Historical Aspects of Polyclonal IgG Preparations

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10.1 Introduction

Today we can choose between several polyclonal IgG products for both replacement and immunomodulation. However, it was a long way to go to reach this stage. In this chapter, we try to illustrate the major stages of IgG product development which began more than 70 years ago.

10.2 Development of Standard IgG

The development of plasma fractionation was a WW II effort with a primary aim to provide human albumin for battlefield injuries. The technique was developed in Boston under the lead of Edwin Joseph Cohn (1892–1953) and was made possible through the strong support of the US Department of Navy, the Office of Scientific Research and Development, and the wartime blood donor program of the American Red Cross (Cohn et al. 1944). Gamma globulin was enriched at high purity in fraction II of the Cohn-Oncley cold ethanol fractionation method (Oncley et al. 1949). This "standard IgG" at increasing amounts became available from 1943 onward, a time point when the fractionation of albumin has been transferred to industry (Armour Pharma at Kankakee, IL, USA). Indeed, between 1944 and 1948, approximately 1 mio doses of "standard IgG" were applied in the USA.

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10.3 The Early Days of Clinical Development of IgG Therapies

From 1941 onward, therapies with protein concentrates from fractioned plasma were developed under contract between the Office of Scientific Research and Development and Boston Harvard University. Charles A. Janeway (1909–1981) was put in charge. At that time, he was running the infectious and immunology laboratory at the Peter Bent Brigham Hospital and was member of the Harvard Medical School Department of Bacteriology and Immunology, and in 1940 he furthermore joined the laboratory of Edwin J. Cohn in the Harvard Medical School Department of Physical Chemistry (Geha 2005; Rosen and Janeway 1994). After initial studies in 1941 in humans with bovine (fatal outcomes) and human serum albumin (successful), in 1943 he turned to study Cohn fraction II (+III), the plasma fraction(s) enriched in IgG. The initial studies largely remained restricted to the prevention or attenuation of viral infections, particularly of measles infections (Ordman et al. 1944). The initial restriction to viral diseases probably was because from the late 1930s onward, the dawn of antibiotic treatment, Janeway built up an outstanding expertise in the treatment of bacterial infections with these emerging new drugs (Smith 1977).

The first human ever receiving an IgG concentrate was Janeway himself—with almost fatal consequences as the lot was contaminated with bacterial toxin (Rosen and Janeway 1994). Aiming for rapid increase of antibodies in the circulation and pursuing the "tradition" set, the "lot-release" for intravenous application of toxin free preparations was a self-infusion to one or the other collaborators of Janeway. Repeated severe and one almost fatal adverse event let Janeway note: "One mystery about normal serum gamma globulin which has defied explanation is its toxicity on intravenous injection. Although reactions have been practically nonexistent on intramuscular injection for measles prophylaxis, intravenous injection of the most highly purified preparations into normals in moderate doses and into patients ill with acute infections in much smaller doses has led to acute vasomotor reactions followed by severe chills and hyperpyrexia. This has occurred so regularly that one wonders whether it has genuine physiologic significance" (cited from Janeway 1948). Therefore, intravenous application of "standard IgG" was given up in favor of the intramuscular route.

10.4 From Intramuscular "Standard IgG" to Intravenous Preparations

Until the early 1950s, two slightly different cold ethanol fractionation methods were established. In the USA the Cohn-Oncley method provided a highly pure "standard IgG." The method was a lavish one with high volumes during fractionation and a low recovery of IgG (Cohn et al. 1944; Oncley et al. 1949). The other was the Kistler-Nitschmann method established as the "European" method for plasma fractionation (Nitschmann et al. 1954). With this method, volumes to handle during fractionation were considerable lower and the recovery higher at cost of some impurities, mainly IgA. Both methods provided a "standard IgG" concentrate.

Most likely gamma globulin therapy would have stayed in the shadow of antibiotic treatment, if not agammaglobulinemia would have been described in 1952 by OC Bruton. Applying plasma electrophoresis to the serum of an 8-year-old boy, he realized an association between recurrent severe infections (starting at an age of four and a half years of age) and a very low gamma globulin in serum. In an attempt to reduce susceptibility to infections, he administered "standard IgG" subcutaneously and demonstrated an increase of gamma globulin in blood, clinically a decrease of infections. Some remarkable facts of Bruton's work have to be highlighted: (a) despite the overwhelming position of the Boston group, he selected the less painful subcutaneous route of administration for his young patient; (b) he detected a new disease; and (c) he provided the therapy. Although less painful, at that time, only low doses of "standard IgG" could be administered via this route, and the need for i.v. preparations allowing administration of larger doses became evident (again).

