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REVIEW

# Clinical Use and Therapeutic Potential of IVIG/SCIG, Plasma-Derived IgA or IgM, and Other Alternative Immunoglobulin Preparations

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**Abstract** Intravenous and subcutaneous immunoglobulin preparations, consisting of IgG class antibodies, are increasingly used to treat a broad range of pathological conditions, including humoral immune deficiencies, as well as acute and chronic inflammatory or autoimmune disorders. A plethora of Fab- or Fc-mediated immune regulatory mechanisms has been described that might act separately or in concert, depending on pathogenesis or stage of clinical condition. Attempts have been undertaken to improve the efficacy of polyclonal IgG preparations, including the identification of relevant subfractions, mild chemical modification of molecules, or modification of carbohydrate side chains. Furthermore, plasma-derived IgA or IgM preparations may exhibit characteristics that might be exploited therapeutically. The need for improved treatment strategies without increase in plasma demand is a goal and might be achieved by more optimal use of plasma-derived proteins, including the IgA and the IgM fractions. This article provides an overview on the current knowledge and future strategies to improve the efficacy of regular IgG preparations and discusses the potential of human plasma-derived IgA, IgM, and preparations composed of mixtures of IgG, IgA, and IgM.

**Keywords** Immunoglobulin preparations · SCIG · IVIG · Polyclonal IgG · Polyclonal IgA · Polyclonal IgM · Host defence · Immunomodulation

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## Introduction

Therapeutic polyclonal IgG preparations, administered as intravenous (IVIG) or subcutaneous (SCIG) immunoglobulins, are purified from the plasma of thousands of healthy donors. Besides replacement therapy for humoral immune deficiency, IVIG/SCIG is increasingly used for the treatment of a wide spectrum of inflammatory and autoimmune disorders with heterogeneous pathogenesis (Kazatchkine and Kaveri 2001; Kerr et al. 2014). Following the introduction of replacement therapy for primary immune deficiencies in 1952 (Bruton 1952), the demonstration of the potent effects of IVIG in immune thrombocytopenia purpura (ITP) (Imbach et al. 1981) opened the door to broad clinical applications of IVIG as an immunomodulatory and anti-inflammatory drug. Since 1981, IVIG has been registered for the treatment of various autoimmune and inflammatory conditions, such as Kawasaki disease (Newburger et al. 1986), Guillain–Barré syndrome (1997), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (Hughes et al. 2008), and multifocal motor neuropathy (MMN) (Van Schaik et al. 2006). Many more off-label indications have been reported (Jolles et al. 2005). In general, the subcutaneous route (Berger et al. 1980) has been proven to be convenient, similarly effective, and eventually safer than IVIG (Haddad et al. 2012; Ochs et al. 2006; Samaan et al. 2014; Wasserman 2012). The success of SCIG in replacement therapies initiated randomized trials in chronic autoimmune conditions, such as CIDP and MMN (Gardulf et al. 2008; Harbo et al. 2009; Markvardsen et al. 2013). Other studies are underway (ClinicalTrials.gov Identifier: NCT02465359, NCT01545076, NCT02027701), and it can be expected that a first market license of SCIG for these and other indications will follow in the near future.

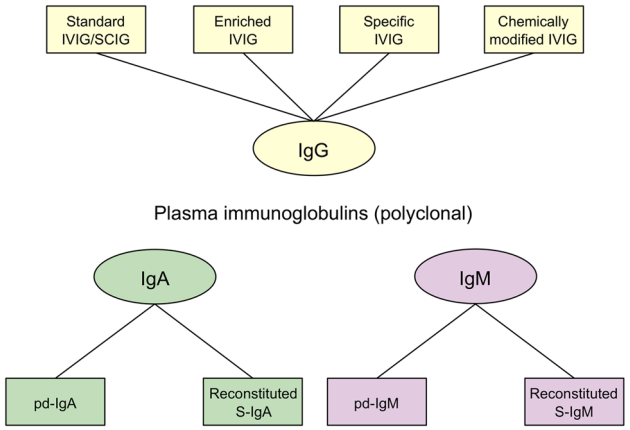


**Fig. 1** Standard intravenous/subcutaneous immunoglobulin (IVIG/SCIG) and alternative preparations aimed at improving clinical efficacy or potency and/or broadening the range of indications. Listed are preparations as discussed in this article. *pd-IgA* plasma-derived IgA, *S-IgA* secretory IgA, *pd-IgM* plasma-derived IgM, *S-IgM* secretory IgM

Due to pooling of plasma from thousands of healthy donors, IgG preparations comprise an immunoglobulin repertoire that exceeds the one of a single individual. The broad range of specificities contributes at least in part to the pluripotency of IVIG/SCIG preparations in infectious and inflammatory disorders (Busse et al. 2002; Kazatchkine and Kaveri 2001; Negi et al. 2007; von Gunten et al. 2014). In fact, both specific Fab-mediated and non-specific Fc-mediated effects of antibodies are thought to contribute to the pharmacodynamics of these preparations (Gelfand 2012; Negi et al. 2007; von Gunten et al. 2014). In this article, we review strategies aimed at improving the therapeutic efficacy of currently used IgG preparations and discuss the potential of alternative immunoglobulin preparations that hold promise for the treatment of further infectious, inflammatory, or autoimmune disorders (Fig. 1).

## Targeting Pathogens by IgG Preparations

Since the early 1950s, IgG preparations were administered as replacement therapy to antibody-deficient patients (Bruton 1952). Doses of 200–800 mg/kg body weight of IgG are considered to be sufficient to decrease the incidence of infections and their sequelae (Kerr et al. 2014). The efficacy of IgG preparation replacement therapies relies on the collective immunological experience of the plasma donor population. IVIG preparations include antibodies against an abundance of clinically relevant pathogens, including *Mycoplasma pneumoniae, Streptococcus pneumoniae, Klebsiella, Chlamydia pneumoniae* and *Helicobacter pylori,* or herpes viruses, Epstein–Barr virus, human parvovirus B19, measles, mumps, or rubella (Krause et al. 2002). Besides stimulating immune effector functions against pathogens, certain studies point to a capacity of antibodies to damage pathogens directly by their potential to catalyse $O_3$ and $H_2O_2$ (Wentworth et al. 2000, 2002). Other studies even propose a concept of modification of gene expression in targeted bacteria following antibodies binding to surface structures (Janoff and Frank 2010; McClelland et al. 2010). Poly-specific immunoglobulin preparations also have the capability to bind superantigens (SAgs) (Norrby-Teglund et al. 2000), which activate T cells and induce their proliferation without MHC restriction. Inhibition of SAg binding to T-cell receptors prevents cytokine production (Norrby-Tegerlund et al. 1996), which may be relevant for the treatment of SAg-related autoimmune disorders or the often life-threatening infectious conditions associated with SAg (Commons et al. 2014).

