Long-Term Treatment and Transfusion of Normal Blood Components Following Tolerance Induction in Patients with Anti-IgA Anaphylactic Reactions

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Keywords

Anti-IgA · IgA anaphylaxis · Anaphylactic reactions · Transfusion reactions · Immune tolerance · IgA deficiency · IVIgG

Summary

Background: In general, patients with significant anti-IgA do not tolerate intravenous (i.v.) administration of normal blood products. Here, we present our experiences in the induction of immune tolerance (IIT) and long-term treatment in a series of such patients affected in such a way. The question whether blood components from IgA-deficient donors are required will be discussed.

Methods: Ten adult patients (4 females and 6 males; age ranging from 36 to 75 years) with anti-IgA were included in this study. All patients required long-term treatment with blood components. One patient had IgA deficiency and paroxysmal nocturnal hemoglobinuria (PNH), and all other patients had common variable immunodeficiency (CVID). The particle gel immunoassay was used for the detection of anti-IgA. Immune tolerance to IgA was induced by controlled subcutaneous (s.c.) and/or i.v. infusions of IgG preparations. **Results:** Prior to IIT, anti-IgA was detectable in plasma samples of all patients and significantly diminished or abolished by controlled s.c. and/or i.v. infusions of IgG. Multiple transfusions with normal blood components could be repeatedly performed with the patient suffering from PNH without any complications. As long as i.v. IgG (IVIgG) infusions were consequently administered as individually required (intervals 2–8 weeks), none of the patients developed reactions during observation (up to 10 years). However, interruption of treatment and re-exposure to IVIgG resulted in adverse reactions. **Conclusion:** Patients with

significant anti-IgA can be safely desensitized and tolerate long-term IgG substitutions independent of the IgA concentration of the used blood component.

Introduction

IgA deficiency alone or in combination with common variable immunodeficiency (CVID) is the most common immune defect in many ethnic populations. At least one third of these patients have circulating antibodies to IgA, and some of these patients are at risk for IgA-mediated anaphylactic reactions following the administration of blood components containing IgA [1–3]. It has been suggested that such reactions can be prevented by providing IgA-deficient blood components collected from IgA-deficient blood donors. Based on this option, registries of such donors have been established in the USA, Canada, and some countries in Europe and Asia [4–7]. However, in practice, the use of these rare products cannot be realized in many instances, particularly in emergencies or where platelets are required [7]. Though platelets can be washed, the recovery and survival of these platelets remain questionable [1, 8].

In addition, there is little information regarding the use of plasma or unwashed blood components from IgA-deficient donors. These products usually contain trace amounts of IgA that may precipitate anaphylaxis in severely affected patients. In fact, IgA-depleted intravenous IgG (IVIgG) preparations, which contain only trace amounts of IgA, have been repeatedly described to cause anaphylaxis [9–11]. This phenomenon is supported by the newly affected patients in the present

Table 1. Relevant data of the new patients on first admission and prior to desensitization

Patient	Age, years	Sex	Diagnosis	Concomitant diseases	Immunglobuline levels, mg/dl			Anti-IgA	History of reactions	
					IgA	IgG	IgM		transfused blood component	anaphylactic reaction
6	57	m	CVID	sarcoidosis	<5	<40	<3	positive	IVIg*	3
7	37	m	CVID		<5	163	<3	positive	–	–
8	56	m	CVID	depression	1	100	53	positive	–	–
9	42	f	CVID	diabetes mellitus	<5	434	31	positive	–	–
10	36	m	PNH	Crohn's disease IgA deficiency	25	1,050	41	positive	3× APC 1× EC 3× WEC	3× APC 1× EC 1× WEC

CVID = Common variable immunodeficiency; PNH = paroxysmal nocturnal hemoglobinuria; APC = apheresis platelet concentrate; EC = erythrocyte concentrate; WEC = washed erythrocyte concentrate.

