

An Overview of Immune Globulin Dosing

How much IG to prescribe differs for each individual based on a variety of clinical and non-clinical factors, as well as physician discretion.

By Kris McFalls



Immune globulin (IG) is not a one-size-fits-all drug. Prescribing the proper dose to administer can be difficult and is dependent on several factors, the most important of which is a clinical assessment. However, other non-clinical variables also are important. Understanding all of the factors that determine proper IG dosing will ensure the patient is being prescribed the amount of the drug that will provide them with the most effective treatment.

Considering the Disease

When prescribing IG, the first clinical consideration is the patient's disease. IG was initially prescribed to treat primary immune deficiency diseases (PIDD) and immune thrombocytopenic purpura (ITP). Over time, IG also has proven to be an effective treatment for numerous inflammatory and immune-mediated diseases affecting the neuromuscular system. Current IG products collectively carry Food and Drug Administration (FDA)-approved indications for PIDD, ITP, Kawasaki disease (KD), chronic inflammatory demyelinating polyneuropathy (CIDP) and chronic B-cell lymphocytic leukemia (CLL). Although there are other FDA-approved indications for intravenous IG (IVIG), the products used to treat those indications are no longer on the market.

Dosing recommendations for FDA-approved indications for each IG product are included in its package insert (PI). These recommendations are based on the results of individual clinical trials, and they change only when a new clinical trial is conducted that results in positive outcomes for new dosing guidelines. Yet, as physicians learn more about diseases and patients' responses to treatment, the amount of IG prescribed does vary from patient to patient and can differ from manufacturer PI recommendations. In addition, physicians also can prescribe IG for off-label indications, but by law, dosing guidelines for off-label indications cannot be included on the PI. Instead, physicians must use peer-reviewed literature, clinical observations and their best judgment when deciding on the proper dose to prescribe for off-label indications. Having so many dynamic variables makes it easy to see why there may be some confusion and inconsistencies in IG treatments.

Using Physician Discretion

Whether or not an indication is FDA-approved, physicians have the option to utilize professional judgment in order to adjust the dose and/or use a particular medication for an off-label indication. While it is illegal for manufacturers to advertise drugs for an off-label indication, once the

drug is FDA-approved, physicians can legally prescribe medications for any other purpose. And, insurance companies often will cover certain off-label indications as long as it is the standard of care for that particular disease.

Empirically Measuring Effectiveness

PIDD associated with hypogammaglobulinemia (low immunoglobulin [IgG] levels) is an example of how IG replacement therapy and dosing have changed over time. It was first treated with intramuscular injections of IG, which were not only extremely painful for patients, but also proved difficult to achieve high enough serum IgG levels to adequately prevent infections. As a result, IVIG became the preferred route of administration in the early 1980s.

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Initially, IVIG replacement therapy for PIDD with low IgG levels was dosed at 100 to 200 mg/kg. In part to assess whether the dose was working, great reliance was placed on trough levels (the amount of serum IgG concentration immediately preceding the next infusion) as indicators of effectiveness. It was thought that an adequate trough level was roughly 500 mg/dL. However, it was later learned that not all patients have the same response when maintaining trough levels in this range. In addition, although trough levels can be used as a guide, a sufficient trough level to prevent serious bacterial infections for all types of patients has not yet been established. According to recent research published in *Clinical Immunology*, "PIDD patients receiving IVIG therapy and experiencing pneumonia are likely to be helped by increasing the IgG trough levels to at least the mid-normal range of IgG. ... [And,] meta-analysis provides evidence that pneumonia risk can be progressively reduced by higher trough IgG levels up to at least 1000 mg/dL."¹

While trough levels can be a useful guide for PIDD associated with low IgG levels, the same cannot be said for patients with immune-mediated diseases affecting the neuromuscular system. These disorders are treated with

IG, but the diagnosis is not based on IgG serum levels. Therefore, using serum IgG trough levels as a benchmark is not a viable option. Complicating matters is the fact that scientists don't fully understand how IG works in CIDP and other immune-mediated neuromuscular diseases such as multifocal motor neuropathy (MMN), myasthenia gravis (MG) and myositis. For these diseases, IG is not a replacement therapy as it is for PIDD. Instead, it is an immune-modulating therapy, meaning it adjusts the body's innate immune response that has gone awry.

Currently, CIDP is the only neuromuscular indication that is FDA-approved to be treated with IG. The generally accepted dosing protocol for CIDP treatment with IG was

determined through clinical trials. But still more studies are needed to gather data to establish more universally accepted standard protocols.

Dosing for CIDP can vary from the PI and should be based on individual response to therapy. Many insurance policies carry a clause in the reauthorization process that requires patients, once stabilized by IG, to try a lower dose of IG to see if maintenance can be attained at a lower cost. Many physicians, trying to optimize treatment and at the same time limit the cost for patients, also may take a similar approach. As with PIDD, the dose needs to be tailored to the individual patient's needs using the clinical findings as a guide. For instance, before FDA approval of

