On the dark side of therapies with immunoglobulin concentrates: the adverse events

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INTRODUCTION – THE TINGE OF THE DARK SIDE OF THERAPIES WITH IMMUNOGLOBULIN CONCENTRATES

Since the initial clinical use of immunoglobulin G (IgG) concentrates of human origin, transmission of pathogens and non-infectious adverse events (AEs) were reported (1–7). Before the mid 90s, transmission of pathogens depended on the pool size and the fractionation methods used, particularly the polishing steps of an IgG concentrate (8). Mode of fractionation, i.e., cold-ethanol or ion-exchange chromatography, contaminants, route of application, i.e., intra muscular (IMIG), intravenous (IVIG), or subcutaneous (SCIG), the rate of increase of the exogenous IgG in the circulation of the recipient over time and, last but not least an eventually existing risk factor from patients’ side (Figure 1) as well as incorrect handling of the concentrate are factors having a role in inducing non-infectious AEs related to administration of IgG concentrates (Table 1). IgG concentrates represent a defined part of the adaptive immune system, are isolated from pooled human plasma of at least 1000 donors, which contribute to the repertoire diversity in the final product. Therapies with IgG concentrates manufactured according to regulators requirements are acknowledged to be safe in general. This does not exclude the occurrence of AEs which in their majority are rare and clinically mild to moderate. Below, we like to give a few insights into various aspects and possible mechanisms of AEs.

PATHOGEN SAFETY OF IgG CONCENTRATES – HOW TO EXCLUDE THE MENACES FROM A DARK AND FRIGHTENING ENVIRONMENT

Manufacturing of modern IgG concentrates has to occur in a regulatory framework and the quality standards implemented by the plasma fractionating industry (Figure 2). The cornerstone of the regulatory framework is current good manufacturing practice (cGMP). A pillar of pathogen safety is the validation of
virus inactivation and virus elimination methods by validating an already performed step of the fractionation process or by introduction of dedicated steps (Figure 3). A hallmark of virus elimination introduced in the late 90s in Berne by the team of Christoph Kempf is the large-scale virus filtration technique (formerly also termed “nanofiltration”) (8). Meanwhile, virus filtration became a versatile tool to eliminate a variety of pathogens, the suspected agent of variant Creutzfeldt-Jakob disease included. Thanks to the tightly implemented regulatory framework, pathogen safety of plasma products is at a level never reached before. This is well supported by the fact of reports missing in the last decade of transmission by IgG concentrates upon infusion/injection inevitably react with occasional pathogens, toxins, or superantigens and concomitantly infusion/injection also results in recognition of a wide array of tissue antigens and V-regions of the recipient’s immune system. Reactions with soluble or membrane-bound forms of cell surface molecules having immunological importance, the last described being the Fc receptors CD16 and CD32 (14). Antibodies reacting with docking structures for viruses or bacteria can have additional first-line defense potential (15). These populations of NABs were described having a peripheral immune network homeostatic and anti-inflammatory function (16, 17). Although the primordial humoral proteins comprising the complement and lectin-like proteins in the plasma play a definite role, another population of self-reactive NABs reacting with, e.g., epitopes conserved over the evolution apparently has tissue homeostatic function and might support the efficient removal of roughly 10^{12} altered/senescent cells of the body per day (for references see below). The signal for research on NABs in IVIG was the description of IgG autoantibody-mediated immune thrombocytopenia (ITP) being corrected by infusion of a polyclonal, polyspecific IgG concentrate (18, 19). This research has expanded ever since.

The populations of immune antibodies and NABs in IgG concentrates upon infusion/injection inevitably react with occasional pathogens, toxins, or superantigens and concomitantly infusion/injection also results in recognition of a wide array of tissue antigens and V-regions of the recipient’s immune system. Reactions with tissue antigens and V-regions are conveyed by the self-reactive antibodies of the many donors in the IgG concentrate. Vice versa, the recipient’s immune system reacts with the infused IgG. A bewildering wide range of possible reactions can occur which primarily are dependent on the immune status of the recipient at the time of therapy and to a smaller part on the IgG concentrate(s).
### Table 1 | The tinge of the dark.

| Symptoms and signs | Frequency | IRR or total dose | PRR System Class, severity, and duration | Part of the product likely being involved in AEs |
|--------------------|-----------|------------------|-----------------------------------------|-----------------------------------------------|
| **Fatigue**        | Common (SCIG as well) | No               | Constitutional or systemic (generalized) | Immediate, mild, transient                    |
| **Malaise**        | Common    | No               | Constitutional or systemic (generalized) | Immediate, mild, transient                    |
| **Fever**          | Common    | Yes              | Constitutional or systemic (generalized) | Immediate, mild, transient                    |
| **Flushing**       | Common    | Yes              | Constitutional or systemic (generalized) | Immediate, mild, transient                    |
| **Chills**         | Common    | Yes              | Constitutional or systemic (generalized) | Immediate, mild, transient                    |
| **Anorexia**       | Common    | No               | Constitutional or systemic (generalized) | Immediate, mild, transient                    |
| **Myalgia**        | Common    | Yes              | Constitutional or systemic (generalized) | Immediate, mild, transient                    |
| **Arthralgia**     | Common    | Yes              | Constitutional or systemic (generalized) | Immediate, mild, transient                    |
| **Joint swelling** | Common    | Yes              | Constitutional or systemic (generalized) | Mild, transient                               |
| **“Flu-like” symptoms** | Common | Yes | Constitutional or systemic (generalized) | Immediate, mild, transient | Increase in A (dimers) |
| **Anaphylactoid symptoms** | Rare | Complement activation | Constitutional or systemic (generalized) | Late, severe, hopefully transient (ICU) | I: IgA, very rare immune complexes |
| **Headache**       | Common    | Yes              | Neurologic                              | Immediate, mild, transient                    |
| **Migraine**       | Common    | Yes              | Neurologic                              | Transient                                     |
| **Dizziness**      | Common    | Yes              | Neurologic                              | Transient                                     |
| **Aseptic meningitis** | Rare   | No               | Neurologic                              | Delayed, moderate, transient                  |
| **Diffuse pain, muscle pain** | Rare | Yes | Neurologic | Transient | Increase in A |
| **Dysesthesia**    | Rare      | Contributes      | Neurologic                              | Increase in A                                 |
| **Weakness**       | Rare      | Contributes      | Neurologic                              | Increase in A                                 |

