



Letter

20% subcutaneous immunoglobulin dosed biweekly for primary immunodeficiency

Approval of 20% subcutaneous immunoglobulin (SCIG) (Hizentra, CSL Behring LLC, Kankakee, Illinois) by the US Food and Drug Administration in 2013 for biweekly (every 2 weeks) administration in patients with primary immunodeficiency disease (PIDD) was based on a pharmacometric model and simulation.¹ To examine biweekly dosing of SCIG in a clinical setting, we conducted a retrospective record review of patients with PIDD treated with 20% SCIG biweekly from June 24, 2010, through July 3, 2014, at 5 clinical practices. Patients were included if they had previously received IgG replacement therapy (intravenous immunoglobulin or SCIG), been treated with the biweekly regimen for 3 months or more, and had 1 or more follow-up IgG levels measured. Patients' diagnoses were confirmed by board-certified immunologists.

Demographics, diagnosis, acute serious bacterial infections (aSBIs), hospitalizations, tolerability, general health, dosing information, and IgG levels for the previous IgG replacement therapy regimen and biweekly 20% SCIG treatment were collected. Data were summarized using standard descriptive statistics, and the aSBI rate was annualized.

Sixteen patients diagnosed as having common variable immunodeficiency had a median age of 47.5 years (range, 9–85 years), 10 were female, and the median weight was 66.2 kg (range, 19.8–123.0 kg). IgG levels reported before switching to the most recent IgG levels during biweekly dosing with 20% SCIG are reported in Table 1. Median treatment duration for biweekly 20% SCIG was 349.5 days (range, 106–945 days).

One patient experienced an aSBI (pneumonia with hospitalization) while receiving 20% SCIG biweekly (total duration of 20% SCIG treatment, 945 days), corresponding to an annualized aSBI rate of 0.036 per patient-year (95% confidence limit, 0.001–0.0199). Two patients reported occasional sinus or sinopulmonary infections, and 1 patient each reported fatigue, fatigue and sinus pressure, and

a respiratory infection that lasted 12 days. All nonserious infections that required treatment were managed with oral antibiotics. The health status of the other 11 patients was reported as good, excellent, or stable/no significant infections. The biweekly regimen was generally well tolerated, with no serious or severe systemic or local adverse events reported.

Monthly doses for patients receiving biweekly treatment with 20% SCIG were comparable with those of previous IgG therapies (Table 1). The trend of IgG levels in the patients described in this report is consistent with the slight variance observed in the pharmacometric modeling study supporting comparable IgG exposure. One patient whose monthly dose was reduced by half because of impaired kidney function experienced an expected 18% reduction in IgG levels. For patients who previously received intravenous immunoglobulin every 4 weeks, no dose adjustments for the switch to SCIG were made. All patients underwent infusion with 80 mL or less per biweekly treatment; 12 of 16 patients (75%) used 2 or 3 infusion sites (range, 2–6). The highest volume at any 1 site was 35 mL. All but 1 patient completed the infusion within 120 minutes or less, including 5 patients who reported infusion durations of 60 minutes or less.

In addition, data are reported for 4 female patients diagnosed as having specific antibody deficiency (normal IgG and a poor response to polysaccharide antigens), median age of 28 years (range, 10–46 years), and a median weight of 77.7 kg (range, 34.2–87.5 kg). One patient was previously receiving biweekly 16% SCIG, and 3 patients received SCIG weekly (16% or 20%). In these patients, the median percent change between the dose of immunoglobulin and the median percent decrease in IgG levels before and during biweekly treatment with 20% SCIG were 8% and 4%, respectively. IgG levels before or while receiving biweekly 20% SCIG ranged from 1,083 to 1,841 mg/dL and 1,087 to 1,828 mg/dL, respectively; doses ranged from 353 to 676 mg/kg and 343 to 744 mg/kg, respectively. Two patients receiving infusion volumes of 45 and 75 mL completed their infusion in 90 minutes or less with 3 and 5 sites, respectively. The treatment duration for patients receiving larger volumes of 130 mL (6 sites) and 150 mL (8 sites) were 135 and 180 minutes, respectively. Median treatment duration of biweekly 20% SCIG was 949 days (range, 553–1,160 days). Because the catabolism of IgG is directly dependent on the IgG level,² the patients with specific antibody deficiencies received higher doses and maintained higher levels than the patients with common variable immunodeficiency.