Contrary to the common belief that carbohydrates (glycans) are T-cell-independent antigens, an increasing number of studies point towards the involvement of $CD4^+$ T cells in the generation of antibody responses following vaccination with glycovaccines or glycoconjugate vaccines, such as for encapsulated bacteria (e.g., pneumococcal or meningococcal vaccines) (Clutterbuck et al. 2012; Feldman and Anderson 2014; Li et al. 2014; Pletz et al. 2008). In support, glycan-array studies investigating IgG-mediated glycan recognition by antibodies in IVIG/SCIG preparations revealed a broad spectrum of class switched, anti-carbohydrate antibodies (Schneider et al. 2015; von Gunten 2014; von Gunten et al. 2009b). Interestingly, in addition to the carbohydrate antigens of pathogens, such as bacterial lipopolysaccharides, capsular polysaccharides, or exopolysaccharides, recognized structures also included glycans on host tissues that serve as attachment sites for bacteria, viruses, or even for secreted toxins, such as the Shigella-like toxins SLT-1 and -2 (Schneider et al. 2015). Such antibodies might provide a natural barrier to limit the dissemination of pathogens and so prevent related sequelae in infectious disease.

## Immunomodulation by Polyclonal IgG Preparations

IgG preparations are increasingly used for the treatment of autoimmune and inflammatory disorders affecting different organ systems (Jolles et al. 2014). For these indications, up to 2 g/kg body weight of IVIG are applied per treatment cycle (Jolles et al. 2005). Such doses are approximately doubling physiological IgG concentrations in the circulation (Bayry et al. 2003b; Kerr et al. 2014). Although the titres of specific immunomodulatory antibodies in IVIG/

SCIG might be low, they can become effective when an IgG preparation is administered at high doses. For instance, antibodies to the regulatory receptor Siglec-9, expressed on distinct leukocytes (Jandus et al. 2011, 2014; von Gunten and Bochner 2008; von Gunten et al. 2005), are present at sufficient levels to be isolated from IgG preparations. When incubated with neutrophils, these antibodies reach similar flow cytometry signal intensities on neutrophil surfaces as observed with a commercial specific antibody (von Gunten et al. 2006). In addition, high-affinity antibodies are known to modulate immune responses, such as lymphocyte proliferation, at remarkably low concentrations (Simon et al. 2003). Furthermore, the threshold of susceptibility of immune cells towards IVIG-mediated effects can be lowered if cells are primed by inflammatory mediators, as shown for neutrophils and eosinophils (von Gunten et al. 2006, 2007; von Gunten and Simon 2006). In a given patient, depending on the stage of the disease, the efficacy of specific antibodies in IVIG/SCIG, may thus depend on the qualitative and quantitative differences of local or systemic levels of cytokines and other inflammatory mediators (Fig. 2) (von Gunten et al. 2009a; von Gunten and Simon 2008).

A further clinical feature of IgG preparations is their glucocorticoid sparing effect (Gelfand 2012). Glucocorticoids are often administered as a first-line or long-term therapy to treat inflammatory disorders, and are thought to down-regulate immune responses by multiple mechanisms, including reprogramming the expression of multiple genes in diverse sets of cells (Oakley and Cidlowski 2011). Thus, polyclonal immunoglobulins and glucocorticoids are both pleiotropic therapeutics (von Gunten et al. 2013, 2014). The combination of these pleiotropic drugs may broaden the range of pharmacodynamic actions on mutually non-exclusive targets within molecular networks in a variety of heterogeneous clinical settings.

## The Clinical Potential of Particular Immunoglobulin Preparations Other than Regular IVIG/SCIG

The costs for raw material represent an exceedingly high portion of the total production cost in the plasma industry: 57 % in 2011 (Robert 2016). This, together with the need for improved treatments, calls for most optimal use of plasma proteins for medication. Reducing the doses of IgG applied is an option. Other measures best are not interfering with the established fractionation techniques and best do not affect established registered products. A promising approach might be the use of specific IgG fractions. Isolation from side-fractions products is a further option, i.e., to get hold of the IgA and IgM fractions. This and further options are reviewed below.

### Hyperimmune Globulins to Fight Infections in Humans

Current polyclonal hyperimmune globulins in clinical use are typically IgG preparations. The starting material for hyperimmune globulins might be high-titre plasma from a selected donor population, e.g., convalescent patients or