(Continued)
| Symptoms and signs          | Frequency | IRR or total dose | PRR | System          | Class, severity, and duration | Part of the product likely being involved in AEs |
|----------------------------|-----------|------------------|-----|-----------------|------------------------------|-----------------------------------------------|
| Persistent headache        | Rare      |                  | Yes | Neurologic      | Delayed, moderate            | Increase in A                                 |
| Shortness of breath        | Common    | Dose             | Yes | Respiratory     |                              |                                               |
| Bronchospasm               | Common    |                  | Yes | Respiratory     |                              |                                               |
| Pleural effusion           | Rare      | Dose             | Yes | Respiratory     | Severe, transient            |                                               |
| TRALI                      | Rare      | Dose             | Likely | Respiratory | Late, severe, transient (ICU) |                                               |
| Hypotension                | Common    |                  | Yes | Cardiovascular  | Immediate, mild, transient   |                                               |
| Hypertension               | Common    |                  | Yes | Cardiovascular  | Immediate, mild, transient   |                                               |
| Tachycardia                | Common    |                  | Yes | Cardiovascular  | Immediate, mild, transient   |                                               |
| Chest/back pain            | Common    |                  | Yes | Cardiovascular  | Immediate, mild, transient   |                                               |
| Arrhythmia                 | Rare      | Dose             | Yes | Cardiovascular  | Severe, hopefully transient  |                                               |
| Myocardial infarction      | Rare      | Dose             | Yes | Cardiovascular  | Severe to fatal              | Increase in A                                 |
| Anorexia                   | Common    |                  | Yes | Gastrointestinal| Immediate, mild, transient   |                                               |
| Nausea                     | Common    |                  | Yes | Gastrointestinal| Immediate, mild, transient   |                                               |
| Vomiting                   | Common    |                  | Yes | Gastrointestinal| Immediate, mild, transient   |                                               |
| Cramping                   | Common    |                  | Yes | Gastrointestinal|                             |                                               |
| Diarrhea                   | Common    |                  | Yes | Gastrointestinal|                             |                                               |
| Colitis                    | Rare      |                  | Yes | Gastrointestinal| Late, severe                 |                                               |
| Tubular swelling           | Rare      | Dose             | Yes | Renal           | Severe, reversible; scars might remain | E: sucrose ñ other sugars                     |
| Renal failure              | Rare      |                  | Yes | Renal           | Delayed, severe, ICU         | Increase in A (Complement deposition)         |
| Infusion site pain, swelling, erythema | Common (SCIG more frequent) | | | Cutaneous | Immediate, mild, transient | SCIG: volume |
| Urticaria                  | Common    |                  | Yes | Cutaneous       | Increase in A                |                                               |
| Non-specific macular or maculopapular eruptions/eczema | Common | | Yes | Cutaneous | Increase in A | |
| Pruritus                   | Common    |                  | Yes | Cutaneous       | Increase in A                |                                               |
| Erythema multiforme        | Rare      |                  | Yes | Cutaneous       | Increase in A                |                                               |

(Continued)
### Table 1 | Continued

| Symptoms and signs                                      | Frequency | IRR or total dose | PRR | System          | Class, severity, and duration | Part of the product likely being involved in AEs |
|--------------------------------------------------------|-----------|------------------|-----|-----------------|-------------------------------|---------------------------------------------|
| Cutaneous vasculitis                                   | Rare      | Dose             | Contributes | Cutaneous | Delayed, severe              | Steel, delayed, severe                      |
| Hemolysis (clinically not significant)                 | Common    | Yes              | Contributes | Hematologic | Delayed, moderate, transient | Increase in A                                |
| Acute hemolysis/hemolytic anemia                       | Rare      | Yes              | Yes           | Hematologic | Delayed, severe              | Increase in A                                |
| Thrombotic phenomena (DVT, stroke, cardial infarction) | Rare      | Yes              | Yes           | Hematologic | Severe, ICU                  | Increase in A                                |
| Hyperviscosity                                         | Rare      | Yes              | Contributes | Hematologic | Immediate                   | Increase in A                                |
| Neutropenia                                            | Rare      | Yes              | Hematologic      | Delayed, mild, transient | Increase in A                  | Increase in A                                |
| Blood borne infectious disease                         | Rare      | No               | No             | Microbiological | Late, severe               | I: blood borne viruses, spongiform encephalopathy agent |
| Inappropriate handling before infusion                 | No        | No               |               |                 | Immediate, mild to severe  | A: incomplete dissolution of lyophilized product; denaturation and aggregate formation due to foam |
|                                                        |           |                  |               |                 |                               | E: lyophilized product dissolved to result in too high concentrations; lyophilized product dissolved to result in too high osmolality; low temperature of concentrate at the time of infusion |

The various manifestations of AEs in recipients of polyvalent immunoglobulins. Frequency, severity, duration, timing, possible causes, risk factors.  
A, active ingredient = IgG; I, impurities; E, excipients/stabilizers; “immediate,” immediate reaction – within 6 h from the onset of infusion; “delayed,” delayed reaction – 6 h to 1 week after infusion; “late,” late reaction: weeks to months after infusion; IRR, infusion rate-related; PRR, patient-related risk factors (acute infection at the time of infusion); ICU, intensive care unit; SCIG, IgG concentrate for subcutaneous application.

The therapeutic effect achieved depends on the disease treated, and can depend on the concentration reached locally, i.e., can have agonistic or antagonistic effects (17, 20–22). In summary, it is our opinion that IgG concentrates always provide more or less the same “bouquet” of IgG specificities (similarity); however, it is the recipient’s actual immune condition which decides from which IgG specificities the patient’s derailed immune system is profiting (diversity).

Parameters of IgG-mediated AEs are: (i) the content in the product of biologically highly active likely beneficial ingredients that have to be kept under control (e.g., content of “dimers” devoid of remarkable complement activation in vivo; see below), and the content in unwanted active ingredients that have to be discarded during manufacturing (alloantibodies); (ii) impurities such as IgA (anaphylactoid reaction); (iii) activated coagulation and contact activation factors (thromboembolic events) and; (iv) excipients such as sucrose (osmotic nephrosis). Below, we like to add and contemplate on how fully native IgG molecules not harmed by the manufacturing process might add to AEs. The above mentioned inevitable interaction of the exogenous IgG with the immune system of the recipient and vice versa in its principle might evoke an inflammatory condition. The sum of the potentially beneficial reactions might overshoot and lead to AEs (Figure 1). The principle of induction of mild inflammatory
unnoticed presence of anti-IgA antibodies) and therefore only IgG concentrates with low or absent ACA is accepted by authorities for human use. Below, we present one instructive case of each type of reaction.

