

Intravenous IgG Replacement in PIDD: Dose and Clinical Expectations

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KEYWORDS

• Immunoglobulin G • Intravenous IgG • Primary immunodeficiency disorders

KEY POINTS

- Advances in the manufacture of IVIG has provided a safer and better tolerated immunoglobulin replacement product for patients with immune deficiency
- The transition from the intramuscular route to the intravenous route has allowed the administration of larger doses of Ig replacement therapy leading to higher serum IgG trough levels
- More recent data has shown that trough IgG serum levels higher than 500 mg/dl approaching 1000 mg/dl are of benefit in reducing serious bacterial infection. In patients with x-linked agammaglobulinemia higher dosages of Ig replacement therapy may help prevent meningococcal infection
- Each patient with immune deficiency may require their own unique dose of Ig replacement therapy to keep them infection free. This is referred to as the “biological trough level”.
- The subcutaneous administration of Ig replacement therapy is of benefit because this route of administration eliminates peak and trough serum levels as seen with IVIG resulting in a more steady state level of serum IgG.

HISTORICAL PERSPECTIVE

A review of the therapeutic use of gamma globulin over the years can provide a perspective on progress in this area. In the early 1950s, intramuscular (IM) IgG was introduced for the treatment of antibody deficiency syndromes, but this therapy was associated with considerable limitations. Only small amounts of IgG could be used, the treatment was very painful, and the serum immunoglobulin level could be raised only to an extremely limited degree. During the next 2 decades, attempts were made to modify the product so it could be administered by the IV route, allowing the use of much larger doses. These efforts led to the approval, in 1981, of 2 IGIV replacement products for the treatment of patients with antibody deficiency syndromes in the United States. Subsequently, in the 1990s, a series of concerns emerged that prompted modifications in IgG manufacturing

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protocols. The first issue that arose was the occurrence of cytomegalovirus infection in association with this treatment. In response, the US Food and Drug Administration, working in conjunction with companies producing IGIV, developed new manufacturing approaches in an attempt to minimize the risk of transmitting infectious agents—particularly viral agents—during such therapy. Techniques adopted at that time included the incorporation of solvents/detergents, pasteurization, and caprylate to prevent transmission of lipid envelope viruses. However, by the start of the twenty-first century, additional issues became apparent—namely, the risk of renal failure in patients receiving sucrose-containing IVIG products, as well as the potential for transmission of prion disease (Creutzfeldt-Jakob disease). The latter observation led to additional changes in the manufacturing process, aimed at making IGIV therapy safer through nanofiltration to remove prions. Other adverse events that came to light during that time were thromboembolic phenomena, which remain a major concern today.

IGIV COMPOSITION AND DOSING

Typically, IGIV replacement products are made from pooled human plasma from 2000 to 10,000 donors, although the number may be as high as 60,000 donors. These products are composed of >95% monomeric IgG with small amounts of dimeric and polymeric IgG.¹ Small amounts of IgM and IgA may also be present, depending on the product. The presence of plasma proteins other than IgG may, in fact, be responsible or at least associated with some of the adverse events noted with the administration of IGIV.

Early assessments of IGIV therapy compared dosing with these products versus IGIM, which was subject to the limitations mentioned above. The IM preparation permitted the administration of a dose of only 0.6 cc/kg, or approximately 100 mg/kg per month. This dose was only able to raise the serum IgG to approximately 200 mg/dL in a patient with agammaglobulinemia. Although some infections were prevented, patients continued to develop serious infections and chronic lung disease. Initial recommendations for the first IGIV products specified a dose of 200 mg/kg per month. Subsequently, studies reported in the late 1980s revealed that the achievement of IgG serum trough levels ≥ 500 mg/dL, in response to a higher IGIV dose (600 mg/kg), substantially reduced the frequency of infections and improved pulmonary function.^{2,3} These results led to modification of the recommendations in the early 1990s, advising the use of IGIV doses ranging from 400 to 600 mg/kg to attain such trough levels. The advantages of attaining IgG levels >500 mg/dL were further confirmed in a retrospective study conducted in the late 1990s.⁴ This work focused on children with X-linked agammaglobulinemia who received prolonged IGIV replacement therapy beginning early in life (median age, 24 months). The achievement of IgG serum trough levels >500 mg/dL was associated with a significant decrease in the rate of bacterial infections requiring hospitalization, from 0.40 to 0.06 per patient per year ($P < .001$). However, even though such trough levels were effective in preventing severe, acute bacterial infections, some patients still developed enteroviral meningoencephalitis and chronic pulmonary disease. The authors therefore recommended intensifying replacement therapy to achieve higher IgG trough levels (>800 mg/dL) capable of preventing enteroviral disease.

Not until recently have more extensive, thorough considerations of this issue become available in the literature. In 2010, Orange and colleagues⁵ published a meta-analysis of data from 17 studies that examined the relationship between trough IgG and the incidence of pneumonia in a total of 676 patients with primary immunodeficiency disease (PIDD). A clear inverse relationship was apparent between trough IgG level and the

occurrence of pneumonia (**Fig. 1**). Specifically, the incidence of pneumonia decreased by 27% for each 100 mg/dL increase in trough IgG levels (incidence rate ratio, 0.726; 95% confidence interval 0.658–0.801). Maintenance of a trough level of 500 mg/dL was associated with 0.113 cases of pneumonia per patient-year, whereas the incidence was 5 times lower (0.023 cases per patient-year) at a trough level of 1000 mg/dL.

