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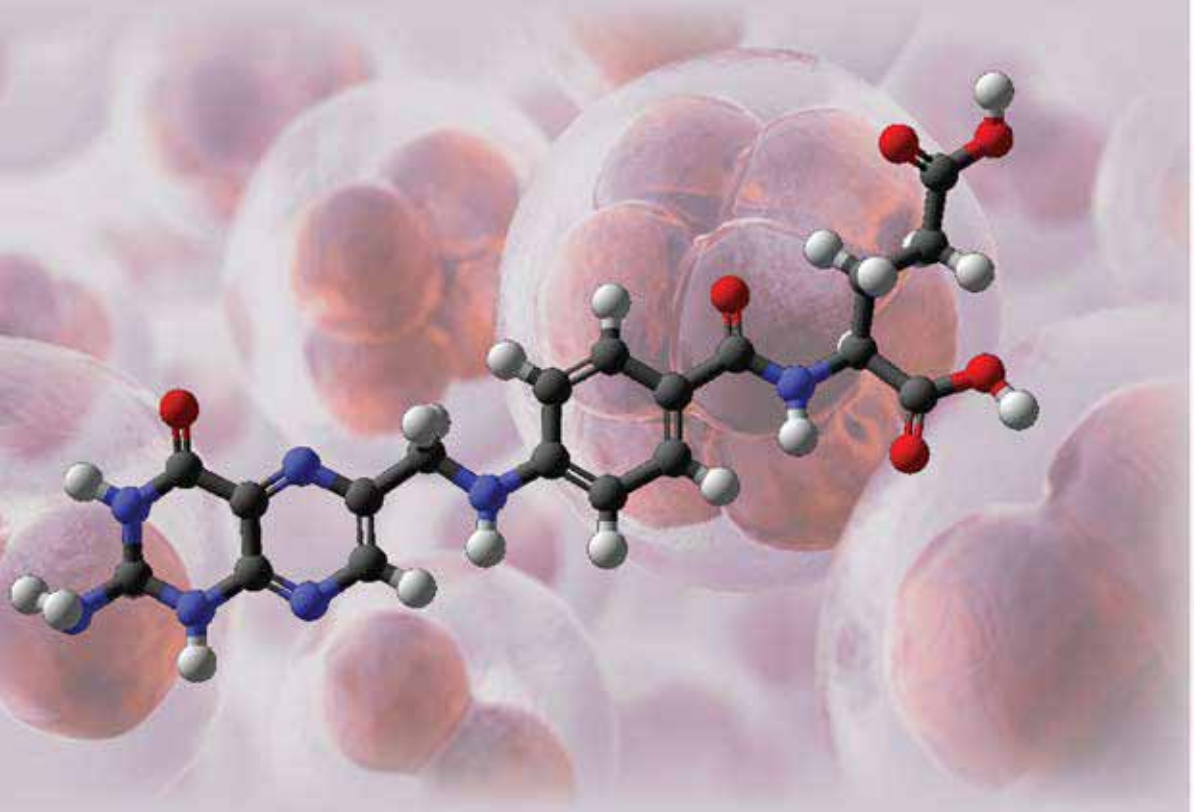

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CHAPTER 16

Intravenous Immunoglobulin

V Pai, Soumya Jagadeesan, Sanjeev Vaishampayan

"Do not rejoice at Success, do not mourn Failure."

—Lao Tzu

Overview

- Introduction
- History and Evolution of IVIG in Therapeutics
- Diagrammatic Overview of Action
- Drug Overview
- Prescribing Considerations
- Other Dermatoses

■ INTRODUCTION

Intravenous immunoglobulin (IVIG) is a therapeutic preparation of normal human polyclonal IgG obtained from plasma pooled from approximately 3–10 thousand individual healthy blood donors. It was first introduced as a replacement therapy for patients with primary and secondary immune deficiencies. IVIG is now widely used for the treatment of a number of autoimmune and systemic inflammatory diseases [*Negi VS et al.*].

