INNOVATIONS JOURNALS

Review Article

Use of Immunoglobulin Replacement Therapy in Clinical Practice: A Review

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Source of Support: None.

Conflict of interest: Joud Hajjar reports sponsored research from ASTRAZENECA AB, grants from Jeffrey Modell Foundation and Takeda, grants and other from Immune Deficiency Foundation, honorarium for talks from Immune Deficiency Foundation, and advisory board role at Pharming. The remaining authors have no conflicts of interest.

Submitted: Feb 21, 2024; First Revision Received: Aug 7, 2024; Accepted: Aug 20, 2024; First Published: Dec 5, 2024.

Ahmed J, Choi Y, Ko T, Lim J, Hajjar J. Use of immunoglobulin replacement therapy in clinical practice: a review. *J Immunother Precis Oncol*. 2025; 8:34–46. DOI: 10.36401/JIPO-24-7.

ABSTRACT

Immunoglobulins (Igs) are produced by B lymphocytes and play a key role in humoral immunity. Igs are classified into five isotypes (IgG, IgA, IgM, IgE, and IgD). Their primary function is to recognize and bind to foreign antigens. When Igs bind to antigens, they facilitate phagocytosis and promote clearance mediated by other immune cells. It is an essential component in protecting the host from outside pathogens. Hypogammaglobulinemia predisposes an individual to severe and recurrent infections. Therefore, replacement therapy is recommended to maintain optimal Ig level. In addition, Igs can modulate immune responses by to neutralizing proteins such as endotoxins or receptor-binding antibodies. They can be used to manage excessive immune reactions and autoimmune-related diseases. In this review, we aimed to summarize the clinical indications for Ig therapy for practicing oncologists.

Keywords: immunoglobulins, cancer, transplant, autoimmune disorders, neurological disorders

INTRODUCTION

Human immunoglobulin G (IgG) has emerged as a cornerstone in the management of a spectrum of humoral immunodeficiencies, demonstrating significant efficacy in reducing infection rates and associated mortality. Beyond its role in immunodeficiency, IgG possesses immunomodulatory properties that make it a critical intervention in a range of hematologic and autoimmune pathologies. This review aims to synthesize current knowledge and best practices in prescribing immunoglobulin therapy, particularly focusing on its crucial role in managing inborn errors of immunity and its evolving applications in the fields of hematology and oncology. Immunoglobulin replacement therapy (IgRT), which is primarily composed of IgG derived from pooled donor plasma, serves as both a supplement in immune deficiency states and a modulator of immune responses. The extensive applicability of IgRT in a variety of clinical scenarios is underpinned by its multifaceted mechanisms of action, which is explored in detail within this article. Although this article comprehensively explores the multifaceted mechanisms of action and clinical applications of IgRT, it specifically excludes experimental uses of immunoglobulins, such as their role in anticancer therapies. The focus of this article is to provide an updated reference for the practicing clinical hematologist/oncologist, summarizing Food and Drug Administration (FDA) approvals for immunoglobulins (Supplementary Tables S1–S4), particularly in the context of cancer and its treatment-related toxicities. In addition, this article offers an update on the potential mechanisms of action of immunoglobulins and their adverse events. Literature search for this review was carried out on PubMed. The selection of topics focused on FDA-approved indications for immunoglobulins and included the most relevant clinical applications as determined by the authors. This approach ensured that the review would provide the most pertinent and practical information for clinical oncologists.

