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ORIGINAL ARTICLE

Substitution therapy in immunodeficient patients with anti-IgA antibodies or severe adverse reactions to previous immunoglobulin therapy

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ABSTRACT

Background: Patients with common variable immunodeficiency often suffer from recurrent bacterial infections. Administration of immunoglobulins is a well-established treatment to reduce the frequency and severity of these infections. However, in patients with anti-IgA antibodies or side effects to previous immunoglobulin substitution therapy, administration of immunoglobulins may lead to anaphylactoid reactions.

Objective: To describe the feasibility of immunoglobulin substitution therapy in patients with anti-IgA antibodies or side effects to previous immunoglobulins.

Methods: A retrospective study was conducted in two university hospital outpatient clinics. Fourteen patients with common variable immunodeficiency were found to have circulating anti-IgA antibodies or have experienced severe reactions to previously administered blood products.

Results: In eight out of 15 patients side effects to immunoglobulins and/or blood transfusions had occurred previously. In four patients these reactions were due to anti-IgA antibodies. No side effects were observed when human immunoglobulin 16% was given by subcutaneous infusion. In all patients with anti-IgA antibodies, as well as in those without, subcutaneous immunoglobulins were well tolerated. In some patients antibodies disappeared and therapy could be changed into intravenous immunoglobulin administration.

Conclusions: Patients with serious side effects to previous immunoglobulin therapy and/or blood transfusions can be safely treated with subcutaneous immunoglobulins and, if necessary, with intravenous immunoglobulins at a later point in time.

INTRODUCTION

In patients with primary humoral immunodeficiencies, such as X-linked agammaglobulinaemia and common variable immunodeficiency disease (syn. CVID, late onset hypogammaglobulinaemia), administration of immunoglobulins is a well-established treatment to reduce the frequency and severity of infections.[1] Originally such immunoglobulin substitution was given by the intramuscular route, but in the 1980s the subcutaneous route gained more acceptance because it met with fewer side effects and higher dosages could be given.[2-4]

Nowadays, most patients are treated with intravenous infusion of immunoglobulin preparations.[5] Although this treatment is generally well tolerated, mild side effects such as malaise, nausea and headache occur in approximately 27% of patients and in about 5% of infusions.[5] The more severe side effects, anaphylactoid reactions, are rare with the modern intravenous immunoglobulin preparations; these have been observed especially in patients with antibodies against IgA.[6-10] Such antibodies are especially common in patients with selective IgA deficiency or IgA deficiency in the context of CVID. The antibodies may have arisen after

[#] J.W.M. van der Meer was not involved in the handling and review of this manuscript.

exposure to blood products including immunoglobulins or because of mechanisms such as adsorption of animal IgA (cow's milk) via the intestinal wall.[7,10] Occasionally, severe anaphylactoid reactions occur in patients without circulating antibodies against IgA or other immunoglobulins. Immunoglobulin substitution in patients with anti-IgA antibodies or a history of severe reactions to intravenous immunoglobulin preparations is considered a difficult problem in the management of hypogammaglobulinaemic patient.
Over nearly two decades, we have successfully substituted immunoglobulins in patients with primary humoral immunodeficiencies and circulating anti-IgA antibodies and/or severe adverse reaction to previous immunoglobulin therapy. The present retrospective analysis describes our experiences.

PATIENTS AND METHODS

The clinical and laboratory data of patients with primary humoral deficiencies with circulating anti-IgA antibodies and/or severe reactions to previous blood products were reviewed. Severe reactions consisted of:
- anaphylactoid reactions (angio-oedema, hypotension and tachycardia, with or without wheezing and/or urticarial rash);
- hypotension and tachycardia without angio-oedema;
- syncope.

These reactions had to occur within six hours following the administration of a blood product.
All patients attended outpatient clinics at two university hospitals with extensive experience in the management of adults and adolescents with primary immunodeficiency. In these outpatient clinics patients were, as a rule, tested for antibodies against IgA before immunoglobulin substitution therapy was started if they were either completely IgA deficient or had experienced serious side effects of immunoglobulin preparations or other blood products in the past.

