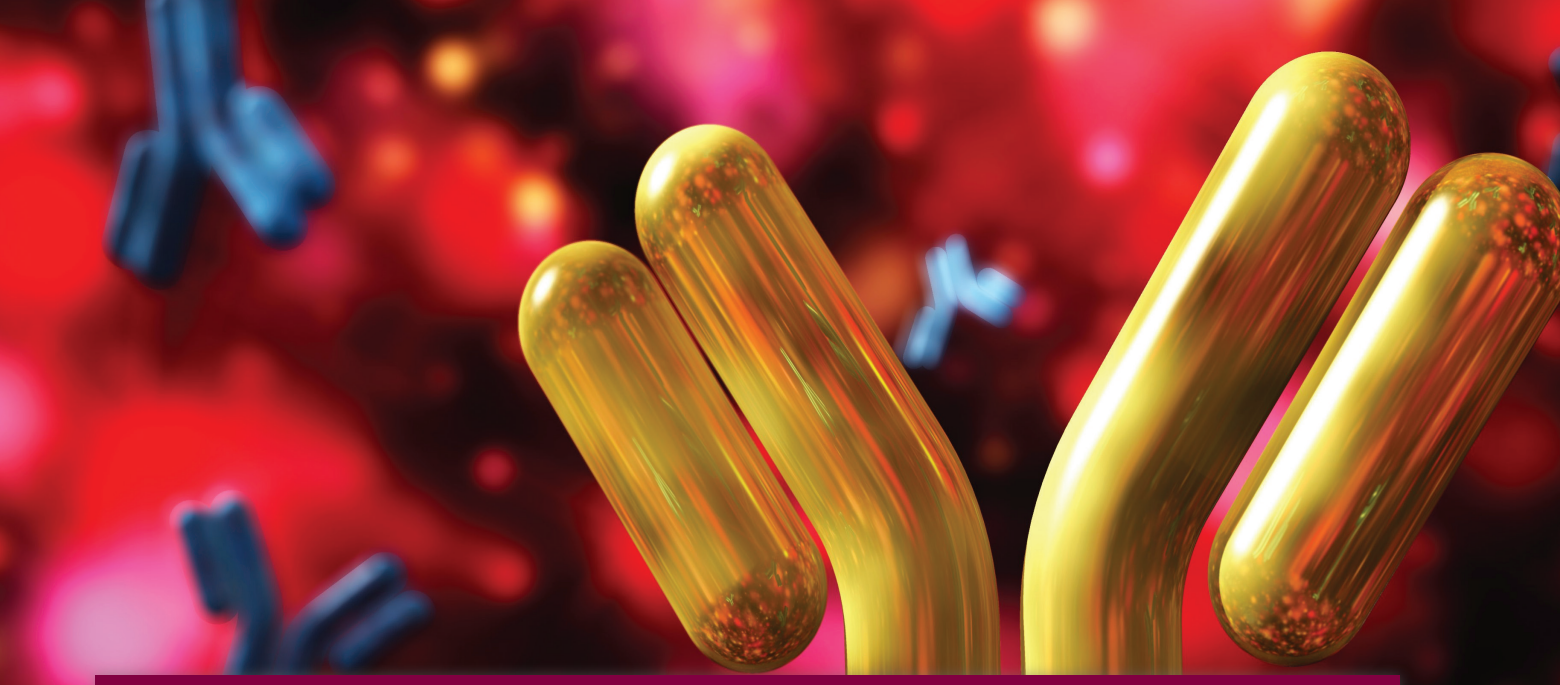

Immunoglobulin Therapy Standards of Practice

By Amy E. Clarke, RN IgCN, Joe DiStefano, RPh, and Luba Sobolevsky, PharmD

PHARMACISTS AND PHARMACY TECHNICIANS

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Learning Objectives:

- Describe patient risk factors affecting Ig therapy
- Identify Ig product formulation factors affecting Ig therapy
- Review common IVIG adverse drug reactions and mitigation
- Discuss common SCIG adverse drug reactions and mitigation