■ HISTORY AND EVOLUTION OF IVIG IN THERAPEUTICS

The first Nobel Prize in medicine or physiology was given to Von Behring for his work where he observed that the rabbits immunized with tetanus toxin demonstrated activity against tetanus and such blood sera transferred to naïve rabbits protected these normal animals against tetanus. This principle was later applied to other infectious diseases. In 1940s, Dr Cohn developed a fractionation method for the separation of plasma proteins into individual stable fractions with different biologic functions. In 1970s, these challenges were overcome when the first generation of IVIGs were developed which could be given in larger quantities with fewer side effects. The second generation IVIGs had added sugars or amino acids instead of pepsin and also a lower pH to make the products more tolerable in large dosages. In the 1980s, with the advent of HIV, there was a fear of contamination with other viruses, so the third generation IVIGs included steps

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such as solvent-detergent and pasteurization to increase safety by specifically removing or destroying unwanted organisms such as potentially harmful viruses, without compromising the quality [*Eibl MM*].

Intravenous immunoglobulin was first licensed by United States Food and Drug Administration **(USFDA) in 1981** and approved for use in six conditions: (1) Primary immunodeficiencies, (2) Kawasaki syndrome, (3) immune thrombocytopenic purpura (ITP), (4) recent bone marrow transplantation (in patients 20 years of age or older), (5) chronic B-cell lymphocytic leukemia, and (6) pediatric HIV 1 infection. In the last two decades, use of IVIG in toxic epidermal necrolysis (TEN) has been well accepted; however, no unanimity has been reached due to the lack of randomized clinical trials. Not only the results differ from center to center but also incidence of mortality is different too. Yet, IVIG remains accepted as drug of choice for initial therapy of TEN [*Vaishampayan S et al.; Jolles S et al.; Dhar S*].

■ DIAGRAMMATIC OVERVIEW OF ACTION

While IgG antibodies play diverse roles in the immune system autoreactive IgG antibodies that target self-tissue antigens can cause an autoimmune disease. The pooled IgG in IVIG has anti-inflammatory properties and these effects are due to different structural components of IgG molecule. The antigen binding Fab component can bind and neutralize pathogenic autoantibodies, whereas the Fc portion can interact with Fc receptors on various cell types regulating distinct cell functions. The various actions are detailed in the **Figure 1** and given in **Box 1**.

■ DRUG OVERVIEW

Pharmacokinetics

Peak serum concentration reaches immediately after injection and is dose related. Within 24 hours, up to 30% of the dose reduces by distribution (intravascular 60% and extravascular 40%) and catabolism. It crosses placenta and may be excreted in milk. Serum half-life is 30 days; hence a repeat dose if needed should be given after 4–6 weeks [*Bonilla FA*].

Drug Interactions

No drug interactions have been reported so far with IVIG products. IVIG products should not be administered at the same time as attenuated live vaccines (German measles, mumps, or measles) since they may inhibit or delay the desired immune response. When high-dose IVIG is administered, there should be a **3–6 months** period between the planned vaccination and the last IVIG infusion [*Prins C et al.*].

Contraindications

Absolute: Anaphylaxis during previous infusions

Relative:

- Congestive cardiac failure and renal failure due to fluid over load. In patients with cardiac or renal impairment, immunoglobulin preparations if indicated should be administered over a longer period of time.
- Rheumatoid arthritis and cryoglobulinemia due to renal failure

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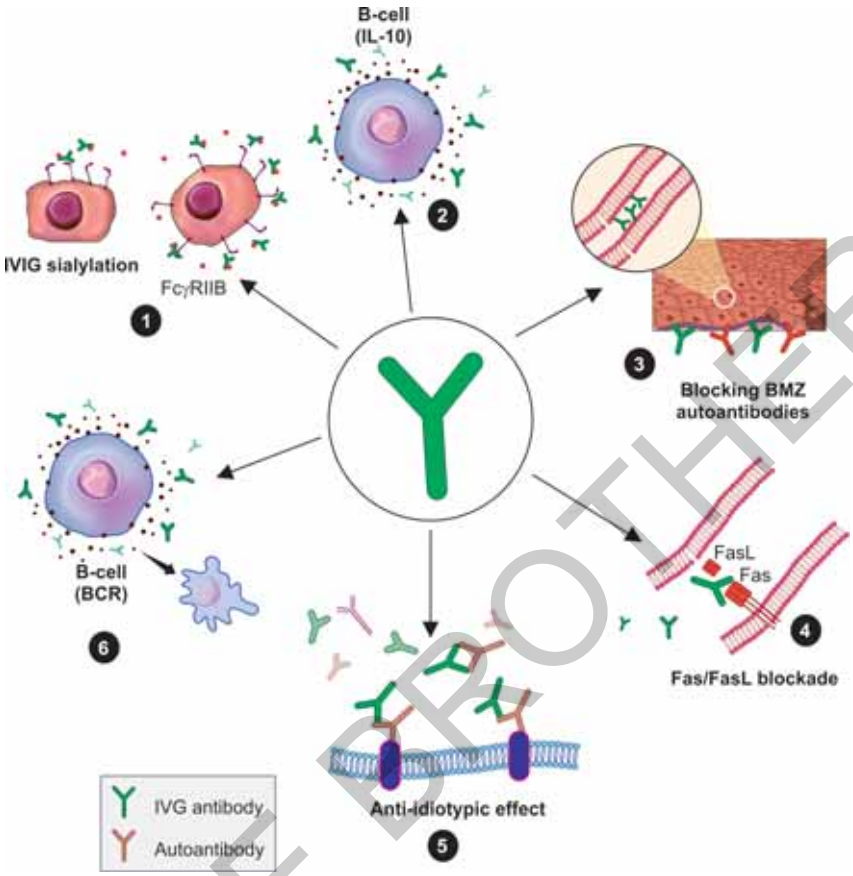

