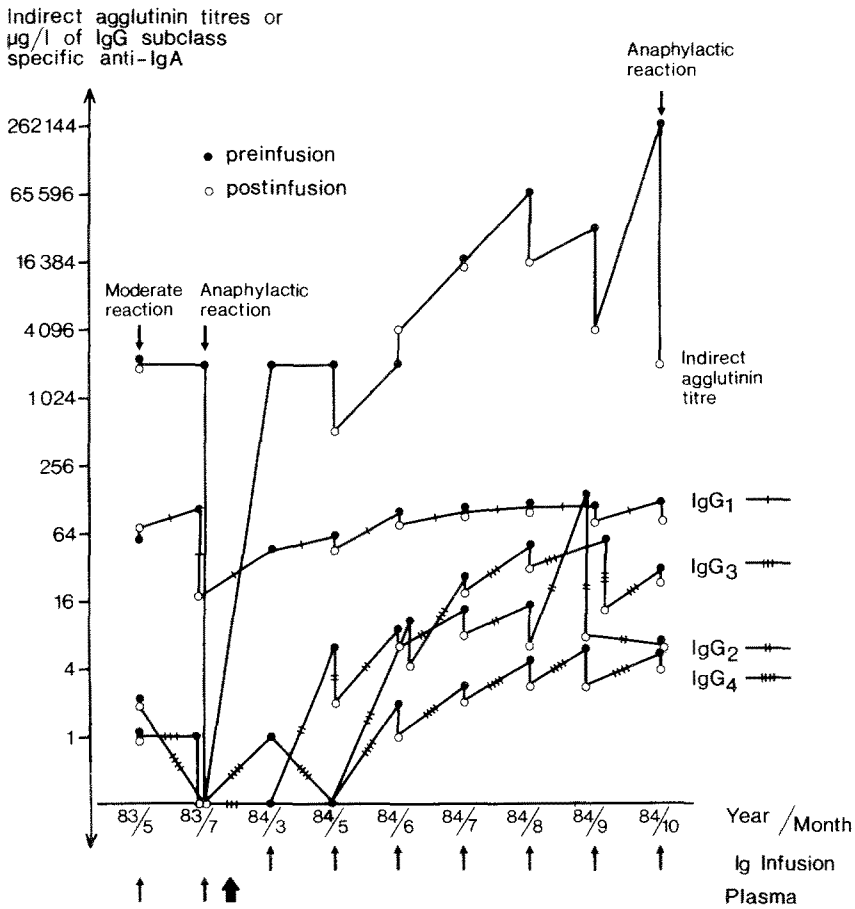


**Fig. 3.** The levels of anti-IgA antibodies determined with indirect agglutination and subclass-specific ELISA for IgG1, IgG2, IgG3, and IgG4, in relation to prophylaxis with plasma or IgA-depleted iv Ig infusions. The untoward reactions are indicated. The infusions are indicated by arrows. The large arrow indicates monthly IgA-free plasma infusions from August 1983 until February 1984.

Of 40,000 im Ig injections in 175 immunodeficient patients in Great Britain, 85 Ig injections caused severe reactions in 32 of the patients (32). Anti-IgA antibodies could have been the cause of a few of the severe reactions. Intravenous Ig prophylaxis previously often gave a higher frequency of adverse reactions (25, 33). Most Ig preparations used today cause less frequently adverse reactions (34). Although this study finds anti-IgA in 22–60% of patients with various antibody deficiency syndromes, reports of severe or fatal reactions due to anti-IgA in immunodeficient patients are rare (2, 17–19, 22–24).

The IgG anti-IgA antibodies were primarily of the IgG1 subclass. Low levels of IgM and IgD anti-IgA antibodies were occasionally observed, while anti-IgA of the IgE class could not be demonstrated with the presently employed technique. With another ELISA technique using different anti-IgE antibodies and an avidin–biotin step, however, the presence of IgE anti-IgA antibodies has been reported in the patient in Fig. 3 as well as in other patients with anti-IgA antibodies and histories of reactions to blood products containing IgA. Thus it is possible that reactions to blood products containing IgA could be due to IgE anti-IgA (24). However, the level of IgE anti-IgA antibodies was reported to be as high as 24 µg/liter and should thus have been possible to detect also in this system, with a minimal detection limit of 1 µg/liter (35). The discrepancies of these two publications are difficult to explain, unless they are due to the methodological differences.

Those patients with a high IgG4 anti-IgA level all had high levels of IgG1 anti-IgA antibodies and high titers of antibodies detected by indirect agglutina-

tion. The patient who reacted with abdominal pains when given the commercial pH 4-treated iv Ig preparation, or other non-IgA-depleted Ig preparations, had IgG1 and a high level of IgG4 anti-IgA antibodies. Shakib and Stanworth proposed in 1979 (36) that IgG4 antibodies caused anaphylactoid reactions in a hemophilia patient given a factor VIII preparation. However, the present study does not permit any conclusions concerning the possible pathogenetic role of anti-IgA antibodies of any of the different IgG subclasses.

The patient reported with anaphylactic reactions was the only one who showed continuously increasing passive hemagglutinin titers and IgGl–IgG4 anti-IgA antibodies during prophylaxis with the IgA-depleted iv Ig preparation. This increase in anti-IgA antibodies may indicate an enhanced risk of anaphylaxis. None of the other seven patients treated with the same Ig preparation had any severe reactions, although they had IgG anti-IgA antibodies. However, none of the seven had ever had previous reactions to IgA except patient 7, who had repeatedly had abdominal pains.

Our findings suggest the importance of measuring the presence of anti-IgA antibodies in all immunodeficient patients receiving Ig products containing IgA. If found to be present, we recommend following the levels before and after Ig prophylaxis to ensure that the supplementation does not cause an increased level of the anti-IgA antibodies. As the presence of anti-IgA antibodies is not rare in immunodeficient patients (Table I), we suggest the use of Ig preparations with a low content of IgA to avoid unnecessary immunization with IgA and to decrease the number and severity of the adverse reactions.

Hepatitis prophylaxis with the IgA-depleted Ig preparation in IgA-deficient individuals with anti-IgA has also been uneventful (Björkander *et al.*, to be published). The information that the presence of IgG anti-IgA in patients with various antibody deficiency syndromes does not necessarily result in adverse reactions to prophylaxis with an Ig preparation low in IgA may be useful.

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