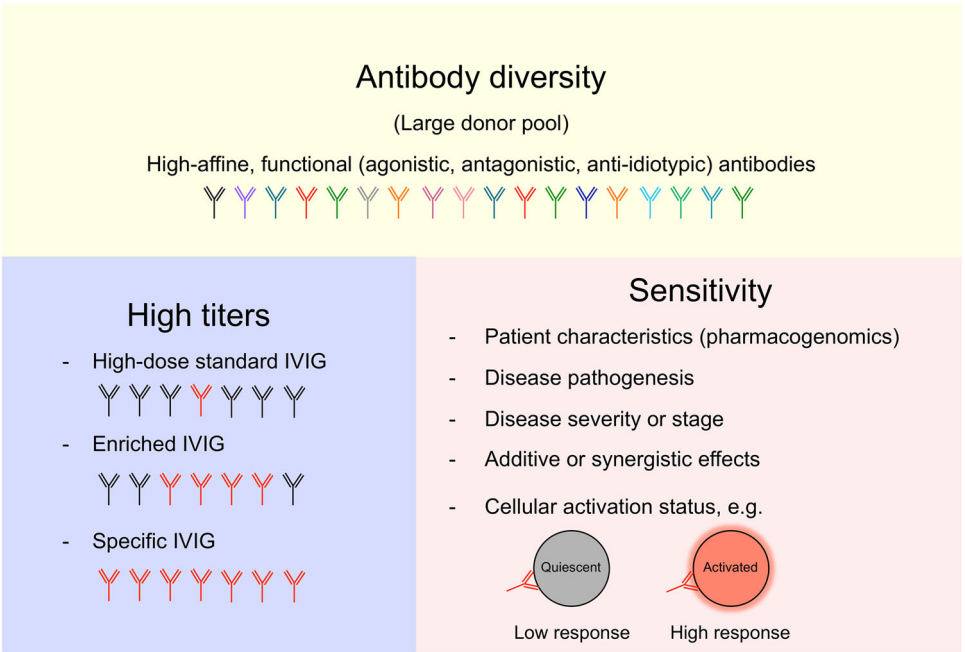


**Fig. 2** Factors that may increase the potency and efficacy of functional antibodies within IgG reparations, even if occurring at low frequencies. Specific antibodies might be present only at low titers. A large donor pools, high titers during IVIG therapy and increased sensitivity of IVIG-targets might, however, contribute to the beneficial effects of IVIG. Details are explained in the text

individuals after vaccination. Hyperimmune globulins, in general, have a guaranteed minimal titre for a given antibody specificity. The manufacture of hyperimmune preparations differs in several aspects from manufacturing of regular IVIG/SCIG. A particular logistic effort has to be made to test, select, and keep separate collected plasma from regular plasma for fractionation. Routine large pool fractionation processes in standard plants are not applicable, because the hyperimmune plasma pools are small. The amount of the final product per lot is also smaller compared with large pool fractionation, though the costs for cleansing the plant and the amount of material needed for testing prior to lot release remain the same.

Recently, hyperimmune IgG preparations have received increased attention due to more frequent global travel raising the risk of outbreaks of infectious disease of international concern. These outbreaks are inevitable and remain unpredictable. In emergency situations with no, or insufficiently available, preventive or curative measures, quick availability of hyperimmune globulins prepared from locally collected plasma derived from convalescent patients might be a useful tool in reducing the spreading of certain emerging pathogens. Novel small-pool fractionation techniques providing appropriate hyperimmune globulins might support host defense to more rapidly overcome infection (Bornholdt et al. 2016; El-Ekiaby et al. 2015; Kreil 2015; Rager-Zisman 2014).

Clinical use of hyperimmune preparations might, for example, be the treatment of West Nile virus (WNV) encephalitis. Such IVIG is produced from donors having anti-WNV antibodies (Ben-Nathan et al. 2009). IVIG preparations, produced based on pooled donations with relatively high titres against cytomegalovirus (CMV) have, in some studies, been shown to be efficient for the prophylaxis of CMV disease associated with kidney or liver transplantation (Snydman et al. 1987, 1993), though this was not the case in pediatric solid organ transplantation (Danziger-Isakov et al. 2015). There are additional hyperimmune globulin preparations, which are predominantly used in solid organ transplantation (Stiehm et al. 2008).

## Hyperimmune Globulins for Immunomodulatory Purposes

The specificity of the only non-pathogen-directed hyperimmune preparations in clinical use is anti-Rhesus D (Rh(D)). Anti-Rh(D) preparations prevent Rh(D) sensitization of Rh(D)-negative mothers by Rh(D)-positive fetus, to avert risk for hemolytic disease of the new-born in subsequent pregnancies (MacKenzie et al. 2004; Pollack et al. 1968). Anti-Rh(D) has also found application for the treatment of ITP (Despotovic et al. 2012).

## The Clinical Potential of Experimental, Plasma-Derived, and Modified Immunoglobulin Preparations

A large body of evidence confirms the presence of specific immunomodulatory antibodies in IVIG that directly modulate virtually all arms of the immune system (Gelfand 2012; Kazatchkine and Kaveri 2001; Negi et al. 2007), including the complement system (Basta et al. 1989; Lutz et al. 1996; Späth 2014), cytokines (Issekutz et al. 2011; Ramakrishna et al. 2011; Simon and Späth 2003), or immune cells, such as neutrophils (Altznauer et al. 2003; Casulli et al. 2011; von Gunten et al. 2006; von Gunten and Simon 2007, 2010, 2012) eosinophils (von Gunten et al. 2007), dendritic cells (Bayry et al. 2003a, 2005; Tjon et al. 2015), and lymphocytes (Kaveri et al. 1996; Kessel et al. 2007; Maddur et al. 2013; Séïté et al. 2010; Trinath et al. 2013). Other functional antibodies in IVIG include anti-idiotypic antibodies to pathological autoantibodies (Fuchs et al. 2008; Rossi and Kazatchkine 1989; Shoenfeld et al. 2002; Svetlicky et al. 2013) or immunomodulatory antibodies (Schaub et al. 2011), as well as anti-hinge natural antibodies that may block the proliferation of B cells (Simon and Späth 2003; Terness et al. 1995; Welschof et al. 1997). Indeed, such specific IVIG subfractions have been proposed as potential therapeutic agents, as they might reach higher pharmacological efficacy at lower concentrations in certain autoimmune disorders (Svetlicky et al. 2013). Other functional subfractions may consist of antibodies with immunomodulatory properties independent of specificity. For instance, it has been proposed that antibodies with certain Fc-glycosylation (terminal sialylation) patterns may exhibit receptor-mediated immune regulatory properties (Kaneko et al. 2006; Schwab and Nimmerjahn 2013; Schwab et al. 2015), yet this concept is based on mice experiments and results are controversially discussed due to conflicting findings from other groups (Bazin et al. 2006; Campbell et al. 2014; Crispin et al. 2013; Guhr et al. 2011; Käsermann et al. 2012; Leontyev et al. 2012a, b; Othy et al. 2014; von Gunten et al. 2014; Yu et al. 2013). More recently, sialylated IgG was found to modulate complement-mediated processes in humans (Quast et al. 2015). Another non-specific sub fraction, composed of dimers/oligomers in IVIG, seems to be a double-edged sword, as was reviewed recently (Späth et al. 2015). This subfraction does appear to have immunostimulatory potential; however, it also might provoke severe adverse events when exceeding a threshold level in a recipient.

Enhancement of efficacy of regular IVIG/SCIG might be achieved by protein-destabilizing factors, such as pH shifts, ferrous ions, reactive oxygen species, or heme, that can also be present in the microenvironment at inflammatory sites and eventually influence the immune response (Brieland and Fantone 1991; Lardner 2001; Sacks et al.