FIG. 1: A depiction of the varied actions of intravenous immunoglobulin (IVIG). (1) Sialylation of the Fc portion of IVIG molecules leads to interaction with SIGN-R1 and upregulation of the inhibitory receptor FcγRIIB and attenuation of inflammation and tissue damage. (2) IVIG increases production of the immunosuppressive cytokine, IL-10, from B-cells. (3) Self antigens in bullous pemphigoid and pemphigus vulgaris are protected by blocking IVIG antibodies from autoantibodies. (4) IVIG binds Fas and prevents the interaction with FasL, leading to blockade of keratinocyte apoptosis. (5) IVIG has anti-idiotypic activity and reduces the pathogenicity of autoantibodies. (6) Binding of the Fc portion of IVIG to FcγRIIB with simultaneous binding of IVIG Fab portion to BCR leads to anergy by abolishing the BCR-induced stimulation of antibody production.

BOX 1 Varied actions of intravenous immunoglobulin (IVIG).

- Complement blockade and degradation
- Neonatal Fcγ receptor saturation
- Induction of immunomodulatory Fc receptors inhibition of B cells
- Altering T cell function, cytokine production and migration

- IgA deficiency due to increased risk of anaphylaxis
- Pregnancy is not a contraindication to IVIG therapy [*Enk AH et al.; George T and Luger TA*]

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■ PRESCRIBING CONSIDERATIONS

It is generally accepted that the use of IVIG should be reserved for those cases that: (1) Fail conventional therapy; (2) have severe side effects or contraindications to conventional therapy; and/or (3) have rapidly progressive disease.

Uses

A list of indications is listed in **Table 1** and will be discussed in the text that follows.

1.Connective Tissue Disorders

Caution should be exercised in the setting of connective tissue disease as the infusion of IVIG in patients with high titer rheumatoid factor (RF) has been associated with renal damage [*Enk AH et al.*].

Dermatomyositis

Dermatomyositis is the dermatological condition in which the highest level of evidence exists for treatment with IVIG besides pemphigus vulgaris. The aim of IVIG is to induce a clinical remission, or be used as an adjuvant treatment with immunosuppressive therapy or used as an immunosuppressive or steroid-sparing drug [*Dalakas MC et al.*]

TABLE 1 **Listed uses of IV IgG [*Cakmak SK et al.; Enk AH et al.; Forbat E et al.; Rütter A and Luger TA*].**

FDA approved	• Primary humoral immunodeficiency • B-cell chronic lymphocytic leukemia • Immune thrombocytopenic purpura • Kawasaki syndrome • Chronic inflammatory demyelinating polyneuropathy • Pediatric HIV infection (to prevent secondary bacterial infections) • Multifocal motor neuropathy • Guillain–Barré syndrome
Dermatological	**More common indications:** • *Adverse drug reactions*: Toxic epidermal necrolysis • *Severe forms of connective tissue disorders*: Lupus erythematosus, dermatomyositis, inclusion body myositis, polymyositis • *Severe forms of autoimmune blistering diseases*: Pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, cicatricial pemphigoid, pemphigoid gestationis, Linear IgA dermatoses, epidermolysis bullosa acquisita • *Severe systemic vasculitic syndromes*: Kawasaki disease • Scleromyxedema • COVID-associated multisystem inflammatory syndrome **Less common indications:** • Atopic dermatitis • Autoimmune urticaria • Severe forms of collagen vascular diseases • Livedoid vasculopathy • Pyoderma gangrenosum