However, other observers have suggested that IgG replacement should be targeted to a so-called biologic level individualized to each patient, rather than a uniform level.⁶ Bonagura and colleagues⁶ have pointed out that some patients with PID, such as those with common variable immunodeficiency, can present with relatively high IgG levels (eg, >400 mg/dL), yet have poor qualitative function as evidenced by poor antibody responses to protein or carbohydrate vaccines. Such patients frequently require higher IgG levels to achieve adequate protection against recurrent sinopulmonary infections and bronchiectasis. The “biologic IgG trough” is that serum IgG level that keeps the patient as free from infections as possible; plotting a patient’s IgG levels against documented infections over time, as illustrated by a case study presented by these authors (**Fig. 2**), can help determine this “biologic IgG trough.”

Recently reported data from a case series have reinforced the concept of titrating IgG to each patient’s unique needs.⁷ A review of longitudinal data from 45 patients showed that the efficacy of IgG maintenance treatment delivered at home via a self-infusion program was optimized by adjusting doses and infusion frequency according to therapeutic response. These benefits were achieved through continuous monitoring of symptoms, inflammation resulting from intercurrent infections, and progression of underlying disease due to low-grade lymphoproliferation.

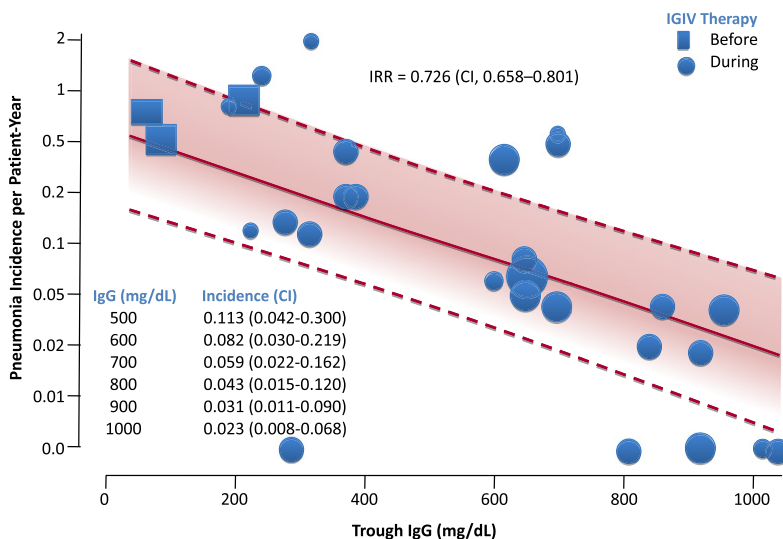


Fig. 1. Effect of trough IgG level on pneumonia incidence per patient-year. Each data point represents a single observation period in a patient group of a particular study. Solid line shows multilevel model predictions, and dashed lines indicate the CI of metaregression. CI = confidence interval; IgG = immunoglobulin G; IGIV = intravenous immunoglobulin G; IRR = incidence rate ratio per 100 mg/dL increase in trough IgG level. (From Orange JS, Grossman WJ, Navickis RJ, et al. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies. Clin Immunol 2010;137:26; with permission.)

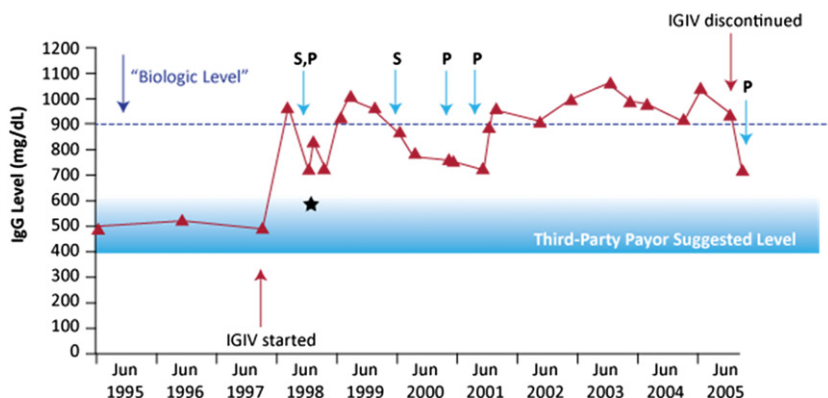


Fig. 2. Example of titrating IGIV therapy to a patient's individual "biologic level." IgG = immunoglobulin G; IGIV = intravenous immunoglobulin; P = pneumonia; S = acute sinusitis. (From Bonagura VR, Marchlewski R, Cox A, et al. Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection. *J Allergy Clin Immunol* 2008;122(1):211; with permission.)

At present, the available data suggest that patients with antibody deficiency should receive IGIV infusions at a starting dose of 400–600 mg/kg every 4 weeks.⁸ The infusion dose and/or interval can be adjusted to shorter intervals depending on the clinical response. In patients who have higher initial serum IgG levels, a rough goal is a serum trough level equivalent to the pretreatment level plus 300 mg/dL.⁸ Rather than treating the "numbers," however, clinicians should follow the clinical response and "biologic" trough IgG levels to maximize efficacy. An additional point is that patients with bronchiectasis will require higher doses.⁹ It should also be noted that several infusions (eg, 3) may be required to equilibrate to a new trough.¹⁰ Finally, the subcutaneous route should be considered to eliminate varying trough levels and provide better tolerability needed by some patients.

SUMMARY

The use of IgG for the treatment of immune deficiencies has evolved during the past 60 years, leading to improvements in preparations as well as strategies for optimizing clinical responses. A key development has been the recognition that the benefits of IGIV can be increased by titrating the dose according to each patient's unique needs to maintain appropriate trough IgG levels. Ongoing research holds the promise of further improvements in the treatment of PIDD in the future.

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