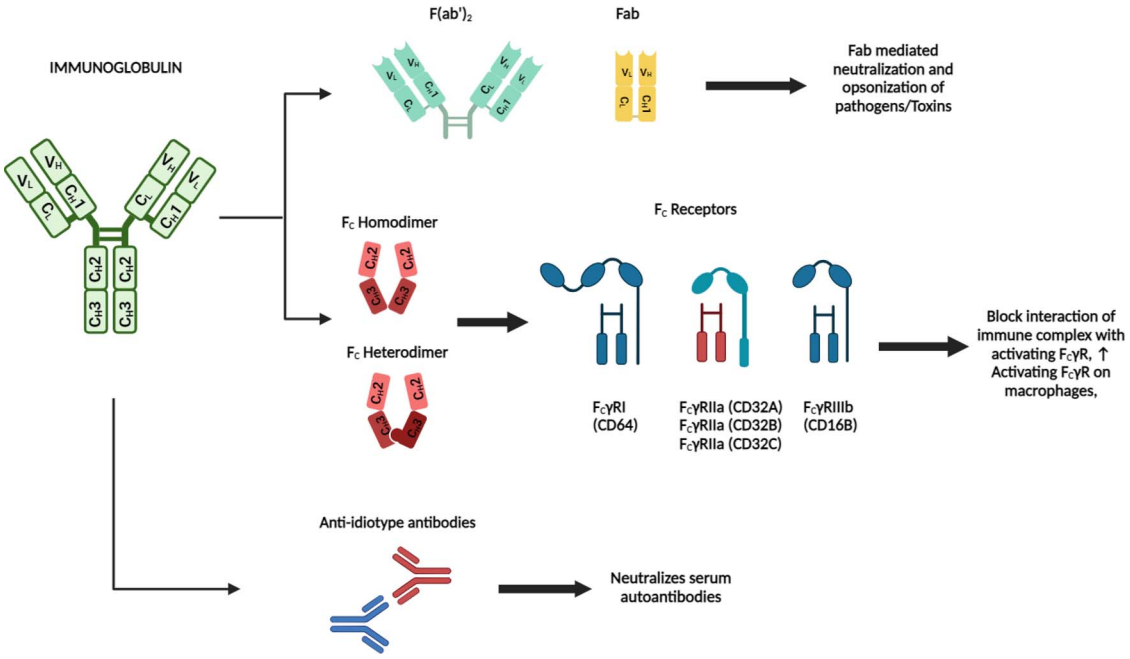

Figure 1. The components of immunoglobulins and the mechanism of action.[111] This figure was created using BioRender.com. CD: cluster of differentiation; fab: fragment antigen-binding region; f_c: fragment crystallizable region; FcγRs: f_c gamma receptors.

THERAPEUTIC MECHANISMS OF IgG

Immunoglobulin therapy (IgRT) serves a dual role in clinical medicine: as a vital replacement in immunodeficiency disorders and as an immunomodulatory agent in various autoimmune and inflammatory conditions. As a replacement, IgRT provides the critical antibodies that patients with inherent or acquired immunodeficiencies lack, effectively replenishing the deficient immunoglobulin G (IgG) and reconstituting the humoral arm of the immune system. This restoration is pivotal in safeguarding against infections and maintaining immune homeostasis.

The immunomodulatory role of IgG, however, is more complex and multifaceted. Through a range of mechanisms, IgG modulates the immune system's activity to curb aberrant inflammation and autoimmunity. It achieves this by influencing various immune cells and pathways, including the regulation of cytokine production, the saturation of Fc receptors, and the inhibition of complement activation, among others (Figs. 1 and 2). For example, immunoglobulins may decrease T cell activation, reduce B cell proliferation, and produce changes in antibody production.[1,2] The role of IgRT in modulating B cell activity is still under investigation and has not been extensively characterized. These actions contribute to a tempered immune response, beneficial in the management of autoimmune disorders, and certain hematologic conditions. The ensuing sections delve deeper into the intricacies of these mechanisms, shedding light on the interplay between IgG and the immune system, providing clinicians with a conceptual framework for the therapeutic use of immunoglobulins.

Supplementary Table S1 outlines the FDA-approved immunoglobulins and their indications for use, offering a clear view of the current approved applications of IgRT. Supplementary Tables S2–S4 provide additional details on FDA-approved subcutaneous and intramuscular products, hyperimmune globulins, and animal-derived products. This information lays the groundwork for exploring the specific roles of IgRT in managing various immunological disorders.

The American Academy of Allergy, Asthma, and Immunology (AAAAI) recommends continuous replacement therapy for primary immunodeficiency disorders starting at a dosage of 400 to 600 mg/kg every 3 to 4 weeks and with most patients appropriate for intravenous (IV) route of administration.[3]

The route of administration results in variations in pharmacokinetics of immunoglobulin formulations. In contrast to intravenous immunoglobulins (IVIGs), formulations of hyaluronidase-facilitated subcutaneous (SC) immunoglobulins (fSCIGs) exhibit reduced variations in serum drug concentrations, whereas the SC immunoglobulin (SCIG) formulations have the lowest variation over time. However, SC formulations also have the lowest bioavailability. fSCIG offers improvement in bioavailability over the SC formulations. The fSCIG also allows for a larger dose and less frequent administration compared with SC formulation. Thus, there is significant variability in the dose and frequency of administration. In addition, flu-like symptoms, mostly mild, are more commonly reported with IV formulations.