**IMMEDIATE ADVERSE EVENTS – THE RAPID ONSET OF DARKNESS**

The first reports of rapid onset AEs concerned either the application of complement-activating fractions in an IgG concentrate or the *in vivo* formation of complement-activating ICs (2–4). A very rare but potentially fatal condition is the formation of IgA/anti-IgA complexes in patients being initiated on replacement therapy and having serum IgG antibodies against infused IgA not recognized before the start of the IVIG infusion (32). Prerequisite for the presence of anti-IgA antibodies is the most common primary immunoglobulin defect, i.e., selective IgA deficiency (sIgAD) or IgAD associated with diminution of other immunoglobulin classes. IgAD is defined by serum levels of <0.05 or <0.07 g/L (depending on laboratories). A marked diminution of serum IgA consistent with IgAD in various ethnic groups is estimated being 1:155 to 1:18,550 (33). The mean frequency in Caucasians is approximately 1:700 (34). Up to 40% of patients with IgAD have been reported having anti-IgA antibodies in the serum with titers ranging between 1:4 and 1:262,144. In approximately 10% of patients with common variable immunodeficiency (CVID), and occasionally in patients with other primary immunodeficiency diseases, measurable anti-IgA can be detected (35, 36). These antibodies are predominantly of the IgG class, but anti-IgA antibodies of other immunoglobulin classes have been described as well (37, 38). The reason for their emergence remains unknown.

Taken the above numbers, the infusion of human-derived products containing IgA resulting in severe anaphylactoid type AEs should be considered. This is not the case (39). Questions about the clinical relevance of above numbers emerge as soon as blood banks (i) estimate the theoretical risk of IgA anaphylactic reactions (32); (ii) assess the relation of severe IgAD with the presence or absence of anti-IgA antibodies (40); (iii) screen donors for very low IgA levels in order to become able to provide blood and plasma-derived products free of IgA and find a considerably lower frequency than expected (41). Alternatively, the test systems may not reliably detect anti-IgA antibodies being as yet insensitive and inaccurate or – at least – do not correspond to the clinically relevant fraction of antibodies. This comes to mind when a more close look to “anti-IgA” gives “unexpected” results, including “anti-IgA” in blood donors with normal serum IgA level or “anti-IgA” that cannot be neutralized with purified IgA (42); or when blood products containing proven anti-IgA do not elicit severe AEs (43).

Among patients on replacement therapy, those with CVID may rarely develop severe immediate AEs (32). The discrepancy between anti-IgA positive patients and frequency of AEs raises the question about the nature of the many reported anti-IgA antibodies and also raises the question about the immunologic condition which allows the formation of anaphylactoid anti-IgA antibodies. There might be some logic in supposing that anaphylactoid anti-IgA cannot evolve at IgA levels otherwise fulfilling the definition of IgAD. Such a condition would constantly generate ICs which in turn could activate complement, react with immune cells, and be deposited in lung and kidney. Indeed, Horn et al. found anti-IgA

**FIGURE 2 | Staying within a regulatory network is mandatory for remaining at the sunny side of the moon.** Handling of blood/plasma products to obtain therapeutic goods has to be performed within a regulatory framework. Manufacturing of stable blood product has to adhere strictly to current good manufacturing practice (cGMP). Application of cGMP starts from the moment of collecting whole blood and isolation of plasma thereof (R = recovered plasma) or the machine-supported collection of plasma (S = source plasma, apheresis plasma). Application of cGMP ends at delivery of blood/plasma products to health care professionals. Not following cGMP can lead to withdrawal of a plasma product from the market from one to the other day.
antibodies in CVID patients missing IgA⁺ B cells and presenting with IgA levels <0.0009 g/L, a level which is more than 50-70-fold lower than the threshold for IgAD (44). However, a possibility for an IgA-mediated anaphylactoid reaction at measurable IgA serum levels might exist. Serum IgA contains approximately 85% subclass 1 of IgA (IgA1) and only 15% subclass 2 of IgA (IgA2). Selective deficiency of IgA2 and—although evidence is lacking—the presence of a highly specific anti-IgA2 antibody theoretically could elicit a severe AE.

The kinetics of anti-IgA after infusion of blood products have been studied in a few cases. In these patients, a fall in anti-IgA titers has been noticed followed by an increase during subsequent weeks or months. This suggests that at appropriate proportions, IgA of the infused material and anti-IgA present in the patients’ serum combine with each other to form ICs. In turn, ICs activate complement that are bound and eliminated by macrophages most likely leading to cytokine release. The increase in anti-IgA titers over time indicates that the infused IgA-containing product has a booster effect (36, 37, 45). Such boosting effect together with the presence of anti-IgA before the application of an IgG concentrate can be taken as the ultimate confirmation of a supposed IgA/anti-IgA reaction. Figure 4 depicts a well-documented case of IgA/anti-IgA reaction in a patient who progressed from slgAD to CVID. The events during the first 12 h at occasion of the first infusion of IVIG were as follows (shadowed area in Figure 4): 2 min after the start of the infusion, having received eight drops of an IgG solution (IgA < 1.2 g/L; 3% solution), she experienced a flush, back pain, rigors, difficulty in breathing, and hypotension. The infusion was immediately stopped. After approximately 1 h, the reaction has weaned, and 2 h later the patient felt well again, and the infusion of total 6 g IgG could be continued without further complications. Although the patient fairly assured having never received any blood or plasma product in the past, the follow-up of her anti-IgA titers from before infusion to 1 year later confirmed a true anaphylactoid reaction mediated by anti-IgA, as the anti-IgA became undetectable immediately after the infusion and showed a boosting phenomenon during the following months. True anaphylactoid reaction was further confirmed by follow-up of total complement hemolytic activity (CH50) on the day of infusion. Interestingly enough, the CH50 value reached its nadir at the end of the infusion when the patient had no complains. Although a single case only, the events during the first infusion call for the following remarks: (i) severe AEs most likely occur at concomitant complement and cell activation with cytokine release; (ii) infusion of minute to low amounts of IVIG hours before the main infusion can “anergize” cells and stop release of pro-inflammatory
American Academy of Allergy, Asthma & Immunology (AAAAI), was obscure. However, it was already known that an AE can be

PRO-INFLAMMATORY CYTOKINES – THE PHLOGISTON OF THE DARK

first infusions, but otherwise IgA is not a major concern (from a clinician has to be aware of the risk, particularly at occasion of New York City, March 1–6, 2002 came to the following conclusion: the Experts” held at occasion of the 58th Annual Meeting of the

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prevalence of this genotype combined with an IgAD or CVID

in the presence of minute amounts of higher oligomers could not be excluded with certainty. Below, we will use the term “dimers” for that fraction of their molecular weight (MW) distribution. The most remarkable differences emerged in the MW range of dimers while the presence of complement-independent cell activation and cytokine release. The TNFα peaks assessed at 2.5 h post initiation of infusions correlated with “dimer” content of the IVIGs and mirrored a clinical score of AEs (49–51).