In this 20-patient retrospective case review, a 20% SCIG biweekly dosing regimen allowed these patients to maintain therapeutic IgG levels, provided effective protection from serious and nonserious infections, and was generally well tolerated. The annualized rate of aSBIs (0.036 per patient-year; 95% confidence limit, 0.001–0.0199) reported is comparable with the rates found

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Table 1

IgG level and monthly dose of immunoglobulin before and during 20% SCIG biweekly regimen in patients diagnosed as having CVID

Age, y	Monthly dose of immunoglobulin before biweekly SCIG, mg/kg	Monthly dose of immunoglobulin during biweekly SCIG, mg/kg	Change of immunoglobulin dose, %	Last IgG level reported before biweekly SCIG, mg/dL	Most recently reported IgG level during biweekly SCIG, mg/dL	Change of immunoglobulin levels, %
Previous Immunoglobulin Therapy: IVIG (10%) Monthly						
45	443	465	5	897	909	1
64	478	455	–5	1020	994	–3
Previous Immunoglobulin Therapy: SCIG (16% and 20%) Weekly						
9	320	320	0	884	907	3
11 (16%)	696	543	–22	1272	1119	–12
16	500	493	–1	901	973	8
17	245	246	0	783	711	–9
17	767	875	14	747	720	–4
19	462	480	4	982	863	–12
50	446.6	422.3	–5	1100	1064	–3
55	357.1	357.1	0	988	1011	2
69	430.8	411.2	–5	1039	926	–11
71	454	451.3	–1	1426	1287	–10
72	312.5	324.3	4	1410	1279	–9
82	347.8	363.6	5	1107	949	–14
85	428.5	214 ^a	–50	942	769	–18
Previous Immunoglobulin Therapy: SCIG 16% Biweekly						
14	744	729	–2	1015	NA	NA

Abbreviations: CVID, common variable immunodeficiency; IVIG, intravenous immunoglobulin; NA, not applicable; SCIG, subcutaneous immunoglobulin.

^aDose decreased because of kidney function.

during the pivotal clinical and extension studies of weekly 20% SCIG administration.^{3–5} Although no safety or tolerability concerns were observed in patients who continued the biweekly regimen (total of 27.9 patient-years), because of the retrospective nature of the study, it is unknown whether minor adverse events would have been identified.

The clinical results presented are consistent with the findings of a pharmacometric simulation study that determined weekly or biweekly SCIG results in bioequivalent steady-state IgG concentrations during a 14-day period used to predict total exposure to IgG over time and IgG levels at different time points.¹ Individualized IgG replacement therapy for patients with PID has been recommended to achieve optimal clinical outcomes⁶ because of the wide interpatient variability in the IgG level needed to prevent infection.^{7,8} The biweekly dosing regimen allows patients to avoid the significant fluctuations in serum IgG levels that can result from less frequent IgG infusions and can increase susceptibility to infection.^{6,9} Limitations of this report include number of patients, which is insufficient to adequately assess SBI rates. The retrospective study design is also an intrinsic limitation of the study. Capture of adverse events was not contemporaneous, meaning nonserious or minor events may not have been reported. In addition, because a central laboratory was not used for the evaluations of IgG levels, these measurements may, in part, reflect variability among different laboratories.

This retrospective case review illustrates the use, efficacy, and tolerability of a biweekly dosing regimen with 20% SCIG in routine clinical practice in patients of different ages. Although pharmacometric modeling was sufficient and the data were robust enough to change US Food and Drug Administration recommendations for the prescribing information, in this report, we describe the biweekly (every 2 weeks) dosing of SCIG in a real-world setting.

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