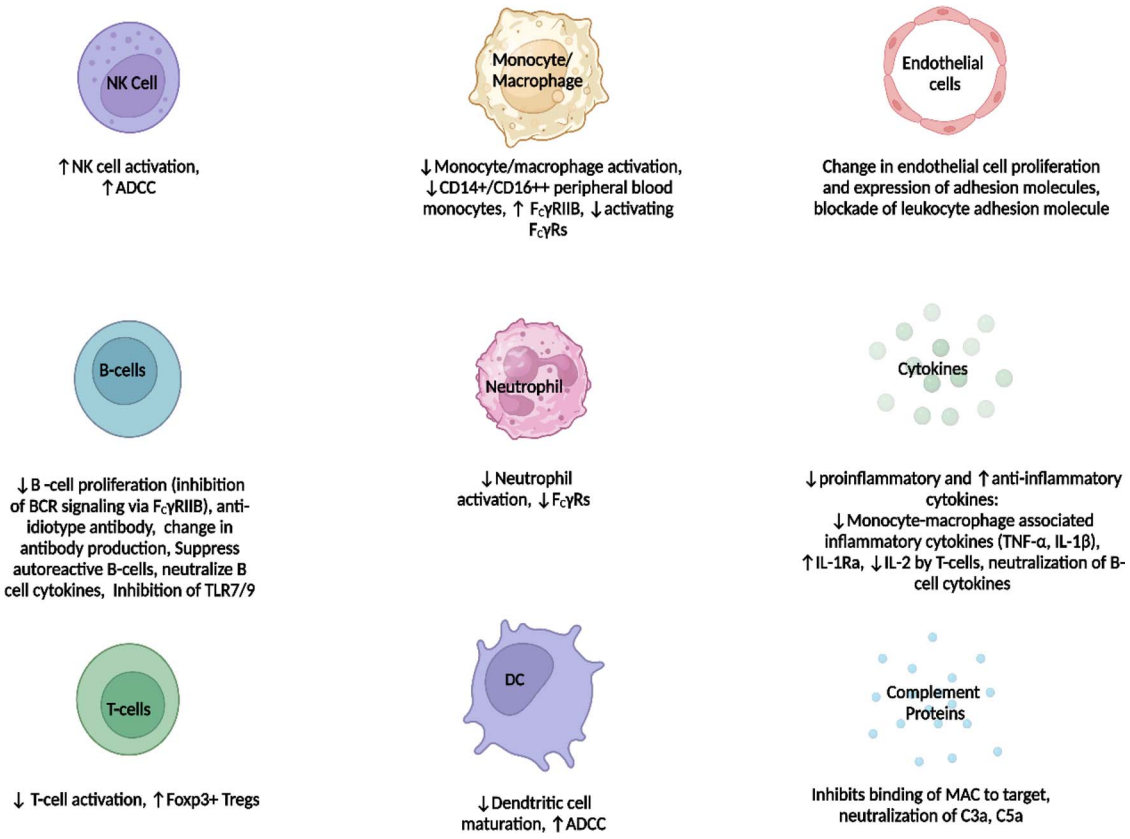

Figure 2. The various immune cells of the innate and adaptive immune response that take part in response to immunoglobulins.[112,113] This figure was created using BioRender.com. ADCC: antibody-dependent cellular cytotoxicity; CD: cluster of differentiation; FcγRs: f_c gamma receptors; IL-1 β: interleukin 1 beta; IL-2: interleukin 2; IL-1 Rα: interleukin 1 receptor alpha; MAC: membrane attack complex; NK: natural killer cell; TNF-α: tumor necrosis factor alpha; TLR 7/8: Toll-like receptor 7 and 8; Tregs: regulatory T cells.

INBORN ERRORS OF IMMUNITY

Inborn errors of immunity (IEIs) are caused by monogenic germline pathogenic variants resulting in impaired function of the encoded protein. IEIs are divided into two broad categories: disorders of innate and adaptive immunity. Disorder of innate immunity consists of deficiency of Toll-like receptors, natural killer cells (NK cells), neutrophils, complements, or cytokines, whereas disorders of adaptive immunity include T and B cell disorders. Specifically, B cells are involved in antibody production and antibody-mediated immunity, ultimately referred to as humoral immunity. As of the latest update from the International Union of Immunological Societies Expert Committee, there are 485 genetic anomalies cataloged, reflecting the vast heterogeneity of IEIs.[4] Consequently, the indications for IgRT are likely to increase particularly in disorders with antibody deficiencies. In the clinical management of these conditions, particularly for those with B cell defects and hypogammaglobulinemia, IgRT is fundamental, serving as a lifeline to bolster the immune system.

The increasing number of diagnostic entities underscores the challenges in diagnosis, and the early implementation of diagnostic modalities, such as next-generation sequencing, may address these challenges in the genetic diagnosis of these disorders.[5] The diagnostic misclassification coupled with unknown etiologies for a significant number of these disorders may result in management disparities.[6]

The subsequent sections provide a concise overview of selected IEIs in which IgRT has been established as the standard of care.

Disorders With Predominantly Antibody Deficiency

X-linked agammaglobulinemia (XLA), known as Bruton's agammaglobulinemia, is an X-linked disorder caused by a mutation in the BTK gene, leading to an early B cell development arrest and global agammaglobulinemia. Affected male children, typically younger than 2 years, present with recurrent, severe sinopulmonary infections, mainly from encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, and gastrointestinal infections from *Campylobacter* and *Helicobacter*.[7] IgRT is the standard of care in patients with these types of infections and lifelong replacement is recommended to prevent severe infections. A target trough IgG level around 1000 mg/dL is suggested to prevent severe illness and recurrent

pneumonia among patients with IEI.[8] Previous data support a higher dose of IgRT >400 mg/kg with primary immunoglobulin defects in general.[9] These earlier data, including the mentioned studies, primarily emphasized maintaining trough levels for preventing infections. However, the current approach favors maintaining a physiological trough that helps prevent patients from experiencing severe infections.[10]

In a recent registry study conducted in United States with 240 patients diagnosed with XLA, 92% reported receiving IgRT.[11] Despite the establishment of XLA and ongoing IgRT, patients continued to experience infections, including episodes of pneumonia, whereas a higher frequency of sinus infections and otitis media was reported. Only the prevalence of bacteremia/sepsis and meningitis decreased before and after diagnosis.