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A non-complement-mediated anaphylactoid reaction was ascribed to the unforeseen release of elastase and other pro-

inflammatory substances from neutrophils activated by the formation of in vivo IgA/anti-IgA complexes. Complement activation or mast cell-dependent release of vasoactive substances was excluded as pathogenic mechanisms. Although the IgA/anti-IgA complexes usually do not cause clinically relevant neutrophil degranulation within the circulation, the presence of a rare genotype encoding a novel gain-of-function IgG receptor on neutrophils may provoke premature degranulation by these complexes. This phe-

nomenon was only relevant in hypogammaglobulinemic patients in the presence of in vivo IgA/anti-IgA complexes (46). The low prevalence of this genotype combined with an IgAD or CVID may add how to explain the rarity of serious anaphylactoid reactions in newly IVIG-treated patients. Authors share the opinion of Janne Björkander who at occasion of a discussion panel “Dilemmas in Diagnosis and Management of Antibody Deficiencies: Ask the Experts” held at occasion of the 58th Annual Meeting of the American Academy of Allergy, Asthma & Immunology (AAAAI), New York City, March 1–6, 2002 came to the following conclusion: a clinician has to be aware of the risk, particularly at occasion of first infusions, but otherwise IgA is not a major concern (from tape record).

PRO-INFLAMMATORY CYTOKINES – THE PHLOGISTON OF THE DARK

In the early days of Ig-therapy, the nature of the “phlogistic” AEs was obscure. However, it was already known that an AE can be prevented or its evolution halted when the patient receives a low dose of IVIG first or the infusion is stopped early and is continued several hours later. Hours later the infusion can be (re)started at high rates without further problems (Figure 5). One of the authors had a particular opportunity to get an insight into what a “phlogistic reaction” might be. At the occasion of a voluntary infusion of an investigational liquid IVIG, he encountered a severe flu-like AE of more than 12 h duration. Before injection, the investigational liquid preparation had passed all release criteria for human use, including spontaneous complement activation assessed by ACA and was free of prekallikrein activator (PKA). In those days, assays for cytokines in biological samples just began to become available and were included into the parameters assessed in the study. Infu-

FIGURE 4 | An individual’s slithering into the dark. A female patient has been suffering from recurrent airway infections since adolescence, occasionally complicated by pneumonia. At age 34, selective IgA deficiency was diagnosed. Ten years later, she was hospitalized with pneumonia. Within these 10 years, her serum IgG had dropped from 7 to 0.87 g/L (long-dashed line) and IgA was undetectable. The diagnosis was corrected into CVID, and IVIG replacement therapy was initiated (shadowed area). Two minutes after the start of the infusion of a 3% IgG solution (IgA < 1.2 g/L; 3% solution), she experienced a flush, back pain, rigor, difficulty in breathing, and hypotension. The infusion was immediately stopped and later continued without further complications (see text). The confirmation of a true anaphylactoid reaction due to anti-IgA in the serum of the patient was achieved by follow-up of anti-IgA (solid line) and CH50 (short-dashed line).

A series of further experiments with investigational and mar-

keted IVIGs was performed. All IgG concentrates were analyzed for their molecular weight (MW) distribution. The most remarkable differences emerged in the MW range of dimers while the presence of minute amounts of higher oligomers could not be excluded with certainty. Below, we will use the term “dimers” for that fraction of IgG with higher MW. Subsequent findings indicated that levels of “dimers” >12% were responsible for complement-independent cell activation and cytokine release. The TNFα peaks assessed at 2.5 h post initiation of infusions correlated with “dimer” content of the IVIGs and mirrored a clinical score of AEs (49–51).
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IgG concentrate has not been adequately addressed (47, 48, 58–61). Knowledge studies in humans of causative factors/fraction in an

tolerability toward dimers remain scarce and to the best of our

understanding of release of cytokines in humans in association with AEs or

inhibition of extensive "dimerization." In summary, AEs might be associ-

ated with the induction of pro-inflammatory cytokines in absence

of measurable complement activation in vivo where all regulatory

mechanisms and removal processes of a body are at disposition. At reasonable IRs in the open system of the human body, clinically

relevant systemic complement activation apparently needs oligomers formed of three or more IgG molecules.

THE MISSING OXYGEN ON THE DARK SIDE – IMMUNOGLOBULIN-INDUCED HEMOLYSIS

There are multiple reports of Ig-induced hemolytic anemia (HA) in patients receiving high doses of IVIG (60, 74–110) (Table 2; Figure 6; www.adreports.eu). By spontaneous reporting, risk factors recognized for Ig-induced hemolysis include beside high doses (more than 100 g IVIG over 2–4 days), female gender and histo-blood group type A, B, or AB of recipients.
Table 2 | The missing oxygen on the dark side – Ig-induced hemolysis in recipients of polyvalent immunoglobulins.

| Publication          | Number of patients | Blood group | Monthly Ig dosage (mg/kg) | DAT | Eluted antibody | Alloantibody passively administered | Hemoglobin drop (g/L) | Outcome        |
|----------------------|--------------------|-------------|---------------------------|-----|-----------------|-----------------------------------|----------------------|----------------|
| Quinti et al. (110)  | 8                  | A+ (5), A- (1), O+ (2) | Low | IgG (2), IgG and C3d (4) | anti-A (5), anti-C (1), anti-C and anti-D (1) | anti-A, anti-C, anti-D | 6.4, 1.5, 5.1, 1.4, 6.9, 1.1, 1, 1 | Recovery (7), death (1) |
| Desbourouh et al. (76) | 1                  | AB+         | High | IgG and C3 | anti-A and anti-B | anti-A and anti-B and anti-D | 6.5 | Recovery        |
| Mohamed et al. (77)  | 1                  | A+          | High | IgG      | anti-A | nd | 4 | Recovery        |
| Rink et al. (78)     | 3                  | A+ (2)      | High | IgG      | nd | nd | 1.2, 3.8, 4.4 | Recovery        |
| Berard et al. (79)   | 4                  | A+ (2), B+ (1), AB+ (1) | High | IgG      | anti-A (1), anti-B (1), anti-A and anti-B (1) | nd | 2.9, 5.8, 5.8, 3.7 | Recovery        |
| Michelis et al. (60) | 1                  | A+          | High | IgG      | anti-A | nd | 3.5 | Recovery        |
| Pintova et al. (80)  | 2                  | AB+, A+     | Low | IgG      | anti-A | nd | 6.6, 72 | Recovery        |
| Morgan et al. (81)   | 3                  | AB+(1), A- (1), A- (1) | High | IgG | anti-A (2), anti-A and anti-B (1) | anti-A (2), anti-A and anti-B (1) | 4.8, 5.0, 1.8 | Recovery        |
| Welles et al. (82)   | 1                  | nd          | High | IgG      | nd | nd | 4.3 | Death          |
| Canadian Group (83)  | 20                 | A (14), AB (6) | High | IgG | nd | nd | 3.2, 2.8, 5.1, 5.6, 5, 3.5, 4.1, 7, 3.2, 5.6, 3.2, 6.6, 2.9, 3.1, 4, 3.9, 7.8, 4.9, 4.8 | Recovery (10), death (1), unknown (6) |
| Gordon et al. (84)   | 4                  | A+ (3), AB+ (1) | High | IgG | nd | nd | 5.3, 5.5, 4.8, 4.8 | Recovery        |
| Kahlwaji et al. (85) | 16                 | A+ (10), A- (2), B+ (3), AB+ (1) | High | IgG | nd | anti-A, anti-B | 5.3, 4.7, 5.6, 4.9, 5.8, 5.7, 3.3, 2.4, 3.1, 4, 3.6, 2.1, 2.2, 2.8, 5.3, 1.9, 2.6, 3.0 | Recovery        |
| Daw et al. (86)      | 16                 | A+ (7), AB+ (1), AB- (1), B+ (6), O- (1) | High | IgG | anti-A (6), anti-B (4) | anti-A, anti-B | 1.4, 3.6, 4.3, 3.6, 3.2, 3.4, 3, 4, 4.7, 5.1, 5, 2.4, 8, 5.2, 1.3, 3 | nd |
| Yin et al. (87)      | 1                  | AB+         | High | Negative | nd | anti-A and anti-B and anti-D | nd | Recovery        |