Two preparations were used for immunoglobulin substitution of these patients, normal immunoglobulin 16% for intramuscular administration (Immunoglobulin I.M.) and 6% intravenous immunoglobulin preparation (Immunoglobulin I.V.), both prepared by the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service in Amsterdam, the Netherlands, using cold ethanol (modified Cohn method) fraction II, which is lyophilised to powder. The powder for the intravenous immunoglobulin preparation was dissolved and treated at pH 4 in the presence of mild pepsin proteolysis and then freeze dried. Powder for the intramuscular immunoglobulin preparation was dissolved and formulated in 0.3 mol/l glycin solution. IgA content in Immunoglobulin I.M. and Immunoglobulin I.V. was ±2.3% of total protein (160 g/l) and ±1.9% of total protein (60 g/l), respectively. Immunoglobulin I.M. was licensed for both intramuscular and subcutaneous administration.

As patients were studied in two hospitals and over an extended period of time, serum IgA was measured by several methods: Elisa, RIA, latex-enhanced nephelometry and Ouchterlony (electrophoresis).[11] The sensitivity of Elisa, latex-enhanced nephelometry and RIA are identical. Serum IgG was measured by nephelometry. Anti-IgA antibodies were measured by passive haemagglutination.[11]

RESULTS

The records of 15 patients (7 males, 8 females) were studied. All patients were classified as having CVID with IgA deficiency (serum IgA <0.001 g/l) (*table 1*). The median age was 48 years (range 26-75 years). Eight patients (#1-8) had experienced severe side effects, such as anaphylactoid reactions, after immunoglobulin therapy and/or blood transfusion.
In four of them (#5-8), anaphylactic reactions were most likely due to circulating anti-IgA antibodies. At the time of the reactions, circulating anti-IgA antibodies were measured in the serum of patients 5, 6 and 8. Patient 7 tested positive for anti-IgA antibodies ten years after the anaphylactic reaction.
In patients 5 and 6, intramuscular immunoglobulin 16% therapy had been discontinued because of the side effects. Despite antibiotic therapy recurrent infections kept occurring, which meant that other ways of substitution had to be considered, i.e., a switch to subcutaneous immunoglobulin administration. Although circulating anti-IgA antibodies in these patients remained present, further adverse reactions did not occur.
Subcutaneous immunoglobulin was administered to patient 7 more than 20 years after a severe anaphylactic reaction caused by blood transfusion. During therapy circulating anti-IgA antibodies disappeared and four years later treatment was changed into intravenous immunoglobulin infusion without any adverse reaction.
The adverse reactions in patients 1 to 4 could not be attributed to measurable anti-IgA antibodies.
Patient 2 was treated with intramuscular immunoglobulin injections for a period of three years before severe anaphylactoid reactions occurred. Because no anti-IgG, -IgM, -IgA or -IgE were detected in his serum, it was suggested that these reactions were caused by aggregates in the normal immunoglobulin 16% preparation, which accidentally entered the bloodstream during the intramuscular injections. Transfusion of plasma also caused anaphylactoid reactions in this patient, even when blood

Table 1
Characteristics of patients challenged with s.c. immunoglobulins

PATIENT	GENDER	ANAPHYLACTOID REACTION (CAUSATIVE PRODUCT)	ANTI-IGA	CURRENT TREATMENT	FOLLOW-UP (YEARS)	DISAPPEARANCE OF ANTI-IGA
1	F	+ (imIg)	No	IvIg	7	n.a.
2	M	+ (imIg; plasma)	No	IvIg	11	n.a.
3	M	+ (ivIg)	No	IvIg	4	n.a.
4	F	+ (plasma; ivIg)	No	IvIg	4	n.a.
5	M	+ (imIg)	Yes	ScIg	9	No
6	M	+ (imIg)	Yes	ScIg	7	No
7	F	+ (blood transfusion)	Yes	IvIg	5	Yes
8	F	+ (ivIg)	Yes	ScIg	2	Yes
9	M	-	Yes	IvIg	8	Yes
10	M	-	Yes	IvIg	12	Yes
11	F	-	Yes	IvIg	6	Yes
12	F	-	Yes	IvIg	12	Yes
13	F	-	Yes	ScIg	4	Yes
14	F	-	Yes	None	10	No
15	M	-	Yes	ScIg	11	No

imIg = intramuscular immunoglobulin treatment, scIg = subcutaneous immunoglobulin treatment, ivIg = intravenous immunoglobulin treatment, n.a. = not applicable.