*Once Octagam® i.v. and twice s.c. preparations

Table 2. IgA and IgG concentrations in used IVIg preparations as indicated by the manufacturer

Preparation (P)	Product	Manufacturer	Solution, %	Concentration	
				IgG, %	IgA, mg/ml
P1	Sandoglobulin liquid®	CSL Behring	12	≥95	<0.015
P2	Privigen®	CSL Behring	10	98	<0.025
P3	Kiovig®	Baxter	10	98	0.03
P4	Ig Vena®	Kedrion	5	≥95	<0.05
P5	Flebogamma®	Grifols	5	≥95	<0.05
P6	Gammanorm®	Bayer	16.5	≥95	<0.0825
P7	Octagam®	Octapharma	5	≥95	<0.1
P8	Intratect®	Biotest	5	>96	<2
P9	Intraglobin F®	Biotest	5	≥95	<2.5
P10	Subcuvia®	CSL Behring	16	≥95	<4.8
P11	Venimmun N®	CSL Behring	5	≥80	<0.6

study. Thus, the only possibility to prevent predictable anaphylactic reactions in such patients is the induction of immune tolerance (IIT) prior to the administration of any blood component containing high or low concentrations of IgA. Here, we describe our experiences in this field during the last decade.

Patients and Methods

A series of 10 patients were included in this study. All patients were referred to treatment in this hospital because of a history and/or a risk of anaphylactic reactions due to transfusion of blood components. The IIT in 5 patients has been described in a previous report [9]. 4/5 new patients (no. 6–9) had CVID. Patient no. 10 had paroxysmal nocturnal hemoglobinuria (PNH) and isolated IgA deficiency (table 1).

The particle gel immunoassay (Biorad, Cressier sur Morat, Switzerland) was used for the detection of anti-IgA [12]. Study approval was obtained from the local ethics committee (EA 1–382–13), and all patients provided written consent.

IVIgG Preparation

Based on our experiences, we initially preferred the use of IVIgG preparations containing the lowest concentrations of IgA. However, the

choice of the used preparation was often dependent on the availability of the product at the local hospital. According to the manufacturers' information, Subcuvia® contains the highest IgA concentration (<4.8 mg/ml) followed by Intraglobin® (<2.5 mg/ml) and Intratect® and (<2 mg/ml) (table 2).

Results

IIT

Dependent on the patients' histories, titer of detectable anti-IgA, availability of the IVIgG preparations, and IgA concentration (table 2), the IIT was achieved by subcutaneous (s.c.) infusions of IgG preparations in 4 patients (no. 6, 7, 9 and 10). Only 1 of these patients (no. 7) developed mild reactions which spontaneously resolved within 1 h following discontinuation of infusion. Subsequently, patient no. 6 preferred s.c. preparations (Subcuvia®), and the remaining patients received IVIgG preparations. Patient no. 8 was extremely anxious and refused any s.c. infusion. In this case, the first IIT was achieved via the administration of isolated drops.

Patient	Day	Anti-IgA	IV IgG	Route	Amount, g	Rate, h	Reactions
6	0	1:64	P1	s.c.	12	3	no
				s.c.	12	3	
	1	1:32	P8	i.v.	2	1	no
				i.v.	8	2	
				i.v.	10	3	
7	3	1:2	P8	i.v.	10	1	no
	4	negative	P6	s.c.	6,4	1	no
7	0	positive	P7	s.c.	20	3	mild*
				s.c.	20	4	
	31	negative	P8	i.v.	40	3	no
8	0	1:32	P5	i.v.	2	1	no ⁺
				i.v.	8	2	
				i.v.	20	4	
9	0	positive	P2	s.c.	20	3	no
				i.v.	20	3	
	28	negative	P2	i.v.	40	3	no
10	0	1:64	P2 + P8	s.c.	80	24	no ⁺⁺
P5 = Flebogamma [®] ; P1 = Sandoglobulin liquid [®] ; P8 = Intratect [®] ; P6 = Gammanorm [®] ; P7 = Octagam [®] ; P2 = Privigen [®] ; i.v. = intravenous; s.c. = subcutaneous. ⁺ Figure 1. ⁺⁺ Figure 2. [*] Discomfort and anxiety.							