1978; Wagener et al. 2001). Indeed, it has been shown that the exposure of IgG molecules to such protein-destabilizing factors can alter $F(ab')_2$- and/or Fc-related properties of antibodies (Bouvet et al. 2001; Dimitrov et al. 2007b; Margiloff et al. 1998). The enhancement of reactivity and induction of natural autoantibody activity following treatment of human immunoglobulin with dissociating agents (urea, sodium thiocyanate, acidic buffers) was described. This effect eventually relies on the exposure of basic polyreactive antibody structures (Bouvet et al. 2001). In this context, heme was identified as an intrinsic ligand of antibodies, leading to a change in the IgG-binding properties and resulting in a broader bacterial recognition (Dimitrov et al. 2007a). Similarly, studies comparing different IVIG preparations exposed to pH shifts during manufacturing associated these shifts with an increased poly-reactivity of IgG (Djoumerska et al. 2005). Subsequent animal studies revealed that the administration of low pH- and ferrous ions-treated IVIG had a protective effect in experimental sepsis (Djoumerska-Alexieva et al. 2010, 2015), and that heme-modified IVIG improved the outcome of experimental autoimmune diabetes (Pavlovic et al. 2011). Under protein-destabilizing conditions, such as may occur at sites of inflammation, increased IVIG-mediated binding to bacterial antigens was observed (Mihaylova et al. 2008). Mechanistically, two explanations for alteration of IgG functions have been proposed. One claims a partial, but transient denaturation of sensitive variable regions, which induces a larger conformational space by increasing the structural plasticity and adaptability of the antibody's paratope. The other explanation is based on co-factors; the antibody might use molecules of low molecular weight (such as heme) as binding co-factors, thereby increasing the polyspecificity (Dimitrov et al. 2008, 2012). Metal-catalysed oxidation of IgG was shown to impair Fc-receptor-mediated binding to macrophages, thereby potentially inhibiting uptake of immune complexes in autoimmune diseases and limiting the subsequent cytokine release (Margiloff et al. 1998).

The approach to generate more efficient IVIG preparations using protein-destabilizing factors might not only lead to novel applications, but could also result in a lower dosage than with unmodified IVIG, at least for certain conditions. This would potentially lower rates of adverse reactions and result in decreasing costs for the treatment itself. However, at the present time, it remains open how far protein-destabilizing agents will diminish intravenous/subcutaneous tolerability of a preparation.

Hints for the clinical benefits of the above-mentioned modified IgG preparations are obtained from animal studies, mostly involving mice. However, the results of some experiments in mice might not be transferable to humans, as the genetic background of the mice might be pivotal to obtain particular results (Leontyev et al. 2012a). Furthermore, it has been highlighted that certain mouse models poorly mimic human inflammatory diseases (Seok et al. 2013; Tjon et al. 2015), which needs to be taken into consideration.

Another general limitation of in vivo studies with IVIG is that human IVIG is xenogeneic in animal models and that certain specific antibodies may not bind an equivalent animal antigen, eventually leading to loss- or gain-of-function effects (von Gunten and Simon 2010). The use of pooled immunoglobulins from the same animal species would not substitute for human preparations, given that the antibody repertoires of IVIG and animal sera differ significantly (Stowell et al. 2014).

## Immunoglobulin Preparations for Human Use, Which Contain Relevant Amounts of Isotypes Other than IgG

Only three preparations containing considerable amounts of IgA and/or IgM have been more widely used in clinical practice: Pentaglobin, Venimmun, and IgAbulin (Table 1). Pentaglobin and Venimmun are intravenous preparations. Despite their IgA content, to the best of our knowledge, no adverse events due to proven sensitization of patients to IgA have been reported. Among others, this might be due to the limited variability of conditions treated when compared with regular IVIG. The reported adverse event rates of these IgM/IgA containing preparations apparently do not exceed the frequencies seen with regular IVIG and the clinical variety of manifestations is similar to other IVIG preparations. To achieve intravenous tolerability, one preparation, Venimmun, was treated by S-sulfonation (Gronski et al. 1982). Pentaglobin, which shows a relative IgA, IgG, and IgM isotype distribution very similar to plasma, undergoes treatment by β-propiolactone and UV light. This treatment results in irreversible alteration of the molecules, as has been shown in detail for IgG. The treatment chemically modifies amino-acid residues, particularly those involved in the binding of the complement subcomponent C1q (Späth 1999; Stephan 1969, 1980; Stephan et al. 1985) and the Fc-recptors (van Gent et al. 2014). The modification of IgM and IgA by β-propiolactone has been studied to a lesser extent. Available data suggest a similar loss of C1q-binding capacity of IgM (Kojouharova et al. 2010; Späth 1999), while modification of IgA seems to be less an issue, as IgA does not activate the classical pathway of complement.

## Clinical Use of Polyclonal, Pentameric IgM

IgM molecules are the first to emerge during the embryonic development and the first to be produced in an immune response after contact with foreign antigens. Human

**Table 1** Immunoglobulin concentrates containing relevant amounts of isotypes other than IgG—isotype distribution, manufacturing, and clinical studies in humans with products for intravenous or topical application