group compatible plasma and premedication with anti-histaminic drugs were administered. When treatment was switched to subcutaneous immunoglobulin, no reactions occurred. After seven years of subcutaneous immunoglobulin, he was switched to intravenous immunoglobulin without side effects.
In patient 1, the second intramuscular immunoglobulin injection had caused an anaphylactic reaction (hypotension, oedema and dizziness). This reaction disappeared after treatment with adrenalin and corticosteroids. As no anti-IgG, -IgE and -IgA antibodies were detected in this patient, it was assumed that this reaction was complement-mediated through aggregates in the product. During therapy with slow subcutaneous immunoglobulin no side effects occurred for several years. Over the years compliance with subcutaneous home treatment waned, resulting in low serum IgG concentrations, and it was felt necessary to try the switch to intravenous immunoglobulin infusions; these were well tolerated.

Because of severe adverse reactions to previous intravenous immunoglobulin therapy, patients 3, 4 and 8 were hospitalised to receive the first immunoglobulin substitution. Treatment consisted initially of subcutaneous immunoglobulin. When after several days no side effects were observed, it was attempted to transfuse low-dose intravenous immunoglobulin. In patients 3 and 4 adverse reactions did not occur, whereas patient 9 developed fever (39°C) after the first intravenous immunoglobulin infusion, but not after subsequent infusions. Besides fever no other reactions occurred.

At the time of diagnosis, circulating anti-IgA antibodies were detected in patients 10 and 11. These antibodies disappeared during subcutaneous immunoglobulin therapy. Recurrent infections and local pain from the subcutaneous infusions necessitated a change to intravenous immunoglobulin in these two patients. Anti-IgA antibodies did not reappear during intravenous immunoglobulin therapy.
In patients 12 and 13 circulating anti-IgA antibodies also disappeared during subcutaneous immunoglobulin, whereas these antibodies remained present in patients 14 and 15 during subcutaneous substitution.

DISCUSSION

The results of this retrospective analysis show that patients with serious side effects to previous immunoglobulin therapy and/or blood transfusions can be safely treated with subcutaneous immunoglobulin even when anti-IgA antibodies are present. If necessary, subcutaneous treatment can be replaced by intravenous immunoglobulins.
When anti-IgA antibodies are present or when serious reactions to immunoglobulins have occurred in the past, our practice to start with subcutaneous immunoglobulin

at a slow infusion rate has proved very successful, since no serious side effects have been encountered. Apparently subcutaneous immunoglobulin can be safely administered to patients with anti-IgA antibodies, despite the presence of approximately 24 mg IgA/g IgG in Immunoglobulin I.M.
In some patients circulating anti-IgA antibodies disappeared during the period of subcutaneous immunoglobulin therapy; when subsequently intravenous immunoglobulin was transfused, anti-IgA antibodies did not reappear. The mechanisms of disappearance of these antibodies have not been elucidated. What is most likely is that the antibodies form complexes with IgA present in trace concentrations in the immunoglobulin preparations. Because of the retrospective nature of our study and the different methods employed for detection of anti-IgA, it was not possible to correlate initial concentrations of anti-IgA with its disappearance.

The feasibility of subcutaneous immunoglobulin substitution, which has also been noted by others,[12] may be explained by the gradual exposure to IgA due to slow resorption of the subcutaneous deposit of immunoglobulin into the circulation. We do in fact know that also IgG appears at a very slow rate after subcutaneous immunoglobulin substitution.[2] The disappearance of anti-IgA antibodies from the circulation could be due to the formation of complexes between IgA in the product and circulating antibodies. These complexes might be removed rather rapidly from the circulation.
Cunningham-Rundles *et al.*[13] reported five patients with immunodeficiency and circulating anti-IgA antibodies who were treated (total of 170 infusions) with IgA-depleted intravenous immunoglobulin (IgA content of 5.4-14.4 mg/g IgG). In these patients only mild reactions occurred. Our results suggest that such an elaborate approach is not necessary.