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The European guidelines recommend it in all severe forms of dermatomyositis, inclusion body myositis and polymyositis, as a second-line therapy if steroids fail to show improvement within 1 month. In certain cases of fulminant severe myolysis or paralysis, its use as a first-line therapy has been justified [*Enk AH et al.; Prins C et al.*]. From the immunological perspective, sufficient bone marrow function needs to be available given the concomitant immunosuppressive therapy. Therefore, treatment onset should not be delayed for too long. If the end point of efficacy is not achieved by six treatment cycles the IVIG treatment should be discontinued.

Lupus Erythematosus

Intravenous immunoglobulins have been used in steroid resistant cases of systemic lupus erythematosus and subacute cutaneous lupus erythematosus. The treatment should be given in combination with adequate immunosuppressive therapy. The therapy can lead to marked improvement in severe photosensitivity and resolution of lupoid type of extremely itchy cutaneous features [*Vaishampayan SS et al.*] of lupus erythematosus.

Systemic Sclerosis

Systemic sclerosis (SSc): Levy Y et al. treated 15 patients with scleroderma with monthly infusions of IVIG 2 mg/kg (over a 5-day period) for 3–6 months. Based on the Rodnan scores, the mean degree of skin involvement decreased by 35% with a significant improvement in patients' well-being and quality of life [*Levy Y et al.*].

2. Cutaneous Adverse Drug Reactions

Toxic epidermal necrolysis is a life-threatening disorder linked to Fas (CD95) and granulysin-mediated apoptosis, as well as annexin A1-mediated necroptosis of epidermal keratinocytes [*Rütter A and Luger TA*]. Herein lies the role of antibodies that interfere with these apoptotic pathways and highlights the role of IVIG [*Huang YC et al.*].

The efficacy of IVIG for TEN remains controversial with many multiple open-label, prospective studies, retrospective case series, and case reports supporting or refuting the use of IVIG [*Fernandez AP et al.*; *Barron SJ et al.*]. The European guidelines suggest early administration of high-dose immunoglobulins given that the potential benefit outweighs the risks considering the severity of the condition.

Dose: The dose recommendation in TEN differs from that in autoimmune diseases. A total dose of at least **3 g/kg** bodyweight given over a 3–5 days duration is generally recommended [*Enk AH et al*]. IVIG should be administered as soon as possible after the diagnosis and a single cycle would suffice. A few authors have also claimed benefit with lower dose of IVIG, particularly in children [*Mangla K et al.*]. We have [*Jagadeesan S et al.]* administered a combination of IV steroids with a lower dose of IVIG in a low-resource setting in TEN patients with faster recovery times when compared to patients treated with steroids alone or supportive care (**Figs. 2A** and **B**).

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FIG. 2A: A patient with toxic epidermal necrolysis (phenytoin-induced) treated with IVIG and steroids.



FIG. 2B: The same patient on day 9.

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3. Autoimmune Bullous Disorders

All severe forms of autoimmune bullous diseases such as pemphigus vulgaris, pemphigus foliaceus, mucous membrane pemphigoid and epidermolysis bullosa acquisita, bullous pemphigoid, linear IgA disease, IgA pemphigus or paraneoplastic pemphigus, which are refractory to therapy or relapsing after therapy represent an indication for the use of IVIG (**Fig. 3**) [*Enk AH et al.; Fernandez AP et al.*; *Svecova D*].

When should it be Instituted?

In a study by *Vaishampayan S et al.* significant improvements of bullous lesions were seen in patients having pemphigus vulgaris, chronic bullous disease of



FIG. 3: One cycle of IVIG was given at dose of 2 g/kg body weight over three days in a case of extensive pemphigus vulgaris. Later the patient was maintained on low dose oral steroids and azathioprine. The second image on the right is three months after therapy.

childhood and paraneoplastic pemphigus. IVIG may be particularly a useful therapeutic option, in the background of sepsis.

It must be emphasized that this form of therapy is not the first-line agent and is an adjunctive therapy and is to be used when there are contraindications to standard immunosuppressive therapy (e.g., aseptic bone necrosis, poorly controlled diabetes or advanced osteoporosis and cataracts). Thus IVIG is not the preferred first-line and is the second-line treatment when combination therapy with steroids (e.g., prednisolone 1–2 mg/kg body weight per day) and another immunosuppressive agent, e.g., azathioprine and/or mycophenolate mofetil have failed.