(Continued)
| Publication          | Number of patients | Blood group | Monthly Ig dosage (mg/kg) | DAT | Eluted antibody | Alloantibody passively administered | Hemoglobin drop (g/L) | Outcome   |
|----------------------|--------------------|-------------|---------------------------|-----|----------------|-----------------------------------|-----------------------|-----------|
| Coghil et al. (88)   | 1                  | A+          | High                      | IgG | anti-A         | anti-A                            | 4                     | Recovery  |
| Chamouni et al. (90) | 1                  | AB+         | High                      | IgG | nd             | nd                                | 8                     | Recovery  |
| Karacsalan et al. (91)| 1                | nd          | High                      | IgG | nd             | nd                                | 3.9                   | Recovery  |
| Trifa et al. (92)    | 1                  | AB+         | High                      | IgG | anti-A and anti-B | anti-A and anti-B               | 7.8                   | Recovery  |
| Nagakawa et al. (94) | 1                  | A+          | High                      | IgG | nd             | nd                                | 2                     | Recovery  |
| Wilson et al. (95)   | 12                 | A+ (11), O+ (1) | High (10), low (2)   | IgG | anti-A (9), anti-A and anti-D (2), anti-D (1) | nd | 3.7, 3.8, 1, 1.6, 1.9, 2.9, 1.4, 1.9, 3, 1.8, 1 | Recovery  |
| Tamada et al. (97)   | 2                  | nd          | High                      | IgG | anti-A, anti-B | nd                                | nd                    | nd        |
| Thomas et al. (99)   | 1                  | A+          | High                      | IgG | anti-A         | anti-A                            | 6.3                   | Recovery  |
| Comenzo et al. (100) | 1                  | nd          | High                      | IgG | nd             | nd                                | nd                    | Recovery  |
| Okubo et al. (102)   | 1                  | A+          | High                      | IgG | anti-A         | anti-A                            | nd                    | nd        |
| Hillyer et al. (103) | 1                  | AB+         | High                      | IgG | anti-A, anti-B | nd                                | nd                    | Recovery  |
| Nicholls et al. (104) | 2                 | nd          | High                      | IgG | anti-A, anti-A and anti-D | nd | nd                  | Recovery  |
| Kim et al. (105)     | 2                  | B+          | High                      | IgG | anti-B         | nd                                | nd                    | nd        |
| Brox et al. (106)    | 1                  | nd          | High                      | IgG | anti-A         | nd                                | nd                    | nd        |

Clinical and immunological characteristics of patients described in case reports. Numbers in parenthesis indicate the number of patients with the given condition.
A significant proportion of patients receiving IVIG develop a positive direct antiglobulin test (DAT) detectable after 24 h for up to 10 days after the IVIG infusion (109, 110). However, it should be underlined that the DAT positivity due to the factors mentioned above (111, 112) is not sufficient per se to diagnose hemolysis and DAT positivity does not necessarily imply the presence of active hemolysis. DAT-positive mild hemolytic reactions can be easily missed and the true incidence of such reactions is difficult to document without careful clinical and laboratory follow-up.

In the majority of reports on HA, intravascular red blood cell (RBC) destruction via complement activation or extravascular RBC sequestration and removal by the reticulo-endothelial system was proposed to result from IgG alloantibodies with specificity for RBC antigens A, B, D, or C.

Hemolytic anemia induced by high-dose IVIG has an average incidence of 5.8% (85). Low-dose IgG replacement therapy is considered universally as safe, and only few cases of hemolysis following low-dose IVIG or SCIG administration have been described (80, 95, 110). A baseline WBC and RBC count prior to IVIG initiation and a close clinical and laboratory follow-up was suggested as a useful tool for early diagnosis and treatment. A possible work up might be to check hemoglobin (Hb) level prior and 48–78 h after Ig infusion. In case of a drop of Hb, the presence of DAT, an increase in unconjugated bilirubin, lactate dehydrogenase (LDH), and reduced haptoglobin level, followed by a rise in reticulocyte count should be assessed (Figure 7). We systematically reviewed case reports related to IVIG-induced hemolysis from 1987 to 2014 and identified 29 articles containing reports of 109 patients. Baseline characteristics of the patients are shown in Table 2. When available, blood group, DAT, Hb drop, and outcome are indicated. All reports showed positive DAT, except for a case of Yin et al. (87); in this case, DAT was performed 10 days after IVIG administration and the DAT negativity might have been due to a rapid removal of sensitized RBCs.

In the majority of patients, the outcome was positive: 106 out of 109 patients recovered with or without packed RBC transfusions; three patients died after HA, with the hemolytic episode representing a precipitating factor of a severe underlying condition. Elution experiments were performed and the search for blood group antibodies revealed anti-A and anti-B specificity in the majority of cases; anti-D specificity was assessed in four reports, often associated with other specificities (95, 106, 110). A search for other specificities such as anti-band 3 or anti-Gal was not performed. Only one report detected anti-C specificity in three patients; in one of them associated with anti-D irregular antibodies (110).