Common variable immunodeficiency (CVID), the most common symptomatic IEI in adults, is characterized by hypogammaglobulinemia, impaired specific antibody responses, and typically, normal B cell counts. To date, a genetic cause can only be identified in approximately 35% of patients previously diagnosed with CVID. When the genetic cause is identified, it offers a more specific diagnosis linked to the specific genetic factor (e.g., CTLA4 haploinsufficiency).[12] Clinical manifestations of CVID are diverse, ranging from serious infection to autoimmune and autoinflammatory disorders.[13] The respiratory tract is the most common site of infection typically caused by encapsulated bacteria. IgRT has been shown to reduce the recurrence of sinopulmonary infection and to some extent the progression of persistent immune activation.[14] A longitudinal analysis of 90 patients with CVID showed an infection prophylactic dose of replacement immunoglubulins ranged from 0.2 to 1.2 g/kg/mo.[15] Clinical outcomes may further improve with tailored adjustments in serum IgG concentration, potentially requiring higher doses of subcutaneous IgRT.[16]

In addition, in severe combined immunodeficiency (SCID), which is characterized by lymphopenia and compromised lymphocyte function, IgRT can be lifesaving similar to other primary immunoglobulin defects, and it is often used as a critical bridge to allogeneic stem cell transplantation.[17] Early diagnosis and prompt initiation of IgRT, along with comprehensive infection control measures while preparing for definitive therapy, such as hematopoietic stem cell transplantation (HSCT), are essential in managing SCID, given its severe and potentially life-threatening nature.

Combined Immunodeficiency Disorders With Hypogammaglobulinemia

Hyper-IgM syndrome is characterized by decreased IgG and IgA levels, along with high or normal IgM levels that have low affinity. The most common type of hyper-IgM syndrome is an X-linked recessive disorder, caused by CD40 ligand deficiency, which affects both T and B cells. The most common autosomal recessive type is deficiency of activation-induced cytidine deaminase.[18] *S. pneumoniae*, *Pseudomonas aeruginosa*, and *Pneumocystis jirovecii* (PJP) are common pathogens causing pneumonia.[19] Patients can also easily acquire opportunistic infections and hepatobiliary diseases. IgRT can reduce the risk of infection significantly.[20]

Transient Hypogammaglobulinemia of Infancy

Transient hypogammaglobulinemia of infancy occurs due to a delay in the onset of antibody production in infants, typically starting around 6 months to 2 years after birth.[21] This condition is partly attributed to the placental transfer of IgG, facilitated by the neonatal FC receptor, predominantly in the third trimester of pregnancy.[22] Although most infants' immunoglobulin levels normalize between 2 and 6 years, a phase of transient hypogammaglobulinemia, lasting 5 to 24 months, may occur.[23] Although most infants do not require replacement therapy, IgRT may be beneficial for those experiencing life-threatening infections or recurrent respiratory infections despite antibiotic therapy.[24]

OTHER INBORN ERRORS OF IMMUNITY

IgG subclass deficiency and specific antibody deficiency (SAD) represent common forms of IEI. SAD is characterized by the inability to produce specific antibody responses despite normal immunoglobulin levels. A retrospective study from two tertiary centers in the United States, comparing prophylactic antibiotics and IgRT in 65 patients with SAD, indicated similar effectiveness of the two modalities in patients with SAD.[25] In addition, in a randomized crossover study in patients with subclass deficiency, with or without specific polysaccharide antibody deficiency, showed comparable efficacy between prophylactic antibody and IgRT.[26] A retrospective study in 350 patients with immunoglobulin subclass deficiency showed that IgRT may reduce recurrent respiratory infections among certain IgG-deficient subtypes.[27]

Selective IgA deficiency, the most common IEI, is associated with recurrent infections, autoimmune disorders, and allergic manifestations. IgRT is not recommended for selective IgA deficiency, particularly owing to the risk of severe allergic reactions. There is limited evidence supporting the benefit of IgRT for isolated IgE and IgM deficiencies.

Secondary Immunodeficiency

Secondary immunodeficiency (SID) differs fundamentally from IEI, as it arises not from genetic errors but from external factors such as infections, malignancy, or drug therapies. Unlike the innate nature of IEIs, SID represents a spectrum of disorders in which the immune system is compromised due to these acquired conditions. For certain categories of SID, immunoglobulin

replacement therapy can be a crucial part of patient care, to mitigate the heightened risk of infections.[28]

Multiple Myeloma

In multiple myeloma (MM), patients face an elevated risk of infections due to dysregulated plasma cell proliferation and the effects of extensive anticancer treatments. This susceptibility to infection, which is particularly prominent at diagnosis and during treatment, remains a leading cause of mortality in MM.[29] Patients with MM have severalfold higher susceptibility to viral and bacterial infections compared with healthy controls. In addition, severe infections may occur at any stage of treatment.[30] This vulnerability to infection, particularly at the time of diagnosis, is linked to various factors, primarily a plasma cell defect, as well as comorbidities like renal dysfunction.[31] This susceptibility is heightened in the context of underlying treatments such as chemotherapy/autologous transplantation, proteasome inhibitors, immunomodulatory imide drugs, monoclonal antibodies, and high-dose steroids among other factors.[32] Thus, prophylactic antibiotics and vaccinations are indicated for these patients. Historical data, including a randomized, double-blinded, placebo-controlled study suggested that the administration of immunoglobulin replacement can reduce the prevalence of infection, sepsis, and pneumonia[33]; however, recent data on this aspect are scarce. Meta-analyses have shown that prophylactic IgRT in MM and chronic lymphoid leukemia can decrease major infections and improve survival outcomes, even if direct survival benefits are not evident.[34] IgRT may be considered for recurrent infections in patients with MM with significant hypogammaglobulinemia (<400 mg/dL), aligning with the International Myeloma Working Group consensus guidelines. Yet, this practice is not uniformly adopted in clinical settings.[35] The implementation of this practice is further constrained by the cost of IgRT and the potential for complications.[36] In addition, studies have indicated that benefits of IgRT during the peri-autologous stem cell transplantation period may be limited due to chronic immune suppression from the disease and chemotherapy.[37] An expert panel on myeloma recommends considering IgRT for patients with frequent, life-threatening infections unresponsive to antibiotics, although the evidence supporting this practice remains limited.[38] There remains an evidence gap regarding the impact of IgRT on prevention of infection in secondary immunodeficiency associated with current treatments like proteasome inhibitors, anti-CD38 monoclonal antibodies, immunomodulatory drugs, and chimeric antigen receptor T cell therapy (CAR-T).[39]

