



Individual IG Dosing Strategies

By Ronale Tucker Rhodes, MS, and Kris McFalls

Studies that examine the relationships between therapeutic doses of IG, trough IgG levels and infection rates shed new light on how IG replacement therapy should be prescribed for individuals.

Immune globulin (IG) replacement therapy is the standard treatment for primary immune deficiency disease (PIDD), either via intravenous (IV) or subcutaneous (SC) routes. Yet, even with IVIG and SCIG treatments, patients continue to suffer acute breakthrough and chronic infections. This is because IG treatment is not a standardized, one-size-fits-all treatment. And, because dosing strategies are unique to each patient, there is sometimes confusion about what is the optimal dosing strategy.

A History of Dosing Regimens

In the U.S., there is no one national guideline for IG dosing, as there is in the United Kingdom and Australia, for example. However, there are several different published IG dosing guidelines that recommend satisfactory IgG trough levels for patients, yet all of them differ somewhat. And, there is the U.S. Food and Drug Administration's minimal criterion for efficacy, which states that the IG treatment should achieve less than one serious infection per patient per year. Most of the published guidelines regarding IgG trough levels recommend patients achieve a level of around 600 to 800 mg/dL with a dose of 400 mg/kg of IG every three to four weeks. The problem, then, says Dr. Melvin Berger, a specialist in allergy and immunology and pediatric medicine in Cleveland, Ohio, and the senior medical director of clinical research and development at CSL Behring, is that some patients may need a biological trough level of only 600 to achieve less than one serious infection per year, whereas other patients may need a trough level of 900 to attain the same measure of health. Therefore, it has been questioned whether treatment protocols that use IgG trough levels as a determinant of the IG dose patients receive during therapy are most effective for reducing infections.

According to Dr. Berger, there have been about 10 studies over the years that have looked at IG dose and effect, comparing lower and higher doses in PIDD patients. All those studies except one, he says, have found that the higher dose was more effective in lowering the incidence of infection. Additionally, several recent studies have shown that while general dosing guidelines are a great starting place, each patient needs individualized dosing to prevent infections.

Study: Lucas et al. (2010), Oxford University

An extensive study published in the *Journal of Allergy and Clinical Immunology* by a group led by Dr. Helen Chapel at Oxford University in the United Kingdom examined the relationships among therapeutic IG doses, trough serum IgG levels and infection rates over 22 years in a single clinic. Its objective was to provide data to support the hypothesis that each patient requires an individualized IG dose to prevent breakthrough infections, rather than to achieve a serum IgG trough level.

The study followed the practice in Dr. Chapel's clinic to adjust IG doses in real time in accordance with infection episodes, rather than to achieve a particular trough IgG level. Patients without chronic lung disease were started

with initial doses of 0.4 g/kg per month of IG, and patients with bronchiectasis were treated with initial doses of 0.6 g/kg per month. Those doses were then adjusted in line with breakthrough infections. If there were no serious breakthrough infections, those patients with a rate of three moderate bacterial infections per year got an increase in IG dosage of around 0.15 g/kg per month, usually given as SCIG or IVIG every two weeks.

It has been questioned whether using IgG trough levels to determine the IG dose during therapy is most effective for reducing infections.

Ninety patients with confirmed common variable immune deficiency (CVID) and 15 with X-linked agammaglobulinemia (XLA) were included in the study. (The group of XLA patients was analyzed in this study for comparison.) To participate, CVID patients were selected if they had a serum IgG level <6.0 g/L (600 mg/dl) and either a serum IgA level of <0.8 g/L or a serum IgM level of <0.5 g/L or both; if they were over 4 years of age at diagnosis; and if there were no other conditions or therapies associated with antibody failure. Patients were excluded if there was less than 12 months of data or noncompliance with therapy or monitoring. The same exclusion criteria were used for XLA patients for comparison purposes.

To collect the data, the Oxford PID Database was created in which demographic and infection data correlating to IG therapy were logged. The specific information logged included data on infections (infection site, pathogen type and treatment details), administration route of IG, IG dose in grams per kilogram per month, and clinical complications. Baseline data were entered from patient notes at the start of IG therapy or on referral to Oxford for patients previously diagnosed.