Although studies were restricted to blood group antibodies, this finding demonstrated that polyvalent IgG preparations might contain clinically significant non-blood group antibodies, which are not part of the lot-release criteria in that their titration is not yet required by the European Pharmacopeia. Antibodies in HA, such as anti-C, may have unexpected hemolytic consequences (113–117). Beside passive transfer of alloantibodies, IgG administration also has been demonstrated to lead to unspecific enhanced erythrocyte sequestration, in particular, in patients with underlying inflammatory disorders (109, 118). In 2009, the Canadian IVIG Hemolysis Pharmacovigilance Group elaborated criteria to define an “IVIG-induced hemolysis” (83). They included a reduction of Hb levels ≥1 g within 10 days after Ig administration, with
appearance of a positive DAT and, at least, two of the following criteria: increase in the reticulocyte count, elevation of LDH and unconjugated bilirubin serum levels, low haptoglobin, hemoglobinuria, hemoglobinemia, presence of significant spherocytosis, in the absence of alternative causes of anemia. The passive transfer of IgG alloantibodies through IgG concentrates is difficult to explain as polyvalent IgG is prepared from plasma of thousands of donors. Since immunization to RBC alloantigens can occur because of past transfusions or pregnancy, the hypothetical numbers of alloimmunized plasma donors should be rather low. Recently, other mechanisms underlying alloimmunization related to molecular mimicry have been demonstrated (119). The mechanism of high-dose IVIG-induced HA is complex and it might vary from patient to patient. IVIG cause hemolysis due to: (i) disease-associated pre-coating of RBCs; (ii) IgG with hemolysis triggered by passive transfer of IgG binding to blood group antigens; (iii) transfer of high levels of alloantibodies to RBC pre-coated at a low level only; or (iv) transfer of clinically tolerable levels of isoagglutinins plus transfer of additional RBC-reacting physiological autoantibodies. Indeed, hemolytic reactions could not be related exclusively to transfer of alloantibodies. Hence, antibodies other than histo-blood group alloantibodies (pre-)coated to RBCs might contribute to hemolysis in IgG recipients need to be identified. In addition, hemolytic episodes may possibly be precipitated by some sort of complexed/denatured IgG that co-purify with other IgG in the product (76, 109, 118, 120). Recently, a two hit mechanism for IVIG-induced hemolysis has been proposed: the passive transfer of alloantibodies through IVIG representing the first hit and the underlying inflammatory state representing the second hit (121). Nowadays all commercial Ig products have to undergo anti-A and anti-B testing and regulatory requirement ask for respective IgG antibody titers of $\leq 1:64$ at 5% solution strength (w/v) (103, 104). Nevertheless, hemolysis might occur even in recipients of IgG products that meet these specifications (76). Consequently, it has been suggested that IgG recipients should be monitored for clinical signs and symptoms of hemolysis (122).

REDUCTION OF HISTO-BLOOD GROUP A AND B ALLOANTIBODIES IN IgG CONCENTRATES RAISES THE CHANCE FOR STAYING ON THE SUNNY SIDE OF THE MOON

With the detection of the immunomodulatory potential of IgG concentrates, their clinical use has continuously increased (123). To cover the need, at a first glance, an increase of the volume of plasma fractionated seems to be the most convenient option. However, this might economically not be viable because fractionation of plasma products is interconnected (124) and before increasing output of one product (e.g., IVIG), the market absorbance of the other products as well (e.g., albumin) must be ascertained. On a longer-run, a more viable option is to improve recovery. Considering recovery, the cold-ethanol fractionation apparently has reached its limits. As of today, four manufactures have invested into a “modern” fractioning technique on the basis of ion-exchange chromatography. Ion-exchange chromatography allows elevated recovery at high purity. As of today, five IVIGs, one SCIG, and one anti-D concentrate are fractionated by ion-exchange chromatography. Pharmacovigilance has shown that all chromatographically fractionated IVIG and SCIG, more or less prominently, show a tendency for elevated frequencies of hemolytic AEs. Anti-A and anti-B alloantibody titers are now lot-release criteria (see above) as they constitute the major risk parameter for hemolytic reactions mediated by IgG concentrates. To overcome the threat of end up on the dark side of the moon, two manufacturers have taken measures to reduce anti-A and anti-B titers in their IgG products. One measure chosen was adsorption of the alloantibodies by affinity chromatography (125). Reported reduction in both alloantibodies was significant and levels were similar to those in cold-ethanol fractionated immunoglobulins (126). The other measure chosen was reduction in anti-A using an automated indirect agglutination test for donor screening and exclusion of high-titer donations (approximately 5.1%) from plasma pooling and fractionation (127). This measure reduced anti-A in the IgG concentrate by one titer step. To ensure staying on the safe and sunny side, the manufacturer has announced the introduction of an alloanti-A and alloanti-B immune-affinity chromatography step into the manufacturing process (128). Preliminary results indicate depletion in anti-A and anti-B by $> 80\%$ in investigational lots. Subsequently, we want to discuss possible consequences of (extensive) removal of antibodies reacting with histo-blood group antigens A and B.

REASONING ABOUT ANTIBODIES REACTING WITH TERMINAL SUGARS OF THE MAJOR HISTO-BLOOD GROUP ANTIGENS A AND B

Three facts have initiated our thinking about possible consequences of removal of histo-blood group A and B reacting
antibodies from IgG concentrates. (I) In collaboration with Hans U. Lutz, formerly Biochemistry ETH Zurich, we have observed the non-intended removal of natural anti-C3 autoantibodies regulating complement activation by large-scale immune-affinity adsorption of IgA from an IgG concentrate (129). Anti-C3 antibodies belong to the family of "NAbS" and have a particular role in homeostasis: they control activation of complement, among others, in the frame of NAb-mediated opsono-phagocytosis of altered or senescent cells, including RBCs (130–132). Thus, the intention to target one particular antibody by affinity chromatography might reduce that antibody specificity but at the same time affect other specificities as well. (II) It should be kept in mind that the blood groups A and B are in fact "histo-blood group" antigens, i.e., they are also found on white blood cells, T lymphocytes, and proteins and also can be found in soluble form (133). Alloantibodies reacting with histo-blood group antigens A and B thus have much broader tissue recognition than RBCs only. In addition, alloanti-A and alloanti-B belong to the population of NAbS recognizing non-self and most likely participate in primary host defense (134). (III) In contrast to cold-ethanol fractionation, where low titers of alloanti-A and alloanti-B are achieved on basis of their isoelectric points (IEPs), the (extensive) immune-affinity removal might affect a much wider IEP range, thereby removing broadly reacting antibodies and impairing some desirable functions of the IgG concentrate. Thus, the struggle for staying on the sunny side of the moon might have consequences for the antibody repertoire in an IgG concentrate.

Antibodies reacting with terminal di-, tri-, and tetrasaccharides belong to the large family of human anti-glycan NAbS. Histo-blood group A and B epitopes in terminal position are tetrasaccharides. Alloantibodies to these tetra-saccharides are found in the plasma of healthy individuals depending on the blood group they have. A considerable body of research into the nature of these NAbS has been performed so far, all using for isolation the corresponding terminal di- or tri-saccharides (135–137). Recently, the repertoire and epitope specificity of such immunoglobulins was addressed in depth by including the tetra-saccharide as well (138, 139). It proved that serum of healthy individuals contain respectable amounts of di- or tri-saccharide-reacting NAbS. These NAbS proved to be pseudo-anti-A and pseudo-anti-B NAbS as they are not reacting with the tetra-saccharide of histo-blood groups A and B. In contrast, alloanti-A and -B antibodies are able to react with tetra-saccharides are reacting with the corresponding terminal di- and tri-saccharides. Reasoning about the biological role of these "high-titer and population conservative" anti-di- and anti-tri-saccharide NAbS and the consequence of their potential removal by immunoaffinity is outlined below.

