

Letter to the Editor

A pilot study of equal doses of 10% IGIV given intravenously or subcutaneously

To the Editor:

Patients with primary immunodeficiency disease are most often given immunoglobulin replacement therapy by the intravenous route.¹ Subcutaneous administration offers advantages that may be important for many patients.^{2,3} Because of differences in the pharmacokinetics of IgG given by the subcutaneous versus intravenous route, the Food and Drug Administration required that the area under the curve of serum IgG versus time must be noninferior for IgG given by the subcutaneous compared with the intravenous route.^{4,5} In contrast, European regulators require only that the trough serum IgG levels maintained on steady-state subcutaneous therapy must be higher than those achieved with intravenous therapy given every 3 to 4 weeks.⁶ These requirements result in the suggestion to use 37% more IgG per month for subcutaneous versus intravenous administration in the United States,³ whereas the same dose is suggested for use by both routes in the European literature.^{6,7} We performed a pilot study to determine the feasibility of comparing the efficacy and tolerability of a single immunoglobulin product (Gamunex, Talecris Biotherapeutics, Inc, Research Triangle Park, NC) given at the same dose by the intravenous and subcutaneous routes to subjects with primary immunodeficiency disease. We used a randomized crossover design to minimize seasonal effects on the incidence of infection and so that each subject would serve as the subject's own control. Because each subject was exposed to the same IgG preparation by both routes, the subject's preference for one route versus the other should not have been influenced by particular features of the individual product (pH, ionic strength, and so forth), nor should the incidence of infection have been influenced by differences in the antibody content of the preparations used for the intravenous versus the subcutaneous route, as has been in the case in other comparisons of the 2 routes.^{3,7}

Twelve antibody-deficient patients already on IgG therapy were enrolled in a randomized, 2-arm crossover, nonblind pilot trial conducted at a single study site. One subject became pregnant and withdrew. The mean age of the other 11 subjects was 29 years (range, 5-59 years). Each was given Gamunex (10% IgG, pH 4.0-4.5, 285-295 mOsm/L) at the same total monthly dose as their previous IgG therapy on a milligram per kilogram basis subcutaneously (divided into 1/4 of the previous monthly intravenous dose per week) for 6 months, and intravenously for 6 months. They were randomized as to who would receive which regimen first, then crossed over to the other regimen to prevent seasonal bias from influencing the outcome.

Each subject or parent was instructed in subcutaneous administration, then continued infusions at home once or twice a week by using a small portable pump and 27-gauge $\times$ 9-mm needles. One to 3 sites were used per infusion, usually over a period of 2 to 3 hours, at rates ranging from 0.1 to 0.25 mL/kg/site/h,⁸ with a maximum of 50 mL per site. Subjects kept daily diaries of infusions, local site reactions, other adverse events, symptoms of infection, and concomitant medications. Diaries were reviewed and serum IgG was measured at visits every 3 or 4 weeks throughout the study. The primary efficacy endpoint was the number of acute serious bacterial infections as defined by the Food and Drug