| Ig preparation[a]/ Ig isotypes | IgG (%) | IgM (%) | IgA (%) | Fractionation technique to obtain raw Ig product | Polishing step to achieve intravenous tolerability (production process)[b] with resulting characteristics and availability | Clinical studies in man | References |
|---|---|---|---|---|---|---|---|
| BT086 | Mean 54 | Mean 23 | Mean 23 | No public information found | No detailed public domain information found; the only description available to us (citation) "…a new manufacturing process for BT086 was established to obtain more native immunoglobulins with highly active binding sites"<br>In clinical trials; not on the market | Clinical trials with i.v. application ongoing or planned<br>Severe community-acquired pneumonia EUDRACT 2010-022380-35 (https://www.clinicaltrialsregister.eu/ctr-search/search?query=BT086; accessed May 2016); additional information posted by the company: http://www.biotest.com/de/de/f__e/pipeline/igm_concentrate.cfm (accessed May 2016) | Shmygalev et al. (2016), Welte et al. (2015) |
| Pentaglobin[c] | ~76 | ~12 | ~12 | The supernatant of Cohn fraction III obtained by cold ethanol fractionation and caprylic acid precipitation is further purified by anion exchange chromatography | Irreversible chemical modification by β-propiolactone/UV[d]<br>Available in some markets; never got marketing authorization in the US | Product for i.v. application<br>Recommending an IgM/A-enriched preparation for the treatment of severe bacterial infections[e]<br>No confirmation found of a superiority of an IgM/A-enriched IVIG in severe bacterial infections<br>No effect found in therapies of peripheral neuropathies as complications of severe infections<br>As immunosuppressive drug-spearing treatment in collagen vascular diseases<br>Immunomodulation in the frame of solid organ transplantation<br>Graft-versus-host disease | Akdag et al. (2014), Alejandria et al. (2013), Azık et al. (2016), Brunner et al. (2013), Enk and Knop 2000, INIS Collaborative Group et al. (2011), Haririan et al. (2009), Ius et al. (2015), Kistler and Nitschman (1962), Klingemann et al. (1990), Reinhart et al. (2010), Schaffer (1998), Stephan et al. (1985), Stephan (1969) |
| Venimmun N | 81–87 | 5–8 | 8–11 | Aqueous solutions of Cohn fractions II, III or Kistler-Nitschmann precipitate A were sulfonated and further purified by ethanol precipitations | Partially reversible S-sulfonation[f]<br>Withdrawn from the market | Product for i.v. application<br>Studies addressing the question of a possible benefit from IgM antibodies in Venimmun/Venimmun N are rare and results reported are contradictory<br>The immunomodulatory potential of Venimmun was tested in various forms of thrombocytopenia (Emmerich et al. 1987), however, without giving attention to the IgM content. In a clinical study, this chemically modified IVIG showed similar efficacy as a non-modified IVIG, while in vitro FcγRII, inhibition by a native IVIG was superior to that of IVIGs treated enzymatically or chemically, including S-sulfonation | Bitzan et al. (1993), Cohn et al. (1946), Fateh-Moghadam et al. (1984), Fortelny et al. (1985), Greinacher et al. (1994), Gronski et al. (1982), Hofstaetter et al. (1983), Nitschmann et al. (1954), Pul et al. (2002), Gronski et al. (1983) |

**Table 1** continued

| Ig preparation[a]/ Ig isotypes | IgG (%) | IgM (%) | IgA (%) | Fractionation technique to obtain raw Ig product | Polishing step to achieve intravenous tolerability (production process)[b] with resulting characteristics and availability | Clinical studies in man | References |
|---|---|---|---|---|---|---|---|
| IgAbulin | 25.9 (15.5–33.3) | 0.7 (0.18–1.46) | 73.0 (66.1–84.2) | *Citation*: "The IgA–IgG preparation was obtained from human serum, Cohn fraction II, by ion-exchange chromatography"<br>Beside IgG and IgA the product contains 10 % transferrin | No particular treatment<br>Was licensed in a few countries; scanned package insert on file | Product for topical application<br>This product was applied orally or nasally only and thus risk of patient-owned anti-IgA antibodies was not a concern. All clinical reports listed<br>Prospective (randomized) studies and meta-analysis of necrotizing enterocolitis in low-birth-weight infants and newborns<br>Oral IgA/IgG treatment of on-NEC enteropathies<br>Protection of the gut mucosa post-bone marrow transplantation<br>Upper respiratory tract infections treated or prevented by topical IgAbulin | Anonymous (1990), Casswall et al. (1996), Eibl et al. (1988), Fast and Rosegger (1994), Foster et al. (2004), Giraudi et al. (1997), Heikinnen et al. (1998), Hemmingsson and Hammarström (1993), Johansson and Ekamn (1999), Lindberg and Berglund (1996), Tjellström et al. (1993) |
| Normal human serum | ~80 | ~7 | ~13 | – | – | – | |

Beside the mentioned preparations, two others for intramuscular application have been used in rather experimental conditions in humans. The products are not on the market these days. Gamma-M contained ~80 % IgG and ~20 % IgM. Case reports of experimental injections in severe bacterial infections have been communicated (Stübner 1979; Flenker 1977; Martin 1973; Tunn 1976). The other i.m. product is IgGAM which was available in two forms, the one enriched in IgM (~50 % IgG, 35–40 % IgM, 2–6 % IgA) and the other enriched in IgA (~52 % IgG, ~12 % IgM, ~35 IgA) (Audran et al. 1975). IgGAM was tested in experimental injections to patients with various antibody deficiency syndromes (Blatrix et al. 1976)

Some experimental IVIGs enriched in IgM and IgA, which were not tested in man are mentioned in the text

[a] A candidate IgG/A/M preparation to control, e.g., Ebola virus infections was described very recently (El-Ekiaby et al. 2015)

[b] Polishing step in the production process is needed to prevent spontaneous activation of cells and the complement system in the recipients. Spontaneous complement and cell activation can result in severe adverse events

[c] Pentaglobin has had a sister product Intraglobin/Intraglobin F. Intraglobin/Intraglobin F was also treated by β-propiolactone, and was practically devoid of IgM and IgA. The product is withdrawn from the market. Directly comparing Intraglobin/Intraglobin F versus Pentaglobin in clinical trials would have been an ideal combination to elaborate in vivo effects of polyclonal IgA and IgM. We know a single study comparing Pentaglobin and Intraglobin

[d] Other products in which intravenous tolerability is achieved by β-propiolactone/UV treatment are Intraglobin (polyclonal IVIG, off-market), Cytotect (hyperimmune anti- CMV), Varitect (hyperimmune anti-varicella), and Hepatect (hyperimmune anti-hepatitis B virus)

[e] Only the most recent meta-analyses, prospective, randomized studies, or guidelines are listed

[f] S-sulfonation served to achieve intravenous tolerability. S-sulfonation is a partially reversible chemical modification of the IgG molecules. S-sulfonation breaks S–S bridges in IgG molecules. The consequences of S-sulfonation on the biological activity of IgG molecules have been studied in vitro, however, not in vivo, at least not under appropriate experimental conditions. To the best of our knowledge, the effect of S-sulfonation on IgA and IgM molecules and the consequences thereof on biological activities has not been studied

pentameric IgM in the circulation is a flexible molecule (Czajkowsky and Shao 2009). Although IgM-Fc fragments (Fcμ) within an IgM molecule are structurally dense and in number high enough to bind C1q, no classical pathway activation occurs in the circulation (Poon and Schumaker 1985). Complement activation occurs after IgM has bound multivalently to antigen and has taken the "staple form" (Czajkowsky and Shao 2009; Feinstein et al. 1986). Under the optimal conditions, a single pentameric IgM bound to antigen can mediate opsonophagocytosis (Al-Herz et al. 2014).