The use of immunoglobulin should not be delayed for too long because adjuvant treatment is useful only when there is adequate bone marrow function [*Enk AH et al.*] and a delay may lead to bone marrow suppression due to ISA. A trial of 6 months is advised failing which IV IgG should be stopped.

4. Vasculitis

Treatment with IVIG has been reported to clinically improve or resolve a variety of vasculitides. All forms of severe vasculitis such as Kawasaki disease, chronic polyangiitis (Wegener's granulomatosis), polyarteritis nodosa, IgA-associated vasculitis, Churg–Strauss disease, microscopic polyangiitis pyoderma gangrenosum, leukocytoclastic vasculitis, livedoid vasculopathy and Behçet's disease can represent potential indications for IVIG. Kawasaki disease is the only disease in this category for which IVIG is the first-line treatment. One such case of Kawasaki disease showed regression of mucocutaneous lesions in 2 weeks' time with IV IgG [*Vaishampayan SS et al.*]. Dose modification may be necessary

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in systemic vasculitis with renal involvement, the infusion rate should be reduced or possibly a reduced dose should be used (e.g., a total of 1 g/kg bodyweight) [*Enk AH et al.*].

5.Scleromyxedema

Scleromyxedema is a severe multiorgan condition characterized by fibroblast proliferation and mucin deposition in skin and internal organs associated with monoclonal gammopathy in the majority of cases. Scleromyxedema is refractory to most classical immunosuppressive therapies, but responds quickly to treatment with IVIG, as documented in many case reports and in small case series. IVIG should be considered treatment of choice in refractory cases of scleromyxedema with either fast deterioration of skin symptoms, the dermatoneuro syndrome or life-threatening involvement of internal organs or in milder cases which are refractory to first line of treatment [*Enk AH et al.*].

6.COVID Associated Multi-inflammatory Syndrome

COVID associated multi-inflammatory syndromes, particularly in children (MIS-C) may present with a skin rash. Though the evidence for the use of IVIG is mostly from case series, there is also indirect evidence supporting its use from similar conditions like Kawasaki disease. The dose here is usually 2 g/kg administered in a single infusion over 8–12 hours [*Henderson LA et al.*]. One of the authors have treated a neonate presenting with ulceration on the buttocks as a part of MIS-C treated with intense supportive management and IVIG *[Kappanayil M et al.*] (**Figs. 4A** to **D**).



FIGS. 4A TO D: (A) Neonate with MIS-C and ulceration on the buttock – day 7 when IVIgG was initiated; (B) On day 13; (C) On day 17; (D) On 3-months follow-up.

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■ OTHER DERMATOSES

***Chronic urticaria*:** The use of immunoglobulin can also be considered as a last resort in severe cases of autoimmunologically mediated urticaria. Several case series with varied dosing ranging from 0.2 g/kg over 1 day to 0.4 g/kg/day for 5 days have been tried with success [*Vaishampayan SS et al.*].

***Atopic dermatitis (AD)*:** Many case series have reported an efficacy of IVIG in atopic dermatitis. IVIG therapy decreased plasma IFN-γ levels and white cell counts, increased serum-soluble CD5 levels and decreased the clinical severity of AD. The literature published to date suggests that in severe childhood AD IVIG can improve skin involvement, when used as monotherapy, but in adults it is not as effective when used as monotherapy [*Paul C et al.*].

***Infections*:** Numerous reports suggest benefit from IVIG in patients with streptococcal toxic shock syndrome (STSS). IVIG inhibits the activity of streptococcal antigens and superantigens. The use of IVIG in treating STSS in one case-control series provided an odds ratio for survival of 8:1 [*Cakmak SK et al.*].

IVIG may also be useful in certain rare case scenarios such as macrophage-activation syndrome triggered by infections like varicella or in patients with rheumatic diseases.

A summary of the therapy guidelines is given in **Table 2**.

What do I need to do before Starting the Treatment?

Investigations

A complete blood cell count, electrocardiogram, hepatic and renal function tests, RF, and cryoglobulin is advised since patients with cryoglobulin have a higher risk of developing acute renal failure (ARF). Tests for antibodies to HIV RNA, HCV RNA, HBV DNA, HAV RNA, and Parvovirus B19 DNA can be done before and after treatment.

How should I Prescribe?