Chronic Lymphocytic Leukemia

Hypogammaglobulinemia is a common feature of chronic lymphocytic leukemia (CLL), in addition to a constellation of immune dysfunctions. These include defective function of T cells and nonclonal CD5-negative B cells, defects in innate immunity including suppressor NK cells, neutrophils, complement system, as well as treatment-related effects.[40] A significant decrease in IgG subtypes, especially IgG3 and IgG4, is frequently observed, with about half of patients with CLL experiencing recurrent infections.[41] Moreover, most encounter complications from infections.[42] Individuals with advanced CLL may experience a more pronounced hypogammaglobulinemia, and its decline may accelerate with disease progression.[43] Therefore, one of the main goals in CLL treatment is to prevent infections. Prophylactic use of IgRT has been investigated in small-scale studies over the past few decades. Earlier randomized controlled trials indicated that patients with serum IgG levels $\leq$50% of the lower normal limit could see reduced infection risk with regular immunoglobulin administration.[44] Additional studies have supported the preventive role of IgRT against infections in patients with CLL.[45] However, responses to IgRT in these trials have varied, ranging from reduced serious infections and hospitalizations to no significant impact on infection rates.[46] Notably, these studies do not demonstrate a survival benefit, and the therapeutic landscape for CLL has evolved substantially in recent years.[46] The optimal dosage and timing of IgRT in CLL, especially in the context of novel therapies like Bruton tyrosine kinase inhibitors (BTKi), are still under debate. The International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines suggest that IgRT may reduce infection incidence in selected patients with recurrent infections and hypogammaglobulinemia, but routine use is not universally recommended.[47] However, IgRT has been used for patients with CLL with low serum immunoglobulin levels who experience a severe infection or recurrent infections without a clear consensus on when to initiate.[48] This practice overlooks several aspects inherent to patients with CLL such as those with high-risk disease and exhausted T cell phenotype compared with low-risk disease with normal immunoglobulin level and immunocompetent cells.[49] Further research is needed to understand the role of IgRT in CLL treatment, particularly with the advent of new therapeutic agents like BTKis.[50,51] The SC route of administration is well-tolerated and efficacious among patient with SID in CLL.[52] However prospective comparative studies are needed in this regard. The role of immunoglobulin therapy in immune thrombocytopenia and autoimmune hemolytic anemia is discussed in the following sections.

B Cell Depletion Therapy

B cell depletion therapies are frequently used in cancers and autoimmune disorders and include anti-CD19, anti-CD20, anti-CD22, anti-CD38, anti-BAFF, anti-BCMA monoclonal antibodies; bi-specific antibodies; cellular therapies including CAR-T therapy; conditioning chemotherapy regimen; and BTKi, among other treatments.

A notable consequence of these therapies is the potential induction of hypogammaglobulinemia in some patients.[53] Particularly, the widely used anti-CD20 monoclonal antibody rituximab is known for its B cell–depleting effect, which can lead to profound hypogammaglobulinemia. This necessitates vigilant monitoring of immunoglobulin levels during therapy.[54] We recommend routinely assessing immunoglobulin levels before starting rituximab and other B cell–depleting therapies. This is particularly important as patients with IEI and hypogammaglobulinemia may initially present with autoimmunity. Without pretreatment immunoglobulin data, such presentations risk being misclassified as secondary hypogammaglobulinemia.[55]

IgRT is advised for patients having symptomatic hypogammaglobulinemia such as severe infection or those with impaired response to vaccination.[56] A case series highlighting rituximab-induced hypogammaglobulinemia showed that IgRT could significantly reduce infection risks and aid in disease control.[57] In a retrospective cohort study analyzing 8633 patients who received rituximab between 1997 and 2017, a notable proportion of patients developed varying degrees of hypogammaglobulinemia post-treatment, with a subset requiring hospitalization, especially those with an underlying diagnosis of cancer. This study also found an association between the cumulative dose of IgRT and a reduced risk of serious infectious complications.[56] In this study, 28.2% of patients needed hospitalization, particularly those with a cancer diagnosis. Furthermore, among the 4.5% of patients who were treated with IgRT, the study demonstrated an association between cumulative dose of immunoglobulins and a reduced risk of serious infectious complications. Therefore, IgRT has been used for preventing infections in patients undergoing monitoring and experiencing hypogammaglobulinemia while receiving rituximab treatment.