Table 3. Anti-IgA in the course of desensitization procedure

Patient	Observation time, months	Interval, weeks	Total, g	Route	Transfused blood components
1	125	4	3,870	i.v.	P7 (×6), P9 (×7), P11 (×2)
		8		i.v.	P8 (×40), P4 (×22), P3 (×44)
2	116	3–4	3,046	i.v.	P5 (×19), P8 (×10)
		2–3		i.v.	P1 (×10), P7 (×27), P2 (×66)
3	123	1–3	4,230	i.v.	P5 (×7), P8 (×12)
		2		s.c.	P1 (×56), P2 (×169)
4	106	4–6	2,860	i.v.	P5 (×3), P8 (×70)
5	26	2–4	1,020	i.v.	P5 (×3), P8 (×44), P7 (×1)
6	73	1–2	3,779	s.c.	P6 (×251)
7	55	4	1,840	i.v.	P8 (×40), P5 (×1), P2 (×1), P3 (×5)
8	42	irregular ⁺	168	i.v.	P2 (×4)
9	32	4–6	960	i.v.	P2 (×4), P8 (×4), P7 (×4), P3 (×4)
		4–6		s.c.	P10 (×13)
10	6	2	280	i.v.	12×EC, P8 (×6), P7 (×5), P2 (×1)
P7 = Octagam [®] ; P9 = Intraglobin [®] ; P11 = Venimmun [®] ; P8 = Intratect [®] ; P4 = IgVena [®] ; P3 = Kiovig [®] ; P5 = Flebogamma [®] ; P1 = Sandoglobulin liquid [®] ; P2 = Privigen [®] ; P6 = Gamma-norm [®] ; P10 = Subcuvia [®] ; EC = erythrocyte concentrate; i.v. = intravenous, s.c. = subcutaneous. ⁺ Patient did not consult clinic regularly.					

Table 4. Long-term follow-up of patients requiring continuous treatment with immunoglobulins and/or other blood components

After roughly 1 h, the rate was gradually increased to 20 g / 4 h without complication (table 3). All available preparations were then infused at the usual rate (roughly 10 g/h) independent of the IgA concentration (tables 3 and 4).

Patient 10 was primarily suffering from anemia and thrombocytopenia due to PNH despite treatment with eculizumab (anti-C5). The patient's anemia could not be compensated

during the last 3 years due to IgA anaphylactic reactions (table 2). In order to induce immune tolerance in this patient, we commenced with a very slow infusion rate for the IgG preparations via s.c. administration (table 3). When anti-IgA significantly diminished (1:64 vs. 1:2), the infusions were continued i.v.

Table 5. Adverse events observed during long-term replacement therapy

AE	Interval to last infusion, days	Anti-IgA	Adverse events		Treatment of side effects	Patient	IV IgG	Further management
			during infusion	post infusion				
1	56	negative		chills, discomfort	non-specific	2	P5	re-exposure i.v. after regular interval
2	49	negative		chills	non-specific	2	P8	re-exposure i.v. after regular interval
3	28	n.t.		chills, headache, articular pain	non-specific	2	P7	re-exposure i.v. after regular interval
4	57	n.t.		chills	non-specific	2	P7	re-exposure i.v. after regular interval
5	51	negative	chills		IVIg discontinued i.v. fluids	2	P2	re-exposure i.v. after regular interval
6	112	n.t.	chills		IVIg discontinued corticosteroids	2	P2	re-exposure s.c. the next day
7	14	1:8		muscular pain	H2 blocker non-specific	3	P1	re-exposure s.c. after regular interval
8	14	1:2		pruritus, articular pain, lymph nodes swelling	non-specific	3	P1	re-exposure s.c. after regular interval
9	41	n.t.	chills		IVIg discontinued	7	P8	re-exposure i.v. the next day
10	115	negative	chills		IVIg discontinued	7	P8	re-exposure i.v. after regular interval
11	35	n.t.	chills		IVIg discontinued	7	P8	re-exposure i.v. after 1h
12	169	positive	skin flushing, sweating		IVIg discontinued H2 blocker	8	P2	re-exposure i.v. immediately
13	253	n.t.	dyspnoe		IVIg discontinued H2 blocker	8	P2	re-exposure s.c. immediately
14	42	n.t.	chills, lumbar pain		IVIg discontinued corticosteroids H2 blocker	9	P8	re-exposure i.v. after regular interval

P5 = Flebogamma[®]; P8 = Intratect[®]; P7 = Octagam[®]; P2 = Privigen[®]; P1 = Sandoglobulin liquid[®]; n.t. = not tested. Pred = Prednisolone. s.c. = subcutaneous.