Premedication

While not essential but this may be administered to minimize the incidence of infusion-related side effects, such as headaches, myalgia, and rigors. Premedication with analgesics, antihistamines, and even low-dose corticosteroids may be of benefit to a subset of individuals with known history of various allergic-reactions.

Precautions

Anaphylaxis is always a potential threat; hence, the treatment room must always have an antianaphylaxis tray (containing injections: Adrenaline, hydrocortisone, deriphyllin, pheniramine maleate, dopamine, and IV fluids) ready. Therapy with high-dose IVIG can cause fluid overload; hence, it should be used cautiously in patients with renal insufficiency or impaired cardiac function.

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TABLE 2 Therapy guidelines for use of IV IgG in select disorders.

Disease	Indication	Duration	Interval	Evaluation of efficacy
Dermato-myositis	• First-line for severe myolysis or arthralgia • Conventional Rx* contraindicated	6 months	4–6 weeks; dose: 2 g/kg	• Normalization of muscle strength • Fading of erythema
Lupus erythe-matosus	• Given in combination with CS/IS • Conventional Rx *contraindicated	6 months	4–6 weeks; dose: 2 g/kg	↓ Protein excretion in ↓ urine
Autoimmune blistering diseases	• Either as combination with oral CS/IS • Conventional Rx contraindicated/ • Not adequately controlled with rituximab	6 months	4–6 weeks; dose: 2 g/kg	• Stoppage of new lesions and healing of existing lesions • IgG autoantibody titers by ELISA of IIF
Vasculitis	• First-line in Kawasaki, others along with other IS or CS • Conventional Rx* contraindicated	3–6 months	4 weeks; dose: 2 g/kg	• Improvement in clinical response • Organ specific laboratory tests showing reduction in titer
TEN	Early administration can be used as monotherapy ± CS	1 cycle	Dose: 2 g/kg	Survival and cessation of ongoing epidermal detachment
Scleromyx-edema	First-line since Rx* with other IS is refractory	6 months	4 weeks; dose: 2 g/kg	↓ Dermatological response, in CNS symptoms or internal organ involvement

* Rx: Treatment.

(CNS: central nervous system; CS: corticosteroids; ELISA: enzyme-linked immunosorbent assay; IIF: indirect immunofluorescence; IS: immunosuppressants; TEN: toxic epidermal necrolysis)

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Dosage Schedule

The standard accepted dosage for IVIG therapy is 2 g/kg given over 5 days (400 mg/kg/day for 5 days). Financial constraints have led to treatment with low-dose IVIG. Few centers have reported satisfactory response with low-dose IVIG in ITP (0.8–1.0 g/kg) and Kawasaki's disease (0.4 mg/kg/day) and a repeat dose if needed but can be given after a gap of 4–6 weeks [*Vaishampayan SS et al.; Parodi E et al.; Lee JH et al.*].

A summary of the mode of administration is given in **Box 2**.

BOX 2 **Mode of administration of IVIG.**

- Dose: Administer IVIG product at **400–500 mg/kg/day on 4–5** consecutive days up to the total dose of **2 g/kg/month** × 6–18 months (3 g/kg bodyweight in toxic epidermal necrolysis)
- **Interval:** Initially every 4 weeks/after 6 months gradually increase to 6-week intervals (only one cycle in Kawasaki disease and toxic epidermal necrolysis)
- Usually the therapy is adjunctive and can be abandoned if there is no response after 6 cycles
- Premedicate patient with 25 mg diphenhydramine and 500 mg acetaminophen 15–30 minutes prior to starting the infusion
- Place peripheral IV and maintain with 0.9% sodium chloride
- Infusion rate: Start at 0.5 mL/kg/h, then increase by 15 mL/h every 15 minutes until target rate of 150–200 mL/h, as tolerated. Maximum rate is 200 mL/h
- Observe vital signs prior to infusion. Blood pressure and pulse every 30 minutes until stable infusion rate, then every hour
- Watch for signs of fluid overload, cardiovascular symptoms, allergic reactions, skin rash, fever, and moderate-to-severe headache
- For adverse events, stop the infusion. Can restart the infusion at the same or lower rate if the symptoms subside

Monitoring [*George T and Luger TA*]

- Complete general physical examination
- Cardiac and renal assessment
- Laboratory tests: Complete blood count, liver and renal function tests, hepatitis B, C and HIV, and IgA levels.
- During infusion: Monitoring of pulse, blood pressure, urine output. Assess for signs of fluid overload.