In the absence of anti-IgA antibodies, adverse reactions to immunoglobulin are probably induced by complement activation. Aggregates in intramuscular immunoglobulin may induce complement activation. Welch and Stiehm suggested such a mechanism in a patient who had had several reactions to intramuscular immunoglobulin.[12] The skin testing for immediate type hypersensitivity to intramuscular immunoglobulin was negative and no antibodies to IgG, IgA or IgE could be measured. In our study complement-mediated reactions probably occurred in patients 1 and 2. In these patients no reactions were observed after the introduction of subcutaneous immunoglobulin. Slow subcutaneous immunoglobulin in the patients presented here and in more than 40 additional patients without a history of previous reactions treated in our hospitals did not result in any systemic reactions.[2,3]
Slow infusion of subcutaneous immunoglobulin probably does not give rise to sizable release of bioactive mediators, such as kinins, complement factors and cytokines.[14,15]
This retrospective analysis suggests induction of tolerance to subcutaneous immunoglobulin, and subsequently, to intravenous immunoglobulins. We are confident that in patients with (persistent) anti-IgA antibodies subcutaneous immunoglobulin can be administered on a weekly basis. In patients with a history of anti-IgA antibodies or who have experienced severe side effects to previous immunoglobulin and in whom subcutaneous immunoglobulin therapy is not satisfactory (e.g. recurrent infections, low serum IgG, painful injections), treatment can be changed into intravenous immunoglobulins. For clinical practice, we propose the following scheme. On days 1 and 2, 5 ml subcutaneous immunoglobulin at an infusion rate of 0.3 - 0.5 ml/h, followed by 10 ml subcutaneous immunoglobulin on the third and fourth day. On days 5, 6 and 7, 3 grams intravenous immunoglobulin can be transfused. During all the infusions, medication such as adrenalin, corticosteroids and antihistaminic drugs should be on stand-by.

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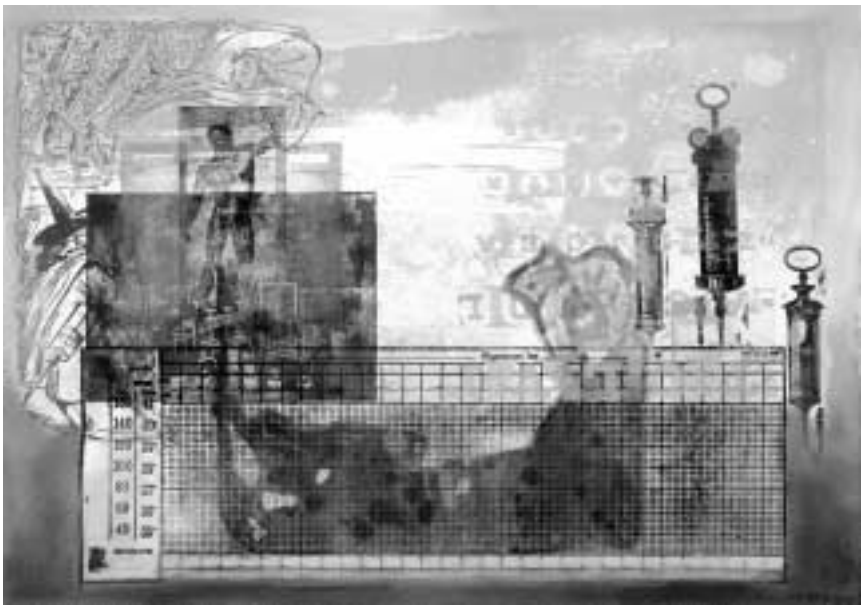
ABOUT THE COVER

'Untitled'

Desire Haverkamp



Desire Haverkamp (1963) studied 'autonomic composition/graphic art' at the Academy of Art in Utrecht. At first she exposed her work in several solo exhibitions. Since 1987, she has been exhibiting mainly in group exhibitions, such as the '7 Sculptors of Utrecht' presented by the 'Love of Art Society' in 2001 and the Graphic shop 'INKT' exhibition in The Hague in 2002. This year her work can be seen at Rhoon Castle in Rhoon and in the 'Oude Haven' museum in Amsterdam. In 1989 she became interested in using medical equipment in her work. This brought her to Adriaan van der Kuip's shop in Utrecht, which specialises in medical instruments. That is where she developed her fascination for all kinds of syringes, pipettes, tubes and box injectors, which were exposed there. Nowadays Desire mostly composes spatial work and graphic art but there will always be a place for a few engravings inspired by medical instruments.

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