The occurrence of severe infections remains a frequent complication of CAR-T therapies and B cell aplasia leading to hypogammaglobulinemia is identified as one of the contributing factors.[58] The Society for Immunotherapy of Cancer (SITC) recommends monitoring IgG levels during cellular therapy. However, clear guidelines on the initiation of IgRT for these patients are still lacking. There is a need for additional risk stratification and prioritization based on specific subgroups of patients.[59]

Hematologic and Solid Organ Transplantation

In the realm of transplantation, immunoglobulins play a pivotal role, not only in preventing infections following HSCT but also in mitigating antigen-antibody-mediated rejection in both HSCT and solid organ transplantation, as well as in managing graft versus host disease (GVHD). The myeloablative conditioning before HSCT leads to severe cytopenia and immune suppression, which may result in life-threatening infections.[60] Therefore, both peri-transplant therapies and the underlying disease conditions like CLL and MM often result in hypogammaglobulinemia.[61,62] Hypogammaglobulinemia in turn has been linked to poor survival rates, increased transplant-related mortality, and an association with acute GVHD in patients who undergo HSCT.[63]

A meta-analysis of several controlled trials showed that immunoglobulins administration prevents the occurrence of acute GVHD; however, there was no reduction in incidence of chronic GVHD.[64] theThe role of prolonged use of prophylactic or therapeutic IVIG therapy for acute GVHD remains unclear and in fact it might hinder restoration of humoral immunity.[65] In transplantation from a matched unrelated donor, chronic GVHD involves more complex immunoglobulin remodeling and deposition, leaving the practical use of IgRT in these cases yet to be established.[66] In addition, several preventive and therapeutic options are now available for acute and chronic GVHD.[67] The American Society for Transplantation and Cellular Therapy (ASTCT, formerly ASBMT), National Comprehensive Cancer Network (NCCN), and AAAAI guidelines have recommended use of IgRT for HSCT-associated hypogammaglobulinemia in specific scenarios including cord blood transplant recipients, HSCT for inherited or acquired B cell deficiency conditions in children, chronic GVHD in patients with recurrent sinopulmonary infections, high-risk or allogeneic HSCT recipients with low IgG level $<$400 mg/dL, and for those HSCT recipients with IgG $<$400 mg/dL with bacteremia or recurrent sinopulmonary infection.[68]

The role of IVIG in solid organ transplantation, particularly as supplementary therapy for infection prevention, remains inadequately explored in terms of safety and effectiveness.

Sensitization to human leukocyte antigen (HLA) and ABO blood group antigens can be a serious challenge to solid organ transplantation. Development of donor-specific anti-HLA antibodies can result in both acute and chronic graft rejection.[69] Research in the 1990s demonstrated that high-dose IVIG could reduce anti-HLA antibody levels in sensitized patients and ultimately improve transplantation rates.[70] In addition to IVIG, other antibody-depleting therapies such as plasmapheresis or rituximab are combined to manage highly sensitized patients. However, a recent randomized controlled trial by Kim et al. [71] reported no additional benefit for adding IVIG to rituximab compared with rituximab alone for decreasing de novo donor-specific antibodies that are associated with graft rejection. In the setting of graft rejection, the IVIG interferes with B and T cell activation, antibody formation, and modulation of complement activation.[72] Local guidelines on dosing and schedule are limited.

A meta-analysis of off-label use in solid organ transplant rejections has shown that the use of immunoglobulins might be beneficial, though the data are limited to

small nonrandomized, retrospective, or observational studies.[73] However, the benefits of high-dose IVIG and plasma exchange with low-dose IVIG have been reported in acute antibody-mediated rejections.[74]

In kidney transplantation, chronic-active antibody reaction mediated rejection (CaARM) is one of the main causes of graft loss and is characterized by a gradual loss of renal function. However, CaARM can be managed with methylprednisolone and immunoglobulins. In a study from the Netherlands, 69 patients were treated with three doses of 1 g IV methylprednisolone and a single dose of IVIG (1 g/kg of body weight). More than 60% of patients show improved graft survival.[75] A retrospective review conducted at a single center of patients with a diagnosis of CaARM also demonstrated a a decrease in graft loss.[76] The role of IgRT in modulating cancer outcomes has not been studied extensively.

Hematologic Autoimmune Disorders

The standard first-line therapy for bleeding due to immune thrombocytopenia (ITP) commonly includes a combination of corticosteroid, platelet transfusion, and IgG.[77] An early study in 1981 reported that high-dose IVIG rapidly increased platelet counts in children with ITP.[78] Subsequent clinical trials have solidified the effectiveness of immunoglobulins, showing that IVIG up to 0.4 to 1 g/kg/d over 2 to 5 days is effective in most patients with ITP.[79] Although the exact mechanisms of immunoglobulins in ITP are still under investigation, several have been suggested, including competing autoreactive T cells, action on Fc receptors, and immunomodulation via dendritic cells.[80] Other proposed immunomodulatory mechanisms include FcγR blockade, saturation of FcRn, inhibition of the complement cascade, and neutralization of pathogenic antibodies.[80] Thus, the American Society of Hematology recommends IVIG as one of the first-line therapies in ITP.[81]

In warm autoimmune hemolytic anemia (AIHA), immunoglobulins are occasionally used as second-line treatment, usually in combination with glucocorticoids and mycophenolate mofetil. In this setting immunoglobulins may be administered at 500 mg/kg/d for 4 days or 1 g/kg/d for 2 days.[82] According to the recommendation from the First International Consensus Meeting, immunoglobulins at 0.4 to 0.5 g/kg/d for 5 days can be used mainly as a bridging treatment for transfusion-dependent life-threatening warm AIHA and as an adjunct to other therapies.[83] However, the effectiveness of IVIG in this setting is limited to a small subset of patients.

