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Review

Immunoglobulin therapy in hematologic neoplasms and after hematopoietic cell transplantation

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ABSTRACT

Immunoglobulins are used to prevent or reduce infection risk in primary immune deficiencies and in settings which exploit its anti-inflammatory and immune-modulatory effects. Rigorous proof of immunoglobulin efficacy in persons with lympho-proliferative neoplasms, plasma cell myeloma, and persons receiving hematopoietic cell transplants is lacking despite many clinical trials. Further, there are few consensus guidelines or algorithms for use in these conditions. Rapid development of new therapies targeting B-cell signaling and survival pathways and increased use of chimeric antigen receptor T-cell (CAR-T) therapy will likely result in more acquired deficiencies of humoral immunity and infections in persons with cancer. We review immunoglobulin formulations and discuss efficacy and potential adverse effects in the context of preventing infections and in graft-versus-host disease. We suggest an algorithm for evaluating acquired deficiencies of humoral immunity in persons with hematologic neoplasms and recommend appropriate use of immunoglobulin therapy.

1. Introduction

Plasma-derived pooled human immunoglobulin for intra-muscular injection has been available for > 70 years and intravenous preparations (IVIG) for > 30 years [1,2]. Immunoglobulin preparations for clinical use are derived from large pools (> 10,000 L) of donor plasma by variations of a fractionation process developed by Cohn and Oncley in the 1940s which used sequential precipitation with increasing concentrations of cold ethanol to obtain albumin for treating shock on World War II battlefields [3]. Immunoglobulin serum globulin (ISG) concentrates were first used to prevent viral infections such as hepatitis, measles and polio [2]. In the 1950s and 60s ISG came into use for antibody replacement therapy in the newly-diagnosed primary immune deficiency diseases such as X-linked (Bruton) agammaglobulinemia (XLA) and common variable immune deficiency (CVID) [4,5]. Because the immune serum globulin fraction (II) caused severe shock-like reactions when given intravenously [2], these preparations were initially given intramuscularly or subcutaneously. The efficacy of pooled immunoglobulins in reducing incidence and severity of infections in these settings eventually led to its use in chronic lymphocytic leukemia (CLL) and other hematologic neoplasms in which the primary disease, therapy or the combination resulted in immune deficiency. In the 1970s it was recognized that aggregates which formed during preparation and storage of the concentrated (16%) immunoglobulin preparations could activate complement and leukocytes and caused most of the adverse effects associated with IVIG infusions. Enzyme treatment and/or chemical modification of the immunoglobulin molecules was used to reduce aggregate formation, and IVIG preparations that safely can be given IV (IVIG) have been available since the early 1980s. Shortly thereafter, serendipitous observations in immune thrombocytopenic purpura (ITP) [6,7] and in Kawasaki disease (a vasculitis of infants) [8] led to the discovery of anti-inflammatory and immune-modulatory effects of high-dose IVIG. Subsequently, IVIG infusions were extended to diverse autoimmune and inflammatory diseases. These indications now account for more IVIG use than immune deficiencies [9].

Despite many clinical trials, rigorous proof of efficacy of IVIG in persons with hematologic neoplasms is lacking, and there are few accepted guidelines or algorithms for use in these conditions. This uncertainty results largely from observations of clear benefit in some persons but failure to reproduce these effects consistently in large, randomized clinical trials likely reflecting heterogeneity of diseases, subjects, treatments and supportive care. Nevertheless, efficacy of immunoglobulin therapy in primary immune deficiency diseases suggests its possible indication in many persons with infections from secondary

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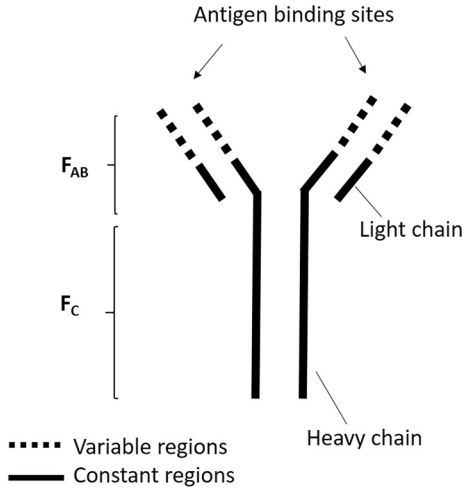

Fig. 1. Immunoglobulin structure.

immune deficiencies associated with hematologic neoplasms and/or their therapies. The rapid development of new therapies targeting B-cell signaling and survival pathways, as well as growing use of chimeric antigen receptor T-cell (CAR-T) therapy suggest an increasing incidence of secondary immune deficiency and infection in persons with cancer. Here, we review current immunoglobulin preparations and uses, suggest an approach to evaluate risks and benefits of immunoglobulin therapy, and discuss studies in persons with hematologic neoplasms.