10.5 Initial Problems with IVIG Administration

The first human immunoglobulin preparations were Cohn fraction II at 16% strength without any dedicated polishing step, i.e., a "crude" IgG concentrate. The effort of Barandun and colleagues shed light on Janeways "mystery about normal serum gamma globulin": "standard IgG" contained IgG aggregates capable of activating the complement system. This activation process generated anaphylatoxins like C3a and C5a and caused acute intolerance reactions if "standard IgG" was given intravenously. Thus, from the beginning of the 1960s onward, research focused on the reduction of aggregates as the cause of anticomplementary activity (ACA) in order to create preparations that were tolerated upon intravenous use. Even today, ACA assessment is a release criterion for IVIG lots.

10.6 Chemical Procedures to Improve Tolerance

Within this chapter, it is impossible to discuss all details of industrial procedures developed in order to make human immunoglobulins applicable by i.v. the route. Thus, only some principles of polishing "standard IgG" are summarized (historical examples mostly with modification of the molecules):

- Harsh pepsin digestion leading to 5S $F(ab')_2$ fragments devoid of Fc-effector functions and shortened half-life in vivo (Schultze and Schwick 1962)
- Plasmin digestion (Sgouris 1967)
- Limited sulfitolysis (Masuho et al. 1976)
- Reduction and alkylation (Wright 1978)
- Anion exchange chromatography and PEG precipitation
- Treatment with ß-propiolactone (Stephan 1969), an IgM/IgA enriched product remained on the market in some countries

Only a very few of these products are still available in some regions of the world, mainly because the above measures to achieve i.v. tolerability provided markedly impaired structures and functions of IgG. Some procedures destroyed IgG3. Currently, the plasma fractionating companies use combinations of procedures to achieve high recovery as well as high purity and leave their product as native as possible, nevertheless well-tolerated by the i.v. route (see Chaps. 12 and 13).

10.7 The First Conference on IVIG Quality

In pivotal trials, rarely placebo controlled, the biological activity of most of the older products was assessed measuring protection from infections of antibody-deficient patients. Head-to-head comparisons of different products in vivo or placebo-controlled trials were rarely performed. A few clinical trials in patients with primary Immunodeficiencies illustrating developmental steps should be mentioned: Ammann et al. 1982; Steele et al. 1987; Garbett et al. 1989; Schiff et al. 1997; Lamari et al. 2000; Roifman et al. 2003; Kallenberg 2007).

In order to define some quality characteristics for IgG preparations a WHO/IUIS expert committee met in 1983 and defined minimal requirements for IVIG products (IUIS 1983):

- Obtained from plasma pools from at least 1000 donors
- Prekallikrein activator (PKA) activity below a predefined threshold level
- Kinins below a predefined threshold level
- Anticomplementary activity (ACA) below a predefined threshold level (a general lot release criterion)
- Plasmin content below a predefined threshold level
- No accumulative preservatives (i.e., Merthiolate)
- IgG content at least 90% (monomers + dimers, low aggregate content)
- IgG as native as possible, i.e., chemically unmodified, retained biological functions such as antigen recognition and Fc functions
- Physiological IgG subclass distribution
- Titer of some selected specific antibodies guaranteed, a lot release criterion varying from brand to brand
- Low IgA, absence or minute amounts of IgE
- Isohemagglutinins below a predefined threshold level
- Alloantibodies (i.e., anti-D and others) below a predefined threshold level

At that time, not all products fulfilled these requirements. However, keeping these goals in mind the different companies intensified their research heading for products that came as close to these requirements as possible. After a one and half decade of development, the first “native” 7S IgG concentrate came to the market in Switzerland: Ig-SRC (SRC = Swiss Red Cross). The clue to reach intravenous tolerability was the polishing of “standard IgG” at low pH and traces of pepsin. This step rendered remaining aggregates ineffective. Other manufacturers applied other

techniques to get rid of IgG aggregates or to render them non-complement activating. Much progress in polishing steps was made leading to different products with lyophilized or liquid formulation needing different stabilizers (Cherin et al. 2016).

10.8 Adverse Events

Severe adverse events (sAEs) from the very beginning of transfusion science and its clinical application have been a threat to the recipients. sAEs encompass incompatible transfusion reactions, TRALI, anaphylactic reactions, organ damage, and transmission of pathogens. Plasma products mediate some of these sAEs as well. Back in the early 1940s, an elevated risk for "homologous serum jaundice" was associated with the use of pooled serum (for stabilizing yellow fever vaccine). The same was true for the first product prepared from pooled plasma, albumin (Spurling et al. 1946). Great efforts made already in 1945 available a virus inactivation method for albumin concentrates, pasteurization at 60 °C for 10 h (Gelli et al. 1948). Unfortunately, this method was not applicable to "standard IgG" and sporadic transmission of hepatitis occurred (see below).