Side Effects and What to Discuss with Your Patients

Adverse effects (AEs) affect <5% of patients treated with IVIG and occur more frequently in patients who are IVIG-naïve or at risk of bacterial infection.

1. **Immediate and Transient**

   The most common side effects are transient and often appear during the infusion or up to 72 hours following the infusion. The transient side effects include headache, nausea, chills, low-grade fever, increased blood pressure urticaria, arthralgia, and myalgia. These side-effects are considered to be possible consequences of low-level aggregation of the IgG, immune complex formation and complement activation or, in certain cases, to the sugar content of the IVIG product. These side effects are usually overcome easily by reducing the rate of infusion, administering corticosteroids, antihistamines and nonsteroidal anti-inflammatory drugs [*Forbat E et al.; Prins C et al.; Dourmishev LA et al.*].

   Hematological side effects such as leukopenia, neutropenia, and mono cytopenia are also seen in IVIGs therapy, which are self-limiting and do not lead to increased susceptibility to infection. **Dermatological adverse**

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effects from IVIG are rare and include pruritus, rash, severe eczematous skin reactions, urticaria, lichenoid reactions, petechia, alopecia, and erythema multiforme [*Dourmishev LA et al.].* One of the authors has seen two patients with autoimmune encephalopathy presenting with pompholyx-like rash on the hands after each infusion of IVIG.

2. **Severe Side Effects**

They can occur in rare instances. Most of the patients with severe side effects have an underlying risk factors mentioned here.

Aseptic meningitis: Aseptic meningitis may occur after the first 24–72 hours of a high-dose IVIG treatment, particularly in patients with a history of migraine. It is possible that in vivo activation of TNFα-primed neutrophils, by atypical antineutrophil cytoplasmic antibodies (ANCA) present in IVIG may contribute to the side effects of IVIG therapy. The symptoms resolve spontaneously and may be prevented by oral hydration, decreasing the rate of infusion and antihistamines [*Negi VS et al.*].

Acute renal failure: ARF is a rare complication of the use of IVIG with an estimated incidence lower than 1%. It can occur following IVIG infusion as a consequence of proximal tubular dysfunction or high osmotic pressure caused by the stabilizing agent included in formulating the IVIG (sucrose more than other sugars). This side-effect is reversible in almost all cases, and in most cases this dysfunction is characterized mainly by a transient increase in blood creatinine levels, rarely by oliguria or anuria. Risk factors for renal failure are male sex, age above 65 years, high infusion rates, preexisting renal disease, diabetes, high blood pressure, hypovolemia and obesity [*Prins C et al.].*

Stroke is a rare, life-threatening, complication of high-dose IVIG therapy seen in 0.6% of the patients. Risk factors for stroke include a prior history of stroke, carotid artery stenosis, chronic hypertension, and high blood viscosity states.

Anaphylactic reactions occur in patients with IgA deficiency which is associated with the development of anti-IgA antibodies that react with IgA in the IVIG preparation. This can be prevented by using IgA-depleted IVIG [*Negi VS et al.*].

Thromboembolic event is another rare event that can occur in patients at high risk of thrombosis due to IVIG-associated increase in plasma viscosity or anticardiolipin antibodies [*Negi VS et al.*].

Severe hemolytic reactions like post-IVIG anemia can be rarely be precipitated by high doses of IVIG (2 g/kg) and blood types A, B or AB. Therefore IVIG has to be compatible with a certain level of ABO blood group antibodies in order to reduce the incidence of severe hemolysis [*Forbat E et al.*].

Risk of infection: There is a theoretical risk, but no reported risk of transmission of HIV by IVIG, although several outbreaks of hepatitis C associated with its administration were reported in the mid-90s. This risk has been largely eliminated by rigorous donor selection and introduction of new manufacturing processes [*Negi VS et al.*].

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Patient Advise

- IVIG does not increase the risk for infection.
- IVIG works in different ways to prevent the body from attacking itself and to decrease several types of inflammation in the body.
- IVIG is given as an intravenous infusion, which takes several hours to complete. Frequency of infusions may vary according to the patient's need.
- Most people do well with IVIG, experiencing only minor side effects in some cases.
- Vaccines may not work as well in the weeks to months after the IVIG is given because the IVIG may block the immune system from responding appropriately to the vaccine.

ACKNOWLEDGMENT

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