Long-Term Treatment and Side Effects

Patients were treated over long period of time (6–120 months). Patients 1, 4, 5, 6 and 10 tolerated all of the administered IVIgG or s.c. IgG preparations with no side effects (table 4). The remaining patients (no. 2, 3, 7–9) developed adverse effects only when treatment was discontinued for a period of time longer than usually scheduled for each patient (table 5). The reactions were mild or moderate but some patients required treatment with corticosteroids (total dose of 100–250 mg) and/or anti-histamine H2 blockers (Dimetrinden, Fenistil[®]). In 3 cases, the infusions could be recommenced approximately 1 h later, when the patient's condition returned to normal. In two cases (no. 2 and 7), the affected patients received their infusion on the following day.

The clinical course in patients 8 and 10 is rather interesting. Patient no. 8 repeatedly disrupted treatment and has been desensitized on three occasions (fig. 1). Although the patient tolerated treatment following IIT, he continuously refuses treatment.

Patient no. 10 did not only tolerate IVIgG infusions but also unwashed red blood cell concentrates. Most importantly, boosting of anti-IgA did not occur in a single patient. Anti-IgA remained undetectable as long as treatment was not interrupted for a long time, and reappeared after discontinuation of treatment without any significant increase of titer, i.e. in patients no. 8 and 10 (fig. 1 and 2).

Fig. 1. Repeated desensitization and treatment of patient no. 8 who interrupted treatment after suffering adverse reactions. Following re-administration of IVIgG, he developed further two adverse reactions with anti-IgA being strongly positive (4+).

Discussion

During the last two decades, a huge effort has been spent in preventing anaphylactic reactions due to transfusion of blood components in patients with significant anti-IgA. Roughly all available IVIgG preparations are IgA-depleted [13, 14], and several preparations are available for s.c. use to minimize adverse reactions [15, 16].

In addition, many registries of blood donors with IgA deficiency have been established in different countries [4–6]. Nevertheless, anaphylactic reactions due to anti-IgA cannot invariably be prevented. Though rare, they still occur in undiagnosed patients and, less commonly, in diagnosed patients. We and others have demonstrated that patients with history of anaphylactic reactions may tolerate slow and controlled infusions of IgA-depleted IVIgG preparations. However, some patients may initially develop mild or moderate symptoms including muscle pain, chills, rigors, abdominal pain, fever, arthritis, and vomiting [9, 17].

Although the reactions appear to be dependent on the infused rate of IgA and anti-IgA concentration in recipients [9, 17, 18], trace amounts of IgA may cause severe reactions [9, 11]. Thus, affected patients may not tolerate blood components collected from IgA-deficient blood donors as has theoretically been suggested. Ultimately, these products invariably contain trace amounts of IgA that may exceed those in some IVIgG preparations. We are not aware of a single study where blood components from IgA-deficient donors were directly infused in patients with history of IgA anaphylaxis. In one

study, 3 patients undergoing liver transplantation received washed RBCs, washed platelets, and plasma from IgA-deficient donors without complications. However, none of these patients had experienced a true IgA-anaphylactic reaction [19]. In addition, all 3 patients appear to have been transfused with washed blood components prior to the administration of plasma from IgA-deficient donors. Since the latter products may still contain trace amounts of IgA, it cannot be excluded that the described antibodies were either insignificant or that they may have been blocked via the administration of the washed components which contain trace amounts of IgA. A similar transfusion procedure has been reported in a patient with multiple myeloma. This patient had no history of IgA-anaphylactic reactions, and received washed blood components and premedication with acetaminophen, diphenhydramine, and hydrocortisone [20]. Thus, it cannot be excluded that patients with significant anti-IgA may, indeed, develop anaphylactic reactions if they receive such products. An additional point is that these blood products are rare and cannot be supplied under many instances [7]. The latter study did not find a necessity to transfuse RBCs collected from IgA-deficient donors and recommends, if the indication is urgent and unequivocal, to transfuse normal blood components in a well-monitored hospital setting [7]. Based on our own experience, we agree to this option if these products are diluted and, at least initially, transfused at a very slow rate. The tolerance may be explained by a subclinical blockage of anti-IgA.