Immunoglobulins are also effective against pure red cell aplasia related to parvovirus B19 infection, likely due to the presence of neutralizing anti-parvovirus B19 antibodies.[84] The initial report demonstrating the efficacy of immunoglobulins against parvo B19 dates back to 1989,[85] after which subsequent case studies have supported this finding.[86] Immunoglobulin treatments have been effective for parvovirus B19 infections in the context of solid organ transplantation, HIV infection, and primary antibody deficiencies.[87]

MANAGEMENT OF IMMUNE CHECKPOINT INHIBIT—ASSOCIATED TOXICITIES

Severe or life-threatening toxicities associated with immune checkpoint inhibitors (ICIs) are managed with immunoglobulin therapy (IVIG) primarily as an adjunct to other immunosuppressive therapies, such as corticosteroids, or in cases where initial treatment with these immunosuppressive therapies is unsuccessful. Although ICIs have revolutionized cancer therapy, they can induce a range of immune-related adverse events (irAEs) due to their mechanism of enhancing immune activation. The management of these toxicities is crucial for maintaining the efficacy of cancer treatment while minimizing harm to the patient (Fig. 1 and Table 1).

The indications for IVIG use in ICI-associated toxicities are often based on expert recommendations derived from limited data or case reports and lack robust evidence from placebo-controlled clinical trials. These recommendations highlight the necessity of IVIG in situations in which conventional immunosuppressive treatments fail or are insufficient. For instance, autoimmune bullous dermatosis, Guillain-Barré syndrome, myasthenia gravis, myocarditis, myositis, and severe neurologic toxicities such as encephalitis or demyelinating diseases like optic neuritis, transverse myelitis, and acute demyelinating encephalomyelitis (ADEM), have been reported to benefit from IVIG therapy. In addition, IVIG has been used in managing severe pneumonitis and conditions like Steven-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) associated with ICI therapy, although these indications are beyond the scope of this paper.

OTHER USES

Treatment of certain neuromuscular disorders such as myasthenia gravis (MG),often incorporates immunoglobulin therapy under life-threatening conditions such as respiratory insufficiency or when patients are unresponsive to other treatments.[96] This recommendation is endorsed by the Task Force of Myasthenia Gravis Foundation of America. In managing MG crisis, IVIG has shown efficacy comparable to high-dose glucocorticoids but with fewer side effects.[97] However, immunoglobulins are not routinely considered a standard therapy for other muscular diseases, although some studies have shown benefit of IVIG in improving disability in patients with chronic inflammatory polyradiculoneuropathy.[98] Immunoglobulins may also be considered in patients with dermatomyositis and polymyositis not responding to corticosteroids or disease-modifying agents.[99]

Table 1. Use of immunoglobulin therapy in immune checkpoint inhibitor–associated toxicities

ICI-related Immune Toxicity	Indication	Recommended Dose	References
Autoimmune bullous dermatosis	Severe or life-threatening in addition to other immunosuppressive treatments	1 g/kg/d	[88]
Guillain-Barré syndrome	In addition to other immunosuppressive treatments	2 g/kg in divided doses	[89]
Myasthenia gravis	Severe or life-threatening in addition to other immunosuppressive treatments	2 g/kg in divided doses	[90]
Myocarditis	After failure of early immunosuppressive treatment in addition to other immunosuppressive treatments	2 g/kg in divided doses over 5 days	[91]
Myositis	Severe or life-threatening in addition to other immunosuppressive treatments	2 g/kg in divided doses	[92]
Neurologic toxicity: encephalitis or demyelinating diseases [optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis]	After failure of early immunosuppressive treatment in addition to other immunosuppressive treatments	2 g/kg in divided doses	[93]
Pneumonitis	Severe disease; after failure of early immunosuppressive treatment in addition to other immunosuppressive treatments	2 g/kg in divided doses over 2 to 5 days	[94]
Steven-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	As part of other immunosuppressive treatments	1 g/kg/day for 3–4 days	[95]

IgG is considered standard of care in Kawasaki disease treatment as it prevents coronary aneurysm formation. The American Heart Association guidelines recommend single IVIG dose of 2 g/kg rather than multiple small doses.[100] Similarly, higher doses of IVIG at 2 g/kg have been used in autoimmune dermatoses such as treatment recalcitrant pemphigus vulgaris, bullous and foliaceus pemphigoid, anti-neutrophilic cytoplasmic antibody (ANCA)-associated vasculitis, and in pregnant patients with complications of systemic lupus erythematosus, including nephritis, immune thrombocytopenia, and neuropsychiatric disease.[101–103]

IMMUNOGLOBULIN ADVERSE EVENTS

Adverse events are commonly seen with IgRT with varying frequency and severity, although severe adverse events are uncommon. (Table 2).[36,104] These may be influenced by factors related to both the patient and the product. Risk factors such as diabetes, renal disease, and elevated IgA levels in the product could contribute to these adverse events.[105] Some preventive measures include administration of subcutaneous formulation instead of IV, slow infusion rates, and restricting use to appropriate indications.