AUTHOR BIOS:

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AUTHOR DISCLOSURES STATEMENT

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Background

Since their first use in the 1950s, immunoglobulin (Ig) preparations have evolved through sophisticated manufacturing processes, resulting in effective and safe products used in a variety of clinical indications and practice settings. Patient risk factors, product differences, dosing, appropriate administration protocols, and emergency preparedness are among the factors that impact patient safety, tolerability, adherence, and treatment success.[1]

Any specialized clinical field requires standardization to ensure best clinical practice, assure health care professional accountability, and protect patients, clinicians, and organizations. The Immunoglobulin National Society (IgNS) has recently published the second edition of the *Ig Therapy Standards of Practice*, a set of guidelines that provide a framework to support multidisciplinary practices in defining and developing Ig policies, procedures, and data collection strategies. IgNS is dedicated to advancing a multidisciplinary health care practice approach through comprehensive education and professional certification for nurses (with a pharmacist certification underway). The organization promotes patient-centric advocacy initiatives and provides critical practice resources to clinicians and organizations.[2, 3]

Ig therapy is used for replacement therapy in immunodeficiency diseases and for immunomodulatory effects in autoimmune and inflammatory disorders. Sixteen Ig therapy products are currently available in the U.S., with multiple new products in various stages of development.[4, 8, 9, 10, 11, 12, 13, 14, 15, 16, 19, 20, 21, 22,23] While all Ig brands have been shown to be effective in respective clinical trials, formulation differences and routes of administration are known to significantly impact tolerability on an individual patient level. Ig products are not interchangeable, and specific Ig products need to be matched to specific patient characteristics to ensure patient safety. It is thus inappropriate to switch Ig products without careful and due consideration, and substitution should only occur with the active participation of the patient, prescriber, and the health care team. In the event of a brand switch, an Ig-naive administration protocol should be initiated for the first several infusions – until the patient's individual tolerability of the new brand is established.[3]

Site of care options include hospital, infusion suite, physician's office, and the home setting. Considerations for safe at-home administration include a patient or caregiver's ability and motivation to participate in care, provider's and nurse's specialized expertise and credentials, Ig standards-based protocols and policies, immediate access to emergency medical services, among other considerations.[3]

Before initiating Ig therapy, the Ig clinician should conduct a thorough assessment that includes outlining the outcome goals, patient's health status and vital signs, hydration status, disease-specific assessments, previous Ig regimen, risk factors and co-morbidities, as well as any history of adverse drug reactions (ADRs). Access to preferred Ig brand and issues with insurance coverage and payer formulary are important patient advocacy factors.[3]

Risk Factors and Considerations

A thorough risk assessment including a patient's individual health risk factors, Ig brand risk factors, and other issues impacting success of therapy must be conducted ahead of every infusion.

Patient risk factors relevant to Ig therapy selection include diabetes mellitus, fluid restriction, cardiac and pulmonary function, blood type, age (especially neonates and geriatrics), obesity, history of thrombosis, and renal impairment/renal failure.

Further, several class-labeled Boxed Warnings exist with Ig therapy. Renal dysfunction and renal failure are class-labeled Boxed Warnings for intravenous immune globulin (IVIG), and are most often associated with sucrose-containing Ig preparations. The last Ig brand stabilized with sucrose (Carimune NF, CSL Behring) is no longer produced and is not commercially available. Patients at risk for renal dysfunction, renal failure, osmotic nephrosis, and death include those with pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis,

paraproteinemia, or patients receiving known nephrotoxic drugs.

Thrombosis is another class-labeled Boxed Warning for all IVIG as well as subcutaneous (SCIG) and facilitated SCIG (fSCIG) formulations. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.

A patient's medical history and health status must be evaluated to determine the Ig product(s) that may be most suitable on an individual basis. Clinicians are advised to review the IgNS Ig Therapy Standards of Practice 2nd Edition, Ig Treatment Planning section for further information. (3-6, 8-24)

Ig Product Risk Factors

Ig product formulations differ in route of administration, concentration, osmolality, stabilizers, sodium, IgA content, FXIa and PKA levels, pH, and anti-A and anti-B levels – characteristics that can impact safety and tolerability through a variety of mechanisms.