Free polymeric IgM and polymeric IgA, both, are bearing the J-chain and both are binding to Fcα/μ receptors. While a binding of antigen-complexed IgA to Fcα/μ on macrophages was shown, the binding of antigen-associated IgM has not yet been studied in detail (Klimovich 2011). Thus, it remains open whether the removal of pathogen-IgM complexes by macrophages is mediated by complement receptors exclusively. If yes, this would represent a significant difference to the removal of complexed IgG, which is mediated by the combined action of complement and Fcγ receptors.

## IgM—Molecules of Innate and Adaptive Immunity

Although IgM molecules are the first to emerge in immune responses to pathogens, "pre-immune" IgM exists in humans and this IgM differs in various aspects from the antigen-induced IgM. "Pre-immune" IgM is mostly encoded by genes, which are characterized by high homology to germline configuration. The specificity of "pre-immune" IgM is considered to be broad. Specificities are directed towards antigens that are evolutionary conserved and have repetitive structures. IgM itself is the most conserved immunoglobulin within vertebrate species. At least a subpopulation of the "pre-immune" IgM may, at the same time, possess self-reactive homeostatic function and participate in a first-line immune defence against invading organisms (Fig. 3) (Avrameas et al. 1981; Boes 2000; Casali and Notkins 1989; Vas et al. 2013). In the first-line defence, binding of IgM (and complement) to invading pathogens facilitates interaction with dendritic cells in the periphery and guides them to organized lymphoid tissue (Berczi et al. 2000; Matter and Ochsenbein 2008; Ochsenbein et al. 1999), where they encounter the main cell population expressing Fcα/μR in humans: the follicular dendritic cells of germinal centers (Kikuno et al. 2007). As in host defence, IgM forms a functional entity with the complement system in assuring immune homeostasis: the binding to altered/senescent/apoptotic self-cell structures ensures their timely elimination (Chen et al. 2009; Ochsenbein and Zinkernagel 2000). Such elimination can run at high flow-through rates without the induction of

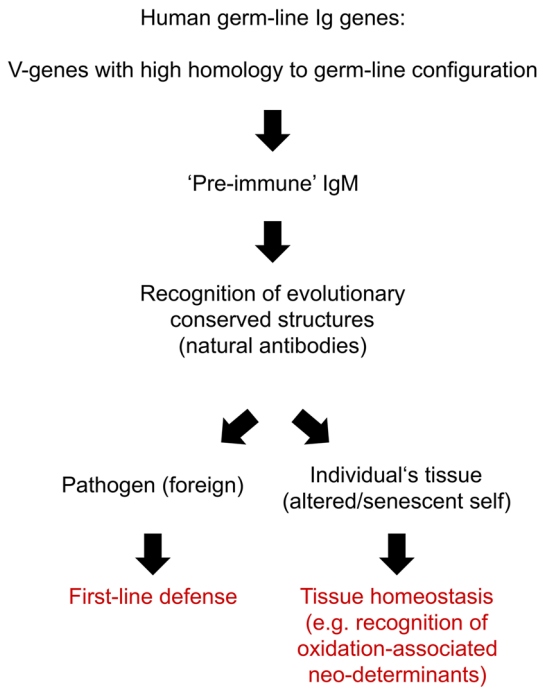


**Fig. 3** Concomitant recognition by the same natural IgM of evolutionary conserved epitopes shared by microorganisms and autoantigens mediate first-line defense and tissue homeostasis. Tissue homeostasis by "natural" IgM antibodies is mediated through the recognition of phosphorylcholine epitopes often being oxidation-associated neo-determinants. These are common inflammatory danger signals of cell injury, oxidative stress, and bacterial capsules

inflammation. Failure of binding, for example, due to genetic defects of IgM, C1(qrs), C2, and C4 results in some cases in severe autoimmune-like diseases (Al-Herz et al. 2014; Louis and Gupta 2014; Stegert et al. 2015). It is believed that in these deficiencies not pathological autoantibodies but the prolonged exposure to the immune system of altered, oxidized, or otherwise damaged self is the driving force for the autoimmune-like manifestations.

## Biological Activity of Polyclonal IgM vs. IgG in Humans

IgM is considered to mediate anti-pathogen effects more efficiently than IgG, because of the 10-valent binding to repetitive structures expressed on viruses and bacteria. Binding is followed by the prompt activation of the classical pathway of complement and efficient opsonophagocytosis. In terms of host defence, the question has been asked over and over whether or not IgM is more efficient compared with IgG. In general, experiments in vitro support this notion, because most experimental setups favour IgM over IgG: (1) coating of purified antigens provides a huge surface with densely packed, repetitive epitopes; and (2) the mass law in such systems is nullified, favouring a fluid phase ligand to bind to large solid-phase structures. However, in infected

mice, the pharmacodynamic superiority of immune IgM compared with IgG was not confirmed (reviewed in Späth 1999). These in vivo experiments were performed with isotype-switched mouse monoclonal antibodies (homologous system) or human immunoglobulin preparations purified from vaccinated volunteers (heterologous system). After 1999, a set of experiments exploring the relative neutralizing activity in vitro of polyclonal IgG, IgM, and IgA antibodies against streptococcal pyrogenic exotoxin A was published. On the one hand, an IgM/IgA-enriched IVIG was more effective than regular IVIG. On the other hand, in proliferation experiments, a highly enriched IgM preparation Hu299 ($\sim$82 % IgM) showed the weakest inhibitory activity among the different preparations tested (Norrby-Teglund et al. 2000).

As our clinical knowledge regarding potential effects of polyclonal IgM in humans has been obtained almost exclusively by the use of a single IgM/IgA-enriched IVIG, below we discuss how far our knowledge on the effects of polyclonal IgM in man might remain incomplete.