A population of the anti-glycan NAbS are the anti-αGal NAbS which recognize Galα1-3Gal and Galα1-3(Fucα1-2)Gal epitopes. Anti-αGal NAbS have been described being xenoreactive, recognizing bacterial Galα1-3Gal (140) and having tissue homeostatic function. The daily removal of altered/senescent cells of the body is ~10^12. Removal is mainly mediated by apoptosis (no inflammation, no necrosis). RBCs, when they do not encounter a pathological condition, over their life span of 100–120 days remain intact although they shrink, do not undergo apoptosis but progressively become senescent, mainly due to cumulative oxidative stress. Removal of intact RBCs with a daily turnover of ~2 × 10^11, corresponding to ~20 g cell mass, is effectuated by increased exposure of otherwise cryptic structures such as spectrin, band 3, or αGal epitopes. These exposed structures are recognized by low affinity, high avidity C3-bearing NAbS, which promote the efficient removal of intact senescent RBCs (130, 141, 142). Immunoaffinity adsorption by tri-saccharides columns of di- and tri-saccharide reacting NAbS from IgG concentrates can eliminate anti-histo-blood A and B alloantibodies while it also eliminates αGal and this might have a Janus effect. The face directed to the sun tells that adsorbing αGal NAbS reacting with altered and senescent self on RBC might prevent an increase in the IgG load of RBCs over the threshold level of relevant hemolysis in individuals at risk. The face directed to the dark indicate that adsorption of tissue homeostatic antibodies might deprive an IgG concentrate of potentially beneficial antibodies. Although they are NAbS, tri-saccharide reacting antibodies can be induced by feeding bacteria bearing the corresponding carbohydrate epitopes (134). These inducible NAbS are considered to participate in primary host defense. Other antibodies possibly involved in primary host defense are the anti-αGal NAbS. They show a broad specificity and can react with a number of related αGal-terminated oligosaccharides, including those on bacteria (143). Thus, the immunoadsorption of di-and tri-saccharide reacting NAbS might diminish the potential of an IgG concentrate to mediate primary host defense. Therefore, when choosing affinity resins for immunoadsorption, there might be some aspects worth to consider.

In summary, the principles of avoiding co-fractionation through cold-ethanol fractionation (144) versus immune-affinity removal of histo-blood group alloantibodies can have an impact on the presence of homeostatic and first-line defense antibodies. According to present knowledge, only resins coated with the corresponding tetra-saccharides can ascertain the selective removal of histo-blood group alloantibodies presumably involved in HA. Resins coated with the corresponding di- and tri-saccharides also remove blood group alloantibodies, however not selectively. Such resins in addition might remove a broad range of NAbS present in IgG concentrates at relative high amounts. In the literature, the use of tri-saccharide-coated resin was reported (145–147). We have found no information available in the public domain indicating which type of resin is/will be used for reduction of the histo-blood group alloantibodies in large-scale fractionation of IgG. Furthermore, we suggest that the effect of reduction of anti-A and ant-B reacting antibodies by immune-affinity on the antibody repertoire of IgG concentrates can only be assessed by, e.g., using pathogens/commensals, which share the saccharide epitopes, that have been used to coat the affinity resins or alternatively by exposing senescent RBCs stripped off the IgGs coated in vivo. Finally, techniques are required, which allow detection of low affinity, high avidity NAbS.

**THROMBOSIS – FALLING INTO A DARK LUNAR CRATER**

IVIG administration-related AEs, including thrombosis, have been extensively described (148). Thrombotic AEs are severe AEs and patients with risk factors require a special care. Reported average incidence of IVIG-induced thrombosis ranges from 3 to 13% (149). Recognized risk factors for IVIG-induced thrombosis...
include male gender; age >60; diabetes; renal insufficiency, dyslipidemia; hypertension; immobility; coronary disease; pre-existing vascular disease, family history of early thromboembolic disease; atrial fibrillation, high-dose and high-speed IVIG infusions. IVIG-induced thrombosis is reported both as venous events such as thrombosis stroke, pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial ischemia events such as myocardial infarct and stroke. The mechanisms leading to IVIG-associated thrombosis are still not completely clear; three main mechanisms have been proposed, emphasizing the role of an increased blood viscosity causing a hypercoagulable state (150), the role of anticardiolipin antibodies passively transferred through IVIG (151), and the role of factor Xla or other biologically highly active factors passively transferred via IgG concentrates, such as PKA. Avoiding activated coagulation factors in IgG concentrates starts with appropriate anticoagulation of donated blood/plasma, i.e., careful mixing of anticoagulant and sample over the whole donation process. Alterations in an established manufacturing process neglecting appropriate controls can also lead to increased risk of transmission of activated coagulation factors. High MW proteins passively transferred by IVIG are probably contributing to this phenomenon (152). In patients with other risk factors, such as vascular disease, the increase in blood viscosity can precipitate thromboembolic events. As elderly individuals are prone for such AEs, we like to point to the possibility of elevated altered/senescent self-reacting with infused homeostatic NAbs being a possible factor facilitating thrombotic events as well. A relationship between IVIG administration and cerebral vasospasm has also been suggested by Sztajzel et al. (153); blood viscosity is a determinant for oxygen delivery to the tissues, and changes in viscosity can lead to a reduction in cerebral or myocardial perfusion.

We systematically reviewed case reports related to IVIG-induced thrombosis from 1986 to 2014 (Figure 8). Literature search identified 35 articles containing reports concerning 65 patients (6, 24, 149, 154–183). When data were available, diagnosis, risk factors, the number of IVIG infusion prior to thrombosis event, and outcome have been indicated. Baseline characteristics of the patients are shown in Table 3. High-dose IVIG induced thromboembolic events in 59 patients at low to medium IVIG doses. Marie et al. (163) observed that the frequency and type of arterial events was inversely related to the time elapsed from IVIG infusion; almost 50% (23 versus 21 reports) of arterial ischemic events occurred within 12 h following IVIG, while about 75% of venous thrombosis occurred after more than 24 h. No correlation between number of infusions and occurrence of AE was observed. The main risk factors observed in this review were hypertension (19 cases, 33% of prevalence), previous vascular disease (18%), and dyslipidemia (17%). Average mortality for thrombotic events was 10% (arterial ischemia 9% versus venous thrombosis 11%, PE representing the main venous fatal event). Predicting IVIG-induced thrombosis is difficult. Risk factors should be assessed for each patient including instrumental exams when needed. Doppler ultrasound can be useful as early diagnostic tool for thrombosis or to detect the presence of abnormal blood flow especially after prolonged immobility. IVIG should be administered at low IR to reduce the risk. The administration of antiplatelet or anticoagulant prophylaxis was suggested in patients with several risk factors (162). However, thrombotic events have been reported even after several previous uncomplicated courses of treatment.
Table 3 | Falling into a deep lunar crater – Ig-induced thrombosis in recipients of polyvalent immunoglobulins.