Understanding formulation differences and individualizing product selection are critical to appropriate and safe Ig therapy management. A thorough review of Ig product parameters, and the corresponding concerns and practice guidelines can be found in the *IgNS Ig Therapy Standards of Practice 2nd Edition, Ig Product Considerations* section.

Intravenous Immunoglobulin (IVIG)

IVIG is typically given via a peripherally inserted angiocatheter (the most common method) or a central line (such as an implanted port), and is administered using an infusion pump which allows controlled titration of rates and volumes. The pharmacokinetic profile of the IV route allows fast absorption and higher initial serum Ig peaks as compared to SCIG and fSCIG. The IVIG serum concentration continues to decline over a three-four week period, when the next dose is administered. Due to its complexity, adverse event profile, risk factors, and potential for serious ADRs at every infusion, regardless of patient experience or brand, IVIG must be administered by a clinician who, per the Ig Therapy Standards of Practice, must remain with the patient throughout the infusion. (3,4,8-16,19-24)

IVIG infusion rates are determined based on product-specific manufacturer's guidelines, patient risk factors, and history of ADRs. Infusions should be initiated at a slow rate and then titrated using at least three rate escalation steps, as tolerated, to the maximum rate.

Common Systemic ADRs Observed with IVIG

The ADRs reported most often include headache, fatigue, nausea, changes in blood pressure, myalgias, arthralgias, urticaria, pruritus, rash, low-grade fever, chills, chest discomfort, and tachycardia. General patient counseling to help with these includes staying orally well-hydrated, pre-medication use and adherence, good rest, and compliance with medications used to treat chronic conditions such as hypertension. (3,4, 8-16, 19-23)

Many ADRs occurring during an infusion may be prevented or decreased in severity by lowering the infusion rate or temporarily discontinuing delivery and restarting at a lower rate after symptoms resolve, and repeating ordered premedication if enough time has passed. Other ADRs may be treated symptomatically. (3)

To mitigate and decrease the severity of ADRs, premedication strategies may be considered. Hydration is recommended for all patients (unless volume-restricted due to specific risk factors) – taken either orally or delivered via infusion. Other management may include slowing the titration and/or maximum infusion rates, splitting the dose over more days, administering multiple day courses over non-consecutive days, as well as adding ancillary medications such as IV hydration. In some cases, changing the brand and/or route of administration may be necessary to achieve better tolerability. (3)

Patient counseling and education on Ig therapy management includes hydration and rest prior to infusion; adherence to concomitant medication regimen – particularly for conditions that may impact safety and/or tolerability of Ig, such as hypertension, migraine, congestive heart failure, thromboembolic conditions, and other risk factors. [3,4,8-16,19-24]

Subcutaneous Immunoglobulin (SCIG)

SCIG is typically administered through a pump or a syringe driver infusion device simultaneously through multiple SC sites. SCIG is available as a 10% (1 g/10 mL) or 20% (1 g/5 mL) solution. The choice of concentration may depend on patient tolerability of Ig therapy as well as the volume infused.

Local site reactions are the more common side effect with SCIG therapy and include local swelling, redness, and irritation. Successful SCIG administration depends on the effectiveness of initial patient education and training by a nurse or prescriber, patient and/or caregiver comfort; proper technique including insertion; and ensuring that the tubing is primed to just short of the needle ("dry-priming") to minimize a localized response, as well as appropriate needle length and gauge; SC tissue and infusion site; and needle phobia. Further, appropriate interventions and trouble-shooting can be instrumental in improving tolerability and a patient's experience. [3, 4, 10, 12, 14, 15]

Facilitated Subcutaneous Immunoglobulin (fSCIG)