## Polyclonal IgM Containing Preparations for the Treatment of Infectious Diseases

Pentaglobin is chemically modified and contains beside IgG and IgM also IgA (see also Table 1). In the earlier reports, it was proposed that the anti-infective potential of Pentaglobin was higher compared with regular IVIG. This superiority over regular IgG was attributed to the content in IgM rather than IgA (see below). Even more, when evaluating data from 9 randomized trials with a total of 435 adult patients with severe sepsis and septic shock outcome of add on "immunoglobulin M enriched", IVIG vs albumin or "no add on treatment" in a meta-analysis was found not only better but also more economic (Neilson et al. 2005). However, more recent meta-analyses question the conclusion that IVIG containing IgM as add on vs albumin or "no add on treatment" is clinically and economically promising for the treatment of adults with severe sepsis and septic shock. The Neilson publication immediately was answered back, because of the meta-analysis having been based on a series of small trials of variable quality (Shafazand and Colice 2005). Furthermore, stating the particular beneficial effect of IgM in "IgM-enriched" concentrates neglects some important facts of the IVIG used. Pentaglobin consists to its major part of IgG; IgM and IgA are at the same concentration as in plasma and a possible beneficial role of IgA is widely neglected. Pentaglobin is, in fact, IgM- and IgA-enriched IVIG. The chance to get at least a glimpse on what IgM might contribute to the clinical effect of Pentaglobin, head-to-head clinical trials are needed with an IVIG, which is chemically modified the same way as the IgM/IgA-enriched IVIG. The prerequisite for such studies was available as long as a β-propiolactone-treated IVIG (>95 % IgG) was on the market (Table 1). The only study comparing the two chemically modified products was in neonatal septic patients, in whom the two brands showed no difference (Haque et al. 1995).

Considering the above, it remains an intriguing fact that a chemically modified IgG/IgM/IgA containing IVIG has repeatedly been reported to show good anti-infectious properties (Alejandria et al. 2013; Neilson et al. 2005), particularly because of being "enriched in IgM". The German Sepsis Guideline is stating that IgM-enriched immunoglobulins might be considered for patients with severe sepsis and septic shock (Reinhart et al. 2010). We read this, conditionally because (1) the chemical modification of the main immunoglobulin isotype in Pentaglobin, IgG, results in an inferior biological activity; this can be deduced from in vitro studies comparing hyperimmune IgG preparations with and without β-propiolactone treatment (van Gent et al. 2014) and from the proven modification of C1q-binding capacity; (2) the effect of chemical modification supposedly is similar for IgM (Späth 1999), and therefore, a particular effect of IgM remains to be proven; and (3) the content in IgA and its biological effect is neglected. Thus, clinical data available from many studies with "IgM-enriched IVIG" make it not be possible to deduce a particular role of polyclonal IgM in anti-infectious therapies in humans. However, the combination of IgG/IgM/IgA in the preparation may have some clinical relevance when compared with regular IVIG/SCIG (Werdan 2007).

## Polyclonal IgM Containing Products for Immunomodulation?

There is increasing evidence, suggesting that IgM of natural antibody configuration may have anti-inflammatory, immunomodulatory, and tumor surveilling potential which might be of relevance in a variety of clinical conditions (Devarapu et al. 2016; Diaz-Zaragoza et al. 2015; Gleissner et al. 2015; Grönwall and Silverman 2014; Nguyen et al. 2015; Tsiantoulas et al. 2015; Villar et al. 2015; Wootla et al. 2015) Therefore, it is widely accepted that immunoglobulin preparations containing polyclonal IgM may harbour a high potential for immunomodulatory, anti-inflammatory, and tissue homeostatic effects (Ehrenstein and Notley 2010). However, reports on an immunomodulatory and/or anti-inflammatory use of IgM/IgA-enriched preparations in humans are rare. A potential role of IgM in Venimmun in autoimmune and inflammatory conditions has not been addressed; while the β-propiolactone-treated Pentaglobin has been used in few studies with various success (Table 1). It might well be that the strength of IgM was too low for a clear demonstration of an IgM-mediated effect. Indeed, it

cannot be excluded that β-propiolactone induce amino-acid side-chain alterations might enhance the capacity of capturing active complement C3b and C4b before they become bound and locally mediate tissue damage.

Despite numerous case reports and clinical trials with immunoglobulin concentrates containing IgM, we were not able to find studies, which, to our opinion, unambiguously could define the effect of polyclonal pentameric IgM in recipients. However, new perspectives are emerging. A line extension of Pentaglobin, BT086, which does not undergo chemical modification by β-propiolactone is in clinical evaluation. BT086 contains approximately 23 % IgM, 23 % IgA, and 54 % IgG. Based on the results of phase I clinical trials, a multicentre, multi-national, randomised, placebo-controlled, parallel-group, adaptive group-sequential phase II study was proposed. The goal of the study is to determine the efficacy and safety of BT086 as an adjunctive treatment in severe community-acquired pneumonia (Welte et al. 2015). The study concept foresees, in addition to the best standard of treatment, BT086 vs. 1 % human albumin as control.

Preparations highly enriched in IgM in future might also serve mucosal protection. Recently, it was shown that plasma-derived IgM can associate with recombinant or colostrum secretory component (SC) in vitro to form a secretory-like IgM (Longet et al. 2013). Secretory-like IgM demonstrates a superior ability to maintain transepithelial electrical resistance and to forestall damage of cell monolayers resulting from *S. flexneri* infection when compared with polymeric IgA or secretory-like IgA (Longet et al. 2014).

## Clinical Use of Polyclonal IgA

IgA is the most abundant isotype in the body and the predominant antibody class at mucosal sites, while it is the second most prevalent antibody in the serum after IgG (Delacroix et al. 1982). There are two subclasses of IgA; IgA1 and IgA2, the latter with two different allelic forms. In serum, the bacterial protease-sensitive subclass IgA1 is prevalent; while on mucosal surfaces, the protease resistant subclass IgA2 is predominant. Protease resistance of IgA2 is due to the absence of a 13amino-acid sequence in the hinge region, rendering IgA2 more resistant to, e.g., bacterial proteases (Kerr 1990; Plaut et al. 1974, 1975; Woof and Kerr 2006). Serum IgA is thought to originate mainly from bone marrow plasma cells (Ben Mkaddem et al. 2013; Kerr 1990). Notably, multiple types of plasma IgA receptors have been described; in humans, the myeloid Fc receptor for IgA (FcαRI; CD89) appears to have a central role for immune defence (Bakema and van Egmond 2011; Monteiro and van de Winkel 2003).