Additional data on treatment and response were collected over a follow-up period of 22 years, and then validated and analyzed. The entry point for each patient into the

analysis was the point at which the serum IgG level was stable (defined as ≤ 1.5 g/L variation from the mean trough IgG over at least four months). Data were analyzed for IgG, IgA and IgM levels against time for each patient, commencement of replacement therapy and dose changes. In addition, the analysis allowed for seasonal variations in infections. And, confirmation of bacterial infection was made using radiologic/laboratory/microbiological findings and responses to antibiotics.

Results of treatment with therapeutic IG doses adjusted in accordance with infection data rather than to achieve a particular trough IgG level showed that overall bacterial infection frequency was low (2.16 infections per patient-year), and the incidence of serious infection was particularly low. And, in any period, the mean trough IgG level correlated strongly with the replacement dose of IG, but there was a weak relationship between infection score per patient-period and mean trough IgG.

Studies show that patients need individualized dosing to prevent infections.

According to the study's authors: "This study provides evidence to support the clinical view that the trough IgG and dose of replacement therapy to maintain minimal infectious burden is unique to the individual." They conclude by stating: "The goal of replacement therapy should be to improve clinical outcome and not to reach a particular IgG trough level."

Meta-Analysis of SCIG: Dr. Berger (2011)

Dr. Berger substantiates the Oxford study's conclusions with his meta-analysis that summarizes seven studies conducted on SCIG. The analysis, which was published as a letter to the editor in the *Journal of Clinical Immunology*, notes that having a consensus targeted trough level is complicated, in part because of the differences in pharmacokinetics of SCIG versus IVIG therapy. Consensus is further complicated by the different regulatory authorities of individual countries and the different practices of different physicians.

The seven studies utilized four different SCIG preparations from three different manufacturers. In total, the reports include data from 322 SCIG patients who were treated in

multiple settings and who received treatments on a weekly basis. Trough levels were reported after 12 to 16 weeks of SCIG therapy. All studies defined serious bacterial infections (SBIs) according to published FDA guidance. Non-serious infections other than SBIs such as sinus or upper-respiratory infections with fever were defined by the treating physician. Mean trough levels in the different studies were reported to be between 810 and 1250 mg/dl (8.1 to 12.5 g/l).

A total of seven SBIs were reported in four of the seven studies, all of which were pneumonias. The remaining three studies reported no SBIs. Studies with a higher mean trough level did not demonstrate a lower incidence of SBIs. Therefore, no linear correlation could be made between the annualized incidents of SBI and the mean steady trough levels of the different studies. In contrast, however, the incidence of non-serious infections showed that a decrease in the number of infections correlated significantly with a higher steady-state serum IG level, and there did not appear to be a plateau above which higher IgG levels did not correlate with lower incidence of infection.

Dr. Berger concluded: "For any individual patient, factors other than the IgG dose and resulting serum IgG level unquestionably contribute to the type and the frequency of infections which may occur. Therefore, treatment regimens, doses, and target serum IgG levels should be individualized to optimize treatment effects and costs for individual patients."

Meta-Analysis of IVIG: Dr. Orange (2010)

Although pharmacokinetics of SCIG and IVIG are not similar, the belief that higher serum IgG levels correlate with lower infection rates also was shown to be true in a meta-analysis published in *Clinical Immunology* that evaluated the incidence of pneumonia with varying doses of IVIG. Conducted by Dr. Jordan S. Orange, a pediatric immunologist at Children's Hospital of Philadelphia and consultant to Baxter Healthcare, Talecris Biotherapeutics (now Grifols) and CSL Behring, and colleagues, this was the first meta-analysis to enumerate the relationship between IgG trough levels and pneumonia in PIDD patients treated with IVIG.

As previously discussed, serum trough IgG levels of PIDD patients historically have been used as a guide to determine appropriate levels of IVIG therapy. However, a sufficient trough level to prevent SBIs has not been established. And, while many immunologists have considered 500 mg/dL a minimum target trough level, the level of benefit gained above 500 has been debated.

