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Review

Management of adverse events in the treatment of patients with immunoglobulin therapy: A review of evidence

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ABSTRACT

Immunoglobulin (IG) therapy is actually used for a broad range of diseases including primary and secondary immunodeficiency disorders, and autoimmune diseases. This therapy is available for intravenous (IV) and subcutaneous (SC) administration. The efficacy of the IG therapy has been demonstrated in numerous studies and across different diseases. Generally, IG infusions are well tolerated; however some well-known adverse reactions, ranging from mild to severe, are associated with the therapy. The most common adverse reactions including headache, nausea, myalgia, fever, chills, chest discomfort, skin and anaphylactic reactions, could arise immediately during or after the infusion. Delayed events could be more severe and include migraine headaches, aseptic meningitis, haemolysis renal impairment and thrombotic events.

This paper reviews all the potential adverse events related to IG therapy and establishes a comprehensive guideline for the management of these events. Moreover it resumes the opinions and clinical experience of expert endorsers on the utilization of the treatment. Published data were classified into levels of evidence and the strength of the recommendation was given for each intervention according to the GRADE system.

Contents

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1. Introduction

1.1. Immunoglobulin therapy

The introduction of human immunoglobulin therapy had tremendously improved the management of several diseases. Actually, immunoglobulin preparations derived from pooled donated human plasma, can be life-saving for numerous patients.

Immunoglobulin therapy was first indicated for the treatment of primary immunodeficiency disorders (PIDs) [1,2]. The benefits of immunoglobulins as a replacement therapy have been demonstrated in a large number of PIDs such as agammaglobulinaemia (either x-linked or autosomal recessive) and common variable immunodeficiency (CVID), but also in secondary immunodeficiency disorders resulting from haematological malignancies such as chronic lymphocytic leukaemia (CLL) and multiple myeloma requiring generally chemotherapy, monoclonal antibody therapy or immunosuppressive therapies [3–11]. Due to their defective immune system, patients with primary and secondary immunodeficiencies are prone to increased risk of infections, particularly upper and lower respiratory tract infections and gastrointestinal infections. Immunoglobulin replacement therapy has been shown to reduce and prevent bacterial infections [2,10,11].

While immunoglobulin replacement therapy remains the mainstay treatment for primary and secondary immunodeficiency disorders, its clinical use has expanded to a number of auto-immune diseases including neuro-immunological and neuromuscular diseases [12]. The anti-inflammatory and immunomodulatory properties of immunoglobulins demonstrated a clinical benefit in idiopathic thrombocytopenia purpura (ITP), Guillain–Barre syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), Kawasaki disease and some myositis [13–20]. The use of immunoglobulins is now indicated in multiple neurological autoimmune diseases refractory to standard immunosuppressive treatments [12,21]. An off-label use of IVIG is reported in several autoimmune diseases such as vasculitis, particularly granulomatosis with polyangiitis [22]. IVIG may also be considered for juvenile chronic arthritis and adult Still's disease [23].

The indications for which immunoglobulins have been licensed by the European Medicines Agency (EMA) are outlined in Table 1 [24,25].

Initially, immunoglobulins were administered by intramuscular injections [1]. This route of administration is now considered outdated; intramuscular immunoglobulins (IMIGs) presented extreme discomfort for the patient and the method is painful for most patients. Moreover required doses to achieve adequate trough levels could not be administered safely. IMIG injections are limited in volume and the resulting serum IgG levels in patients with hypogammaglobulinaemia are not comparable to physiological levels [2]. Therefore intravenous immunoglobulins (IGIVs) became the standard-of-care in patients treated for primary immunodeficiency [2]. IVIGs are generally well tolerated and larger doses were given via this route, resulting in significant improvements in patients' conditions and outcomes. In 2005, the first commercial preparations for subcutaneous immunoglobulin (SCIG) were approved by the EMA [26]. These injections given in smaller doses and more frequently than IVIG provide a consistent level of IgG [27,28]. Furthermore, this administration route is associated with few systemic side effects and was shown to improve patients' quality of life, especially in replacement therapy [20,29].

1.2. Available products and contents

Commercially available products are derived from pooled blood donations from thousands of healthy patients [21,30,31]. The use of large plasma pools for the production provides a diversity of immunoglobulins that may enhance the therapeutic effect. Donors of blood used for the production are screened and tested for human immunodeficiency virus (HIV) 1 and HIV 2, hepatitis viruses B and C and syphilis. Immunoglobulin-rich fractions, containing 95–99% IgG with varying trace amounts of IgM, IgA, IgD and IgE are isolated using the Cohn-ethanol procedure, and then treated with solvents and detergents to inactivate residual viruses [32]. New procedures have now been introduced for maximal viral safety, including addition of caprylate or the use of nanofiltration [33,34]. The resulting solution contains sodium in various amounts and stabilizing agents such as sucrose, glycine, glucose, maltose, D-sorbitol and L-proline to prevent aggregation of IgG. The formulation should contain high levels of IgG (>95%) with less than 5% aggregated IgG [35].

There are currently different immunoglobulin preparations available in Europe (Table 2). They vary in IgG concentration, pH, stabilizing agents, final osmolality and content of IgA. Preparations are supplied in lyophilized powder or as a premixed solution, and for different routes of administration (intravenous or subcutaneous). All of these characteristics should be considered carefully when selecting a product for a specific patient. While there are no substantial differences between

Table 1
European Medicines Agency (EMA) approved indications of immunoglobulin.

Indications for intravenous immunoglobulin (IVIG)
As a replacement therapy in:
• Primary immunodeficiency syndromes with impaired antibody production. • Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed. • Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase in multiple myeloma (MM) patients who have failed to respond to pneumococcal immunization. • Congenital AIDS and recurrent bacterial infections. • Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).
As an immunomodulatory therapy in:
• Primary immune thrombocytopenia (ITP) in patients at high risk of bleeding or prior to surgery to correct the platelet count • Guillain Barré Syndrome (GBS) • Kawasaki disease
Indications for subcutaneous administration (SCIG) As a replacement therapy in:
• Primary immunodeficiency syndromes with impaired antibody production. • Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated. • Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients. • Hypogammaglobulinaemia in patients pre- and post-allogeneic haematopoietic stem cell transplantation (HSCT).
Indications for subcutaneous administration (SCIG) or intramuscular administration (IMIG) Hepatitis A prophylaxis If the SC/IMIg has a minimum antibody content for HAV of 100 IU/mL it is also used for: In adult and children or adolescents (0–18 years):
• Pre-exposure prophylaxis, preferably in combination with vaccination, in unvaccinated individuals travelling in less than 2 weeks to areas of hepatitis A risk • Post-exposure prophylaxis in unvaccinated individuals within 2 weeks of hepatitis A virus (HAV) exposure.