The recommendations by the WHO/IUIS expert committee in 1983 were based on causes of adverse events known at that time. A major problem at that time were immediate anaphylactoid reactions caused by anti-IgA antibodies (IgG or IgE isotype) in the patients and "phlogistic" reactions delayed by about 2–3 h after start of the infusion (= patient-related) or anticomplementary, PKA or kinin activity in the products (= product-related).

10.8.1 Pathogen Transmission

The worst of the adverse events with IgG concentrates which occurred after the WHO/IUIS recommendation was the transmission of hepatitis C virus (HCV; "hepatitis non-A, non-B" termed at that time) by some polyvalent IgG preparations (Lane 1983; Lever et al. 1984; Stephan and Dichtelmüller 1983; Weiland et al. 1986; Welch et al. 1983; Williams et al. 1989) as well as with an anti-D immunoglobulin prepared in the former German Democratic Republic. It became apparent that Cohn fractionation II of human plasma alone was limited in its capacity to inactivate transmissible viruses while products remained free from the threat of virus transmission, particularly those prepared by the Kistler-Nitschmann fractionation technique, most likely due to the low pH applied at polishing. Several patients infected by HCV experienced a severe course of infection and a few died (Björkander et al. 1988; Razvi et al. 2001) making viral safety a crucial issue for IgG products (Cuthbertson et al. 1987). Driven by the virus transmission risks of blood transfusion and the obvious elevated risk of virus transmission by coagulation factor concentrates, authorities always orient themselves to the highest risk level and require accordingly measures to guarantee product safety. IgG therapy on one hand comprises a particular set of risks, while on the other hand the fractionation technique

and the polishing steps offer particular opportunities for virus inactivation/removal. The particular risks with IgG therapy are:

- Economic reasons force manufacturers to manipulate at once large volumes of pooled plasma.
- One contaminated plasma unit can contaminate thus a large pool.
- One lot of IgG concentrate has many vials for clinical use.
- The many vials are applied to a certain (high) number of patients and in case of contamination infections are usually clustered in a patient population.
- Recipients might be individuals with genetically impaired antibody production. Such patients are particularly vulnerable to infections. Such patients receive IgG concentrates for replacement therapy possibly lifelong, and patients are prolonged and repeatedly exposed to (a theoretical) risk of pathogen transmission.
- Patients with inherited immunodeficiency might need lifelong replacement therapy which exposes them to repeated risk of virus transmission.
- Patients with chronic autoimmune and/or inflammatory diseases are treated with "immunomodulatory" doses of IgG. The doses are high and usually are applied repeatedly, and this again exposes patients to an elevated level of risk for pathogen transmission (Table 10.1).

Table 10.1 Transfusion medicine from the very early days onward was struggling with transmission of pathogens, particularly viruses

Genus	Viruses
Herpesviruses	Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesviruses (HHV)-6, -7, -8
Papovaviruses	John Cunningham (JC) and BK (initials patients) viruses
Parvoviruses	**Parvovirus B19V**, adeno-associated virus (AAV)
Hepadnaviruses	**Homologous serum jaundice (HBV)**
Circoviruses	Transfusion transmitted virus (TTV), TTV-like mini virus or torque teno mini virus (TLMV)
Retroviruses	**Human immunodeficiency virus (HIV)-1,-2**, human T-cell lymphotropic virus (HTLV III, LAV)
Flaviviruses	**Hepatitis C virus (HCV)**, **West Nile virus (WNV)**, **Zika virus (ZIKV)**, yellow fever virus (YFV), other arboviruses
Alphaviruses	Chikungunya virus (CHIKV), (W,E,V) equine encephalosis viruses (EEVs)
Coronaviruses	**SARS-associated virus**
Bornaviruses	Borna disease virus
Picornaviruses	**Hepatitis A virus (HAV)**, human enteroviruses
Bunyaviruses	La Crosse, Sin Nombre, Hantaan
Arenaviruses	Lassa fever, Junin, Machupo
Hepaviridae	**Hepatitis E virus (HEV)**

Listed are some viruses found in blood donations. Pooling of plasma elevates the risk of infecting clusters of recipients by a single lot of a plasma product. Those viruses, which might represent a potential threat for transmission by plasma products, are depicted in bold

In order to lower the risk of pathogen transmission, validated processes for elimination/inactivation of pathogens became mandatory for plasma products (see Chap. 12).

It needs to be mentioned that up to date not a single case of HIV infection acquired through IgG preparations even before dedicated virus inactivation and removal steps have been introduced to the fractionation and polishing processes. Furthermore, no case of variant CJD transmission by plasma products has been reported worldwide (Helbert et al. 2016). The problem with hepatitis C seems to be solved because since more than 25 years no new cases of HCV transmission have been reported. Nevertheless all companies producing IgG concentrates are extremely alert with respect to pathogens possibly emerging/re-emerging in the future.