Table 2. Adverse events associated with use of immunoglobulin replacement therapy

Adverse Effects	Clinical Presentation and Risk
Immediate	
Anaphylaxis	Histamine mediated, related to IgA level. Rare (severe anaphylaxis incidence 0.23/10000 IVIG administrations)
Skin reactions	Varied presentation commonly urticarias, papules, pompholyx and eczema. Incidence 0.4–6%
Flu-like symptoms	Possibly related to cytokines such as IL-6, TNF-α
TRALI	Possibly related to anti-leukocyte/anti-HLA antibodies
Cardiovascular	TACO, arrythmias such as SVT, hypotension
Delayed	
Thromboembolism	Arterial more common, possibly related to patient-related risk factors such as malignancy
Fever	Common, seen in almost half of the patients treated
Headache	Cause unknown, related to high infusion rates; seen in almost half of the patients treated
Neurological disorders	Aseptic meningitis, PRES, seizures
Hematologic	Hemolysis, neutropenia
Electrolyte abnormalities	Hyponatremia, rare
Infection risk	Risk is rare due to quality measures for screening
Renal impairment	Related to patient-related risk factors such as CKD

CKD: chronic kidney disease; HLA: human leukocyte antigens; IgA: immunoglobulin A; IL-6: interleukin 6; IVIG: intravenous immunoglobulin; PRES: posterior reversible encephalopathy syndrome; SVT: supraventricular tachycardia; TACO: transfusion-associated circulatory overload; TNF-α: tumor necrosis factor alpha; TRALI: transfusion-related acute lung injury.

IVIG and SCIG have distinct profiles of adverse events, with the severity and frequency of side effects varying accordingly. With IVIG, the most commonly reported side effects are flu-like symptoms such as fever, malaise, and chills, likely induced by cytokine release (e.g., interleukin [IL]-6, tumor necrosis factor [TNF]-α).[106] Headaches are another frequent complaint, often related to the rate at which the IVIG is infused. Dermatological reactions, which can range from urticaria to eczema, also occur with some regularity.[107] Cardiovascular events, particularly transfusion-associated circulatory overload (TACO), are a risk due to the potential for fluid overload during rapid infusions.

In the case of SCIG, the adverse events are typically localized to the infusion site, manifesting as redness, swelling, or discomfort. These reactions are generally mild and tend to decrease with repeated infusions.

Rare complications are associated with both IVIG and SCIG. Anaphylaxis is a risk primarily in IVIG recipients with IgA deficiency.[108] Transfusion-related acute lung injury (TRALI) is a serious but infrequent reaction linked to the presence of anti-leukocyte or anti-HLA antibodies in the IVIG.[109] Thromboembolic events, although rare, are a serious concern and may be precipitated by underlying risk factors such as active malignancy or a history of thrombosis.

Preventive strategies for IVIG include premedication with antihistamines or corticosteroids, adequate hydration, and slow infusion rates to reduce the likelihood of common side effects.[110] Screening for IgA deficiency is crucial to prevent anaphylaxis in susceptible individuals. For SCIG, proper infusion technique and a gradual increase in infusion rates can help minimize local reactions. Warm compresses and gentle massage post-infusion are additional measures that may provide relief.

Both IVIG and SCIG require a proactive approach to prevent adverse events. This involves screening patients for risk factors, adjusting dosages appropriately, and closely monitoring them during and after administration. For individuals with diabetes, renal disease, or high serum IgA levels, personalized risk assessments and therapy adjustments are vital. Adhering to the use of IgRT strictly for appropriate indications ensures that therapeutic benefits are maximized while risks are minimized.

In conclusion, although IgRT is indispensable in treating a range of immunological conditions, careful consideration of the administration route and the implementation of tailored preventive measures are key to ensuring patient safety and therapeutic efficacy.

SUMMARY

Patients with primary and secondary immunodeficiencies are at heightened risk for a wide spectrum of infections, making immunoglobulin therapy a cornerstone of their management, particularly for disorders arising from B cell dysfunction. Beyond merely bolstering immune defenses, IgRT's immunomodulatory capabilities also position it as a viable therapeutic strategy for a range of disorders characterized by immune dysregulation. The evidence base for these applications continues to grow, with numerous studies, both completed and ongoing, underscoring the efficacy of IgRT. Consequently, a variety of FDA-approved immunoglobulin products are now available, enabling clinicians to tailor treatments to the specific needs of their patients.

Although IgRT is invaluable in these clinical contexts, the potential for adverse events necessitates a judicious approach to its use. Before initiating therapy, it is imperative to assess patient-specific factors such as baseline immunoglobulin levels, the presence of comorbidities, and the individual's past history of infusion reactions. Subcutaneous administration may be preferred for its lower incidence of systemic adverse events, and the infusion rate of IV preparations should be carefully controlled to minimize risks.

In conclusion, the use of IgRT represents a significant advancement in the treatment of immunodeficiencies and immune dysregulation disorders. With an informed approach that carefully weighs the benefits against the potential risks, IgRT can be safely integrated into patient care plans, improving quality of life and clinical outcomes for those with complex immune conditions.

Supplemental Material

Supplemental materials are available online with the article.

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