In the present study, we have demonstrated the induction of immune tolerance IIT to IgA and long-term treatment not

Fig. 2. Desensitization and treatment of patient no. 10 with IVIgG preparations. Due the patient's history with repeated anaphylactic reactions and relatively high titer of anti-IgA, the IVIgG preparations were given by s.c. route. When anti-IgA became largely blocked (titer 1:4) IgG was given by i.v. route without reaction. Subsequently he was repeatedly treated with IVIgG at normal rate (10 g/h), and with unwashed red blood cell concentrates (EC).

only in patients requiring IVIgG but also in a patient requiring repeated blood transfusions. This has been achieved by s.c. administration of IVIgG preparations. Subsequently, all available IVIgG preparations could be normally infused without any complications. We prefer the use of IVIgG preparations to s.c. Ig (SCIG), because we do not find it necessary to use pumps for s.c. administration. Gravity alone makes it possible to do so without any additional help. The fairly large volume is in practice irrelevant. This view is supported by a previous large medical record review demonstrating that the s.c. rapid push can be performed safely and quickly with a high degree of acceptance [16]. Based on our experience, the infusion can be placed on the lateral abdomen, and diffusion can be accelerated using hand massage.

Most importantly, patient 10 could also be transfused with normal blood components (fig. 2). A similar observation has been described in a patient in whom desensitization was achieved by using diluted IVIgG preparations [22]. The patient was subsequently transfused with normal components without complications. If immune tolerance can be easily achieved in this manner as well as via s.c. IVIgG or SCIG administration, it is reasonable to ask whether the preparation, storage, and usage of blood components from IgA-deficient donors is remains justifiable. These products are rare, cost- and time-consuming, and have no beneficial effect either from a therapeutic or prophylactic effect. The idea that alloimmunization against IgA could be prevented by using these products in patients with IgA deficiency has not yet been proven. None of our IgA-deficient patients have been immunized, and

a boosting effect did not occur in a single patient following the re-administration of IgA-containing blood components. This is also supported by other studies [10, 17, 18], encouraging the idea that these antibodies are the result of an autoimmune rather than alloimmune process [9, 23]. In addition, like other autoantibodies in other diseases, anti-IgA antibodies are often insignificant, and high-dose IgG appears to inhibit the production of significant antibodies [9]. Otherwise, the permanent production of immune complexes due to continuous treatment with IgG preparations containing IgA molecules would result in immune complex diseases, such as vasculitis. Similar to a previous finding [16], none of our patients has developed symptoms or abnormal laboratory findings that could be related to any systemic affliction. Based on this observation, the impact of treatment with high-dose IgG appears to simultaneously result from the inhibition of circulating anti-IgA and IgA production [9, 18].

Finally, the impact of IVIgG on anti-IgA may somewhat resemble that observed in autoimmune thrombocytopenia (ITP). The duration of response to IVIgG in ITP is 2–3 weeks. Similarly, anaphylactic reactions occurred if patients discontinued their treatment for a relatively long period of time, which allowed the reactivation of anti-IgA in the circulation (table 3, fig. 1). The reappearance of these antibodies appears to be dependent on the antibody concentration and infused amount of IgA. While patient no. 3 developed a reaction following a 2-week interval, patient no. 2 reacted after 4–5 weeks (table 3). However, several factors, including the isotype and specificity of the causative antibody as well as the route and

rate of IVIgG infusion, may play a contributory role. During observation, none of the remaining patients developed an anaphylactic reaction that may be attributed to anti-IgA.

Further studies addressing the use of blood components from IgA-deficient donors are required before a final conclusion can be drawn.

Disclosure Statement

The authors A. Salama, R. Kardashi, and O. Arbach report that their institute received study fundings from CSL Behring, Octapharma, Biotest, and LFB/France to study the efficacy of 10% IVIgG preparations in patients with ITP.

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