Polymeric IgA (pIgA) is found only at low concentrations in the blood, whilst it is abundant on mucosal surfaces. The dimeric pIgA is linked by a joining chain (J-chain). The transport of pIgA from the sites of biosynthesis to the luminal mucosal surfaces is mediated by the polymeric immunoglobulin receptor on the basolateral membrane of epithelial cells. After transcellular transport and release, a part of this receptor remains as so-called secretory component (SC) attached to form secretory IgA (S-IgA). The SC provides stability and protects from degradation by intestinal proteases. In the gut, S-IgA is thought to mediate the immune exclusion of luminal antigens and homeostasis of commensals as well as protection against pathogens (Barone et al. 2011; Benckert et al. 2011; Thurnheer et al. 2003).

### Plasma-Derived IgA as an Anti-Infectious Agent

So far, the plasma-derived IgA (pd-IgA) preparation, IgAbulin, has only been used intranasal or orally. Anaphylactic reactions are due to pre-existing anti-IgA antibodies in the circulation of the recipient, therefore, not posing a problem. pd-IgA has potent anti-microbial properties by mechanisms that include neutralization of superantigens or toxins, activation of the alternative pathway of complement, phagocytosis, and neutrophil extracellular trap formation (Aleyd et al. 2014; Janoff et al. 1999; Johnson et al. 1995; Norrby-Teglund et al. 2000). Given its anti-infectious activity, one pd-IgA preparation has been tested clinically, and a few case reports and one double blind, placebo-controlled study were reported (for references see Table 1). The largest study involved pd-IgA for the prevention of necrotizing enterocolitis (NEC), a life-threatening condition primarily of preterm infants. Despite promising initial results, a meta-analysis of three trials (including a total of 2095 neonates) concluded that the oral administration of IgG or an IgG/IgA combination does not result in a significant reduction in the incidence of definite or suspected NEC (Foster et al. 2004).

Recently, it was shown that 15 % of pd-IgA purified from human plasma carries a J-chain. Such plasma-derived polymeric IgA (pd-pIgA) displays the capacity to associate in a 1:1 stoichiometry with recombinant or colostrum-derived SC when incubated for 30 min at room temperature in vitro (Longet et al. 2013). The association of pd-pIgA with SC delayed degradation of the pd-pIgA by intestinal proteases, and yielded secretory-like antibodies with similar biochemical and functional characteristics as mucosa-derived immunoglobulins.

### Immunomodulatory Potential of Plasma-Derived IgA

In a series of in vitro experiments, IgAbulin showed an anti-inflammatory effect: it was inducing IL-1 receptor

antagonist and downregulating the CD89-mediated release of pro-inflammatory cytokines from human monocytes (Wolf et al. 1994, 1996). This in vitro effect of IgAbulin, however, did not translate into the prevention of NEC. Nevertheless, these early observations of immunomodulatory potential of pd-IgA were substantiated later and were reviewed in a number of excellent articles that highlighted the basis for the potent anti-inflammatory capacities of pd-IgA. To a substantial part, these appear to rely on FcαRI signalling (Bakema and van Egmond 2011; Ben Mkaddem et al. 2013; Blank et al. 2009). FcαRI appears to have dual functions in immunity: whilst cross linking of FcαRI by polymeric IgA or IgA immune complexes initiates activating signals through the tyrosine-based activating (ITAM) motif of the FcRγ subunit, following monovalent targeting of FcαRI, by anti-FcαRI Fab or monomeric IgA, this ITAM can propagate inhibitory signals in a conformation also referred to as inhibitory ITAM (ITAMi) (Blank et al. 2009; Pasquier et al. 2005). The ITAMi pathways seem to involve the recruitment of the inhibitory Src homology 2 domain-containing phosphatase 1 into polarized intracellular molecular clusters, so-called "inhibisomes" (Pfirsch-Maisonnas et al. 2011). It has been proposed that in the context of an infection, cross linking of FcαRI by IgA-opsonized pathogens might lead to pro-inflammatory responses, whereas monomeric serum IgA that is not complexed with an antigen might propagate regulatory effects to dampen excessive immune responses (Blank et al. 2009). Interestingly, we recently found that targeting FcαRI by monoclonal anti-FcαRI antibody or soluble, pooled plasma IgA regulates the survival of neutrophils (Wehrli et al. 2014). In fact, cell death is considered the main mechanism to control these innate effector cells which are the most predominant leukocytes in human blood and accumulate in tissues under the inflammatory conditions (Geering et al. 2013; Simon 2003).

Together, these findings indicate that donor-derived native, or engineered secretory-like, IgA preparations display promising anti-infectious and anti-inflammatory features that might be exploited for the treatment of certain medical conditions. However, the most effective type of IgA preparation and route of administration for potential indications remain to be defined.

## Concluding Remarks

The last decades have witnessed a growing understanding for the mechanisms of action and an expanding field of clinical applications for plasma-derived IgG-based immunoglobulin preparations. Learning about the effect of polyclonal IgM in humans remains limited, despite many clinical studies with a chemically modified preparation containing IgM and IgA. A preparation of plasma-derived IgA was applied in humans endonasally and orally only. Current attempts are being made to enhance the efficacy of polyclonal IgG preparations by the identification of relevant immunoglobulin sub-populations, or through mild chemical modification. IgG that has been engineered and altered in its Fc-part carbohydrate side chains may have particular anti-inflammatory and immunomodulatory potential. Furthermore, new preparations enriched in IgA and/or IgM have their own characteristics that might be advantageous at least in certain medical conditions. Combined efforts in basic, translational, and clinical research will be required to better delineate advantages or overcome shortcomings of these preparations. Inherent challenges remain, such as testing human preparations (xenoantigens) in animal models or the polyclonality of pooled preparations, that may lead to uncontrolled on-target and off-target effects (Gelfand 2012; von Gunten and Simon 2010; von Gunten et al. 2014). Testing of specific preparations and confirmation of concepts in human experimental systems are, therefore, imperative. Recent achievements in the field are encouraging and promote the increasing use and testing of classical and alternative immunoglobulin preparations in different clinical settings or novel indications. The exploration of current or alternative immunoglobulin preparations will lead to a better use of the precious starting material, namely human plasma, and to novel tools in the therapeutic use of human plasma products.

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