Facilitated-subcutaneous infusion of Ig 10% and recombinant human hyaluronidase improves absorption (vs. SCIG), is infused less frequently, and minimizes the need for multiple infusion sites. Of note, swelling at the infusion site usually presents as diffuse and soft, rather than raised and nodular as compared to those commonly observed with SCIG. Local site reactions and management of fSCIG are similar to SCIG. Facilitated-SCIG is approved in adults with PID; during the clinical trial, some patients developed non-neutralizing antibodies to the hyaluronidase component. The clinical significance is unknown and may be a consideration in reproduction. [3,16]

Treatment Success Factors

There are multiple factors that contribute to patient tolerability, adherence, and response to therapy. Appropriate product selection, healthcare professionals' expertise in administration, and education provide key opportunities to ensure success. Additional considerations influencing a positive patient outcome may include psychosocial issues, caregiver support, nursing resources, insurance coverage, and financial impact. [3]

Conclusion

Ig therapy requires a high degree of specialized education and advanced, standardized clinical practice to ensure safety and good clinical outcomes. Adherence to the *Ig Therapy Standards of Practice* is critical, as it guides all major aspects of practice, including appropriate product selection and dosing, route and method of administration, mitigation of risks, management of adverse events administration protocols, and other aspects. The standards facilitate collaboration of care, serve as a foundation to organizational policies, support clinicians, and most importantly, help protect the patients.

References

1. Gelfand EW. Differences between IGIV products: impact on clinical outcome. Int
2. Immunoglobulin National Society. www.ig-ns.org. Accessed March 12, 2018
3. Immunoglobulin Therapy: Standards of Practice, 2nd Edition (IgNS 2018)
4. Cuvitru [package insert] Westlake Village, CA: Baxalta US; 2016.
5. Dalakas MC, Clark WM. Strokes, thromboembolic events, and IVIg: rare incidents blemish an excellent safety record. Neurology. 2003;60(11):1736-1737.
6. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology. 1994;44(2):223-226.
7. Epstein JS, Zoon KC. Important drug warning: immune globulin intravenous (human) (IGIV) products. Neonatal Netw. 2000;19(2):60-62.
8. Flebogamma 5% DIF [package insert]. Barcelona, Spain: Grifols Biologicals, Inc.; 2017.
9. Flebogamma 10% DIF [package insert]. Barcelona, Spain: Grifols Biologicals, Inc.; 2018.
10. Gammagard Liquid [package insert]. Westlake Village, CA: Baxalta US; 2016.
11. Gammagard S/D IgA<1µ/mL[package insert]. Westlake Village, CA: Baxter Healthcare Corporation; 2014.
12. Gammaked [package insert]. Research Triangle Park, NC: Grifols Therapeutics, Inc.; 2016.
13. Gammaplex 5%[package insert]. Durham, NC: BPL Inc; 2009.
14. Gamunex-C [package insert]. Research Triangle Park, NC: Grifols Therapeutics, Inc.; 2017.
15. Hizentra [package insert]. Kankakee, IL: CSL Behring LLC; 2016.
16. Hyqvia [package insert]. Cambridge, MA: Shire US, Inc.; 2016
17. Caress JB, Kennedy BL, Eickman KD. Safety of intravenous immunoglobulin treatment. Expert Opin Drug Saf. 2010;9(6):971-979.
18. Lin RY, Rodriguez-Baez G, Bhargave GA,et al. Intravenous gammaglobulin-associated renal impairment reported to the FDA: 2004 - 2009. Clin Nephrol. 2011;76(5):365-372.
19. Octagam 5% [package insert]. Hoboken, NJ: Octapharma USA, Inc.; 2015.
20. Octagam 10% [package insert]. Hoboken, NJ: Octapharma USA, Inc.; 2015.
21. Privigen [package insert]. Kankakee, IL: CSL Behring LLC; 2017.
22. Panzyga [package insert]. Hoboken, NJ. Octapharma USA Inc.; 2018.
23. Gammaplex 10% [package insert]. Durham, NC: BPL 2017
24. Siegel J. Immune globulins. Therapeutic, pharmaceutical cost, and administration considerations. Pharmacy Practice News. February 6, 2018.