2. Immunoglobulin products and therapy

Immunoglobulins are glycoproteins composed of a basic unit containing two identical heavy and light chains (Fig. 1) [10,11]. The four major isotypes of immunoglobulins (IgA, IgE, IgG, and IgM) are defined by their respective heavy chains (α, ε, γ, μ). Each light chain (κ or λ) has a variable region and a constant region, and each heavy chain has a single variable region and 3 constant regions, except IgE which has an extra constant region. The variable regions of one pair of heavy- and light-chains align to form each of two antigen-binding sites specific to each immunoglobulin molecule. Because of amino acid substitutions in the variable regions, a person's immune system can produce approximately 10^{12} distinct antibodies each with a unique antigen-specificity (idiotype) [12]. The constant domains of the heavy chains form a dimer (Fc region) which binds other proteins and/or receptors on cell surfaces.

The specificity or target of an immunoglobulin molecule is determined by the antigen binding sites, and its effector functions are mediated by the Fc region. The Fc portion of some immunoglobulins can activate complement, facilitate phagocytosis and/or enhance cell-mediated cytotoxicity. Actions independent of the Fc regions can be reproduced by the $F(ab')_2$ fragment including neutralization of toxins, adhesins and other molecules necessary for microbial pathogenesis. Because immunoglobulin molecules are at least bivalent (with two identical antigen binding sites in IgG, 4 in dimeric IgA, and 10 in IgM) they agglutinate infectious particles in an Fc-independent manner [12].

Modern production of immunoglobulin products involves at least one ethanol precipitation step but chromatographic methods have largely been substituted for repeated fractional precipitations. These methods yield IVIG products which are > 95% pure immunoglobulin G (IgG). With improved manufacturing processes enzyme treatment or other chemical modifications of the IgG is no longer needed. Nevertheless, trace amounts of pre-kallikrein, activated coagulation factors, complement proteins, IgA, and IgM are occasionally found in IVIG preparations and may contribute to infusion-related adverse effects (see “Adverse Effects and Contraindications”) [13].

Only plasma obtained in the US can be used for products marketed in the US. Donor screening and testing is rigorous; intermediate pools undergo polymerase chain reaction (PCR) testing for viruses such as HIV, hepatitis A, B and C and parvovirus B19 [14]. All preparations undergo multiple treatments to inactivate and/or remove potential blood-borne pathogens and prions. These rigorous steps include treatment with fatty acids, alcohols or solvent-detergent regimens designed to disrupt the lipids in enveloped viruses, treatment at pH 4 and/or pasteurization (prolonged incubation at 60° C) to disrupt coat proteins of non-enveloped viruses, and nano-filtration. These methods result in > million-fold reductions in test pathogens added to plasma pools and are sufficiently robust to inactivate/remove HIV and newly-recognized potentially blood-borne viruses including West Nile and Zika viruses [15]. Current methods for donor screening, product fractionation and viral inactivation are highly effective and transmission of pathogens has not occurred with any currently available products [16].

Several IgG products are commercially available in the US, European Union (EU) and Latin America (summarized in Table 1). These preparations vary in IgG concentration, manufacturing procedures, composition and availability. Pharmacokinetics of subcutaneous IgG differ from those of IVIG. After subcutaneous (SC) administration peak plasma concentrations are not reached for 36–72 h, whereas with IVIG a very high peak is achieved rapidly [17]. Recently, there is renewed interest in SC administration of immunoglobulins because of fewer adverse effects than IVIG and self-infusion at home [18–20]. Some manufacturers have introduced highly concentrated (20% w/v) IgG preparations to facilitate this route of delivery [21].

Regardless of route of administration, once in the intravascular space, IgG distributes into the total volume of extracellular fluid over 36–48 h. Following this rapid re-distribution phase, pharmacokinetic curves show first order catabolism with a half-life of 28–30 days in most

Table 1
IgG formulations available in the US.

Trade name	IgG concentration	Stabilizer/other components	Route of administration
Gammagard S/D (low IgA)	50 mg/mL (< 1 μg/mL IgA)	NaCl, Glycine, PEG, albumin, glucose	IV
Gammagard Liquid	100 mg/mL	Glycine	IV
Gammaplex 5%, 10%	50 mg/mL 100 mg/mL	Albumin, sucrose, glycine	IV
Carimune NF	30, 60, 90, or 120 mg/mL	Sucrose, NaCl	IV
Bivigam	100 mg/mL	Glycine, Polysorbate 80	IV
Privigen	100 mg/mL	Proline	IV
Hizentra	200 mg/mL	Proline	SC use only
Flebogamma DIF 5%,10%	50 mg/mL, 100 mg/mL	D-sorbitol, PEG	IV
Octagam 5%, 10%	50 mg/mL, 100 mg/mL	Maltose	IV
Cuvitru	200 mg/mL	Glycine	SC use only
Gamunex-C	100 mg/mL	Glycine	IV or SC use
Gammaked	100 mg/mL	Glycine	IV or SC use
Hyqvia	100 mg/mL	Glycine	SC, with hyaluronidase