Dosing Recommendations For All U.S.-Approved Immune Globulin Products

Product	Manufacturer	Indication	Administration Route	Dosing Recommendations
Carimune NF	CSL Behring	PIDD	IV	0.4 to 0.8 g/kg every 3 to 4 weeks
Flebogamma DIF 5%	Grifols	ITP	IV	0.4 g/kg over 2 to 5 consecutive days
		PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
Flebogamma DIF 10%	Grifols	PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
Gammagard S/D	Baxter Healthcare	PIDD	IV	300 to 600 mg/kg infused at 3- to 4-week intervals
		CLL	IV	400 mg/kg every 3 to 4 weeks
		ITP	IV	1 g/kg
		Kawasaki	IV	Either a single 1 g/kg dose, or a dose of 400 mg/kg for 4 consecutive days beginning within 7 days of the onset of fever
Gammagard Liquid	Baxter Healthcare	PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
Gammaplex	Bio Products Laboratory	PIDD	IV	300 to 800 mg/kg every 3 to 4 weeks
Gamunex-C	Talecris Biotherapeutics	PIDD	SC	1.37 x IVIG dose in mg/kg/iv dose interval in weeks, weekly
		PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
		ITP	IV	2 g/kg
		CIDP	IV	Loading dose: 2g/kg Maintenance dose: 1g/kg every 3 weeks
Hizentra	CSL Behring	PIDD	SC	Initial dose: 1.53 x IVIG dose (in grams)/ No. of weeks between IVIG doses
Octagam 5%	Octapharma	PIDD	IV	300 to 600 mg/kg every 3 to 4 weeks
Privigen	CSL Behring	PIDD	IV	200 to 800 mg/kg every 3 to 4 weeks
		ITP	IV	1g/kg IV daily for 2 consecutive days (2g/kg total)
Vivaglobin	CSL Behring	PIDD	SC	1.37 x IVIG dose (in grams)/No. of weeks between IVIG doses, weekly

Key: CLL = chronic B-cell lymphocytic leukemia
ITP = immune thrombocytopenic purpura
IV = intravenous

IVIG = intravenous immune globulin
PIDD = primary immune deficiency disease
SC = subcutaneous immune globulin

Note: All information taken from product package inserts



Gamunex to treat CIDP, many experienced clinicians started treatment using a loading dose of 2 g/kg over two to five days. The patient was then observed and asked to immediately report any signs of recurrence. Once symptoms started to reappear, a maintenance dose of 1 g/kg was given. The patient was again observed for signs of returned symptoms. That interval of time between the

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infusion and the first sign of returned symptoms became the interval for maintenance therapy. For many patients, that interval was between two and four weeks.

Research presented in the *Journal of the Peripheral Nervous System* has shown that dose frequency, once established, should not be changed. In addition, the

research shows that “lower dose treatment is not associated with shorter intervals between courses, and lowest effective dose is independent of weight and disease duration.”² Additional studies are needed to establish standard protocols for CIDP patients. In the meantime, dosing for off-label immune-mediated indications will continue to rely on experienced physicians and peer-reviewed data to establish standard-of-care protocols.

Too Little or Too Much Can Make a Difference

Clinical trials and scientific studies help to establish maximum and minimum IG dosing standards. The clinical effects of IG dosing can have significant consequences. Knowing how much is too much and how little is too little is crucial for maximizing health outcomes and minimizing costs. Yet, because the amount of IG to prescribe can be both disease- and patient-specific, there are no clear-cut universal boundaries.

It is not well-known how much IG is too much. When treating PIDD, it is believed that after a certain amount, there is no medical benefit to increasing the dose. Currently, there are not enough studies to determine exactly what that amount is. In general, however, the goal is to prescribe enough IG to prevent serious breakthrough bacterial infections from occurring. When treating other diseases, the amount of IG to prescribe is even less clear. Using more IG than is medically necessary may result in increased costs for all, increased risk of fluid volume overload, increased risk of side effects (especially if high doses increase the propensity to speed up the infusion), and an artificially increased need for the limited natural resources needed to make IG.

No matter what the disease state, treating with too little

IG results in ineffective treatment and a poor clinical response. Because IG protocols frequently lack universal standardization, undertreatment may be more common than is realized. Undertreating may cause the patient and physician to mistakenly believe treatment is not working; cause breakthrough infections or symptoms that result in more expensive hospitalizations, treatments, testing and increased disability; decrease productivity for employers of patients; increase workload for the treating physician; and decrease quality of life for the patient.

Many factors can lead to undertreating patients. Some of the more common problems include:

- Insurance policies that attempt to standardize treatments without taking into account the treating physician's ability to base IG dose on the clinical outcome of the patient
- Prescribers and providers not staying current on the latest research
- Limited research funding for rare diseases treated with IG
- Product shortages resulting in rationing of supplies
- Patient tolerance to treatment
- Patient compliance

Other factors also can affect dosing of IG. Specifically, the vial sizes of each product can play a small role in tailoring the dose. Each manufacturer produces a limited number of vial size options for each product, and the dose

is based on the weight of the patient. If a patient's weight requires an odd-sized dose that does not evenly match up with the vial size, the dose is generally rounded up to the nearest size available.

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Because a patient's IG dose is directly related to their body weight, obesity is one variable that may warrant a deviation from the dosing formula. Fat tissue contains proportionally more fluid than other tissues. In addition, IG has very little distribution into the fluid in fat tissue. Therefore, the dose should be adjusted down for a person when fat is a larger part of their overall body weight. Studies suggest the dose for patients with a body mass index greater than 30 kg/m² be adjusted to correlate with the ideal body weight rather than the actual body weight.³

Maximizing Patient Outcomes

IG dosing is unique and complicated. Many variables have to be considered to ensure patients get the full benefit of this expensive, lifesaving treatment. Much more research is needed to determine adequate dosing. In the meantime, following dosing recommendations and staying educated is the best way to maximize patient outcomes. ■

KRIS MCFALLS is IG Living's full-time patient advocate.

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