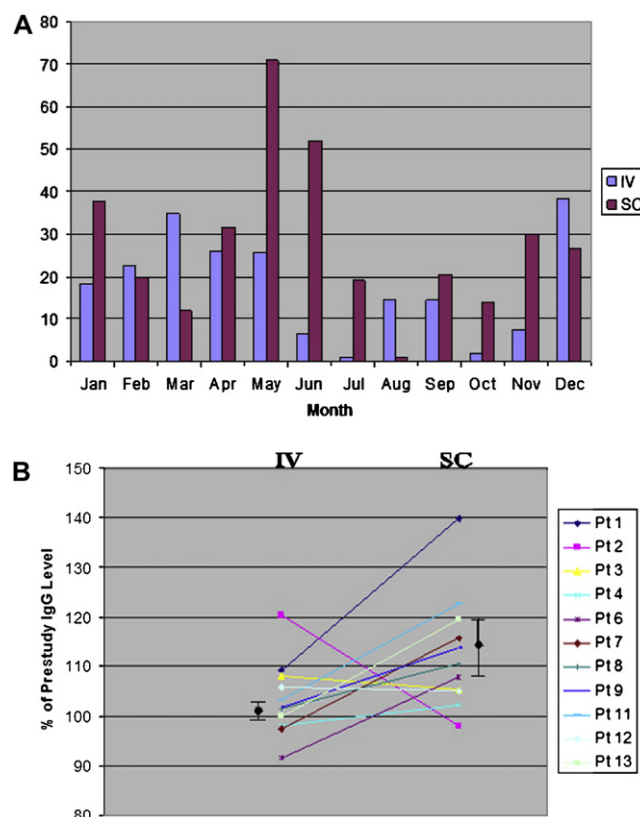


FIG 1. A, Patient days on which symptoms suggestive of infection were reported. The bars represent the total number of days in each month on which subjects reported symptoms of illness, fever, antibiotic treatment, or inability to attend work/school. Any 1 day in the year was counted only once per patient. Because all subjects completed 12 months in the study, the days of risk for all subjects on each route are the same. These data suggest that there was no difference between the number of days of illness in the winter (November-March), 412, and the warmer months (April-October), 415. **B,** Percentage of prestudy IgG trough level. The figure represents the normalized percentage of prestudy IgG trough level for each patient (Pt) on intravenous (IV) and subcutaneous (SC) therapies, with the prestudy level of each patient set at 100%. Each point represents the mean of 3 determinations in the last 3 months of therapy by each route. The overall mean increase on IV therapy was 1.7% (SD, 5.3), and the overall mean increase on SC therapy was 14.2% (SD, 11.2; $P \leq .004$ by t test).

Administration.⁵ Serum IgG concentrations were measured at each visit. Subjects' preference for one route versus the other was determined by questionnaire at the end of the study. The protocol was reviewed by the Food and Drug Administration and the institutional review board of University Hospitals of Cleveland—Case Western Reserve University. Written informed consent was obtained for all subjects.

Only 1 serious infection occurred: fever and a new density on chest radiograph that was considered to meet the definition of pneumonia developed after coronary artery bypass surgery in 1 subject. Thus, therapy by both routes met the Food and Drug Administration criterion for efficacy of <1 acute serious bacterial infection/subject/y. Two other serious adverse events occurred, but none were judged "related" or "possibly related" to the study drug or treatment regimen. A total of 18 episodes of infection (3.27/patient/y; SD, 2.99; median, 4) were recorded during

intravenous therapy (most commonly fever with upper respiratory or nonspecific systemic symptoms) and 26 during subcutaneous therapy (4.72/patient/y; SD, 3.22; median, 4). This difference was statistically significant ($P = .038$ by paired t test; $P = .025$ by Wilcoxon rank-sum test). The number of days on which subjects reported symptoms of infection with each route is shown in Fig 1.A. This increased in subcutaneous subjects during May and June because of illnesses in 2 subjects, 1 of whom reported the same number of days of symptoms while on the intravenous route. There was no difference between the 2 routes in the number of systemic adverse events. During their 6 months of subcutaneous therapy, the 11 subjects used a total of 603 infusion sites. Mild local reactions were reported at 400 sites, and moderate reactions were reported at 18 sites. Severe reactions, requiring a doctor visit or medication, occurred at only 2 sites.

In this study, subcutaneous therapy was started 1 week after the patient's last intravenous infusion. This causes somewhat higher trough serum IgG levels initially, which gradually drop to a steady state after several weeks. Therefore, we compared the serum trough IgG concentrations during the last 3 months on each route of therapy. On the intravenous arm, the mean trough level was 1079 mg/dL (SD, 221), whereas it was 1160 mg/dL (SD, 164) on the subcutaneous arm ($P \leq .004$). When normalized as a percentage of the prestudy IgG trough level for each subject, the overall mean increase on this intravenous preparation was 1.7% (SD, 5.3), and on the subcutaneous preparation, it was 14.2% (SD, 11.2; $P \leq .004$). When asked to complete a simple questionnaire expressing their preference for continuing on intravenous versus subcutaneous therapy at the end of the 12-month study, 10 of the 11 patients indicated they would prefer subcutaneous therapy.

This small pilot study showed that a single preparation of IgG was well tolerated and had acceptable efficacy when given by the subcutaneous route. Total systemic adverse effects were not significantly different, and 91% of patients preferred the subcutaneous route. The overall incidence of acute serious bacterial infection (0.091/subject/y) and all episodes of infection (3.98/subject/y) were comparable to other IgG trials in primary immunodeficiency disease, but there was a significant difference in the overall number of infections with subcutaneous compared with intravenous therapy. The incidence of infection during subcutaneous therapy, 4.72, is similar to that reported in a larger licensing trial of subcutaneous IgG (SCIG) in the United States.³ Our experience suggests that a larger trial with greater power is feasible and may be better able to compare the efficacy and incidence of infections and other symptoms with the 2 routes of IgG therapy. Longer trials will be necessary to compare the effects of

subcutaneous versus intravenous IgG on chronic infection and other possible complications of primary immunodeficiency disease. Although the subjects may have been self-selected as being willing to try subcutaneous therapy, the percentage that preferred the subcutaneous to intravenous route is striking.

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