Pneumonia was chosen for this meta-analysis because it

is one of the most frequent manifestations of PIDD that can result in hospitalization and require the use of intravenous antibiotics. Additionally, it is one of the primary validated SBIs used to determine efficacy of IG therapy.

A total of 17 clinical studies reported from 1982 to 2009 comprising 676 total patients and 2,127 patient-years of follow-up were included in the meta-analysis. Of the total studies conducted in the United States, Canada, Europe, the Middle East and Argentina, 11 were prospective and six were retrospective. All the studies included PIDD patients predominately diagnosed with CVID and XLA. However, no patients with subclass deficiency were enrolled in 14 of the 17 studies. Other PIDD diagnoses such as hyper-IgM, hypogammaglobulinemia and ataxia telangiectasia also were included.

Incidence rates of pneumonia were analyzed at serum trough levels of 500, 600, 700, 800 and 1,000 mg/dL (10 g/l), and at doses of 100, 200, 300, 400, 500 and 600 mg/kg. The median IVIG treatment interval between doses was 24.6 days. Results were highly statistically significant and showed that pneumonia incidence declined by 27 percent with each 100 mg/dL (1 g/l) trough increment.

Dr. Jordan and colleagues concluded that "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," which they defined as up to at least 1,000 mg/dL. No apparent plateau in efficacy was observed. However, they stated additional research "is needed to determine whether a general threshold trough of optimal protection against pneumonia may exist above 1,000 mg/dL."

From Paper to Practice?

What do these research findings mean for PIDD patients being treated with IG? Is it possible that they could result in a national guideline for IG dosing in the U.S. such as those guidelines in effect in Australia and the U.K.? Dr. Berger doesn't see a need for a national guideline. "I don't know what role published guidelines actually play," he says. "There's no obligation for a doctor to follow a published guideline. In general, the idea of a guideline is just a suggestion of where to start. It's not an end unto itself. I think most doctors probably recognize that." However, guidelines should not be used by payers to limit doses that patients receive or to restrict doctors' prescribing practices.

What these findings do provide, however, is evidence-based guidelines from which treatment protocols can be developed that will result in a higher quality of life for a

large portion of PIDD patients. For instance, Dr. Berger says, "What is the goal of therapy? To keep the patient barely alive or to produce a normal citizen who can go to school or work?" The goal, he says, is the latter and that can be achieved only by reducing the number of infections. So, since these studies show that higher doses of IG

Study findings provide evidence-based guidelines that can be used to develop treatment protocols that result in a higher quality of life for PIDD patients.

will produce higher IgG levels and lower rates of infection, there are two take-home messages: 1) higher doses lead to lower morbidity due to infection, and 2) there's no threshold value. And, he says, this information needs to be incorporated into the currently available guidelines.

However, change will not happen overnight. A change like this requires a paradigm shift from the way things have been done for decades. Even within the field of immunology, there will be doctors who want to see more evidence. At the end of the day, though, doctors prefer to treat patients, not numbers. And, this type of research encourages them to do just that.

RONALE TUCKER RHODES, MS, is the editor of *IG Living* magazine, and **KRIS MCFALLS** is *IG Living's* full-time patient advocate.

Editor's Note: This article is a summary of three published studies: 1) Lucas, M, Lee, M, Lortan, J, Lopez-Granados, E, Misbah, S, Chapel, H. Infection Outcomes in Patients with Common Variable Immunodeficiency Disorders: Relationship to Immunoglobulin Therapy Over 22 Years, Journal of Allergy and Clinical Immunology, Vol.125, No.6:pp1354-1359. More detailed information about this study can be obtained online at www.jacionline.org/issues. 2) Berger, M. Incidence of Infection Is Inversely Related to Steady-State (Trough) Serum IgG Level in Studies of Subcutaneous IgG in PIDD, Journal of Clinical Immunology, June 4, 2011. 3) Orange, JS, Grossman, WJ, Navickis, RJ, Wilkes, MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies, Clinical Immunology, 2010 Oct;137(1):21-30. Epub 2010 Aug 1.