10.8.2 Noninfectious Adverse Events

A coevolution of noninfectious adverse event profiles with "improved" products, routes of application, doses applied, increased infusion rate, and the more broad therapeutic use of IgG concentrates has occurred (Feldmeyer et al. 2010; Berger 2013; Dantal 2013). Reasons for the adverse effects are multiple (Späth et al. 2015).

Parameters controllable by, e.g., polishing steps or the use of appropriate stabilizers:

- Harming of the IgG molecules inherent to any fractionation process.
- Chemicals to stabilize the concentrates during their shelf life.
- Inappropriate handling of the concentrates during their shelf life.
- Alteration of the IgG molecules due to inappropriate handling before infusion (foam).
- Presence of too high amounts of preformed dimers in the preparation.
- Skin reactions at site of infusion/injection.
- Too rapid increase of exogenous IgG in the circulation, a combination of infusion rate and strength of the solution infused.
- Increase in recovery might lead to an altered population of IgG molecules resulting in an altered adverse event profile.

Parameters not controllable:

- The immune status of the diseased patient at the time point of the infusion, i.e., the subtle and extreme wide array of recognition by infused IgG of the patients' immune structures and vice versa, the recognition by patients' immune system, the exogenous IgG (for details see P. Späth et al. 2015).

Delayed adverse reactions might all be associated with risk factors the diseased patient brings along. These factors are discussed to render patients particularly sensitive to effects of the interrelation of applied IgG and patient's immune status. Such

"risk factors" may exist subclinically. Some of the more common adverse events seen primarily with IVIG are (modified from Cherin et al. 2016):

- Migraine headaches
- Aseptic meningitis (patient dehydrated? Local meningeal inflammation induced by IgG on the basis of infused IgG recognizing "risk factors?") (Sekul et al. 1994; Scribner et al. 1994; Hopkins and Jolles 2005; Berg and Fuellenhals 2016)
- Osmotic nephrosis caused by sugars like saccharose in the products, associated with "risk factors" of the kidney
- Other renal impairments due to diuretics and renin–angiotensin system inhibitors
- Thrombosis/embolic events and myocardial infarction (probably caused by activated faxtor XI, high sodium content, and high osmolality) (Hefer and Jaloudi 2004; Elkayam et al. 2000; Ammann et al. 2016)
- Hemolysis (probably caused by isohemagglutinins and alloantibodies)
- Neutropenia (cause unknown)
- Transfusion-related acute lung injury (TRALI; speculation on pathogenetic role of anti-neutrophil antibodies)
- Hyponatremia, pseudohyponatremia (rare, defect in urinary free water excretion?)
- Hyperviscosity syndrome (possibly caused by preexisting very high levels of IgG in patients) (Hague et al. 1990; Oh et al. 1997)
- Necrotizing enterocolitis in newborn babies (cause unknown, immaturity?) (Figueras-Aloy et al. 2010; Kara et al. 2013; Navarro et al. 2009; Yang et al. 2016)

These observations have stimulated further improvements of the products: Saccharose was replaced by other stabilizers, by validation studies elimination of potential procoagulant activity (demonstrating activated factor XI) during the manufacturing process has had to be shown by each company; some of these studies have been published (José et al. 2013; Williams et al. 2013). The rate of hemolytic adverse events has increased with chromatographically produced IgG concentrates. Attempts to reduce these rates include screening of individual plasma donations and withholding from pooling very high isohemagglutinin titer donations and/or polishing by affinity column chromatography steps to lower these titers (Dhainaut et al. 2013; Siani et al. 2014; Gerber et al. 2016). With the expanding use of IgG concentrates for subcutaneous application, any adverse events have declined considerably.

10.9 Summary

Manufacturing and safe clinical use of IgG concentrates has gone a long stony but finally successful way. Compared to "old" products currently available, IgG concentrates combine better recovery and higher purity, are more convenient in their

use due to liquid formulation and storage at room temperature during their shelf life, and have a higher pathogen safety, tolerability, purity, and efficacy than the products 40 years ago (Gelfand 2006; Cherin et al. 2016).

The development of products for s.c. administration expanded the spectrum of treatment options. The option of self-administration by patients increased their quality of life because this treatment can be given at home. S.c. products also help to treat patients who have repeated intolerance reactions to IVIG. S.c. products are increasingly studied in chronic autoimmune/inflammatory conditions, e.g., chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), and various dermatological and collagen-vascular diseases. Results from clinical trials will be available soon. Whether or not ITP can be treated by s.c. route remains to be clarified. One boy with ataxia telangiectasia developed ITP while being on s.c. replacement for his immunodeficiency (Heath and Goldman 2010).

The availability of human IgG has enabled clinicians all over the world to treat several diseases with relatively low toxicity. Nevertheless, the obstacles illustrated in this chapter should be kept in mind to motivate authorities and the plasma industry to enforce efforts to further optimize their products.

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