| Publication | Number of patients | Age | Diagnosis | Ig dosage | Predisposing factors | Number of IVIG infusion prior to thrombosis event | Thrombosis (arterial or venous) | Time from the last infusion | Outcome |
|-------------|--------------------|-----|-----------|-----------|----------------------|-----------------------------------------------|-------------------------------|----------------------------|---------|
| Vinod et al. (154) | 1 | >65 | Guillain-Barre | High | | First | Arterial | 72 h | Recovery |
| Sin et al. (157) | 1 | <65 | Solid organ transplantation | High | | First | Arterial | 48 h | Recovery |
| Min et al. (24) | 1 | <65 | CVID | Low (SCIG) | Hypercoagulability (oral contraceptive) | Several | Venous | | nd |
| Rajabally et al. (149) | 5 | <65 (2), >65 (3) | CIDP | High | Diabetes (2), hypertension (2), immobility (4), coronary disease (2), arrhythmia (1) | First (3), several (2) | Arterial (3), venous (2) | 14 days | Recovery (4), death (1) |
| Al-Riyami et al. (156) | 1 | 11 | ITP | High | | Several | Venous | 10 days | Recovery |
| Iroh et al. (155) | 1 | 13 | ITP | High | Estrogen treatment | First | Venous | 12 h | Death |
| Barada et al. (158) | 1 | 11 | XLA | Low | | Several | Venous | nd | nd |
| Lee et al. (159) | 1 | 56 | ITP | High | | First | Venous | 72 h | Recovery |
| White et al. (160) | 1 | 43 | Dermatomyositis | High | | First | Arterial | 2 h | Recovery |
| Feuillet et al. (161) | 1 | 38 | Multiple sclerosis | High | Oral contraceptives | Seventh | Venous | 6 days | Recovery |
| Marie et al. (162) | 2 | 51, 55 | Polymyositis nodosa (1), polymyositis (1) | High | | Third, 15th | Venous (2) | 2 h, 7 days | Recovery |
| Marie et al. (163) | 6 | 76, 49, 63, 45, 64, 64 | AHA (1), polymyositis (5) | High | Hypertension (3), hypercholesterolemia (3) | Second, sixth, several (4) | Venous (3), arterial (3) | 2 days, 6 h (5) | Recovery |
| Geller et al. (165) | 1 | 28 | Streptococcal toxic shock syndrome | High | | First | Venous | 8 days | Recovery |
| Sheehan et al. (167) | 1 | 43 | Pemphigus vulgaris | High | Immobility, hypertension | First | Venous | 16 days | Recovery |
| Hefer et al. (164) | 1 | 85 | ITP | High | Hypertension, chronic myelogenous leukemia | Second | Arterial | 3 h | Recovery |

(Continued)
| Publication                     | Number of patients | Age | Diagnosis                                                                 | Ig dosage | Predisposing factors                                                                 | Number of IVIG infusion prior to thrombosis event | Thrombosis (arterial or venous) | Time from the last infusion | Outcome |
|--------------------------------|--------------------|-----|---------------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------|-----------------------------|----------|
| Feuillet et al. (166)          | 1                  | 38  | Multiple sclerosis                                                        | High      | Oral contraceptives                                                                  | First                                            | Venous                        | nd                          | Recovery |
| Vucic et al. (168)             | 7                  | 57, 69, 75, 81, 79, 62, 80 | CIPD (4), anti-MAG neuropathy (1), multifocal motor neuropathy (1) | High      | Hypertension (3), hypercholesterolemia (3), previous stroke (2), arrhythmia (1)    | Second (1), third (2), several (5)               | Arterial (6), venous (1)      | 1 h (2), 2 days (3), 2 weeks (2) | Recovery (5) |
| Stamboulis et al. (169)        | 1                  | 36  | CIPD                                                                      | High      | Heavy smoker                                                                        | First                                            | Arterial                      | nd                          | Recovery |
| Katz et al. (170)              | 2                  | 67, 65 | *Pemphigus vulgaris, dermatomyositis*                                     | High      | Hypertension                                                                        | Second, first                                   | Arterial (1), venous (1)      | 6 h                        | Recovery |
| Zaidan et al. (171)            | 3                  | 47, 65, 70 | GBS (1), CIDP (2)                                                        | High      | Hypercholesterolaemia (1), diabetes (2)                                            | Third (1), several (2)                           | Arterial (3)                  | 1 h (2), 1 day (1) | Recovery (2) |
| Brown et al. (172)             | 3                  | 70, 91, 42 | CVID                                                                     | Low       | Diabetes (1), myocardial infarction (2)                                            | Arterial (3)                                    | 6 h                          | Recovery |
| Evangelou et al. (173)         | 1                  | 54  | CVID                                                                      | Low       | High platelets count                                                                | Several                                          | Venous                        | 24 h                       | nd       |
| Emerson et al. (174)           | 2                  | 54, 33 | ITP, Evans Syndrome                                                     | High      | Obesity (1)                                                                          | Second                                          | Arterial (2), venous (1)      | 2 h, 2 days                 | Death (1), recovery (1) |
| Alliot et al. (175)            | 1                  | 63  | ITP                                                                       | High      | Hypertension                                                                        | Fifth                                           | Venous                        | 3 days                     | Death    |
| Sherer et al. (176)            | 2                  |     |                                                                            |           |                                                                                    |                                                 | Venous                        |                            |                      |
| Elkayam et al. (177)           | 4                  | 60, 41, 67, 67 | ITP, polymyositis, connective disease, CIDP | High      | Hypercholesterolemia (2), hypertension (2)                                        | several (3), first (1)                          | Arterial                      | 4 days                     | Recovery |
| Go et al. (178)                | 1                  | 52  | ITP                                                                       | High      |                                                                                    | First                                           | Venous                        | 1 day                      | Recovery |
| Turner et al. (179)            | 1                  | 60  | Miller-Fisher syndrome                                                   | High      |                                                                                    | Fifth                                           | Arterial                      | 5 days                     | Recovery |
| Harkness et al. (180)          | 1                  | 40  | CIDP                                                                      | High      | Hypercholesterolemia                                                                 | Arterial and venous                             | 7 days                        | Recovery |

(Continued)
In such cases, patients should be examined for signs and symptoms of thrombosis during each courses of IVIG.

Immunoglobulin G concentrates are widely acknowledged to offer a safe, high-dose, long-term therapy option for a variety of diseases. AEs occur rarely and mainly are mild to moderate. Deviations from this rule of thumb are addressed by authorities and the plasma fractionation industry to achieve corrections. Above, we have reviewed two types of AE which have shown elevated frequency in the near past. We tried to give some insights which might help in reducing frequencies of AEs bed side.

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