ABSTRACT

Objectives: To examine dose adjustments that occurred in the real world when patients with primary immunodeficiency (PI) disease switched from intravenous immunoglobulin (IGIV) to subcutaneous immunoglobulin (IGSC) 20%, and to evaluate the impact on immunoglobulin (Ig) utilization and costs.

Methods: Pharmacy claims were extracted from 5 specialty pharmacy dispensing databases. Administration routes, when not available, were identified by prescribed brand and dosing frequency. Patients with ≥2 claims for any IGIV who subsequently switched to IGSC 20% were included. The dose adjustment ratio was calculated as the ratio of grams per 30 days of IGSC 20% to IGIV. Wilcoxon signed rank test was used to test the hypothesis that the dose adjustment ratio differed from 1.0. The model was analyzed to estimate the impact of dose adjustment on IgG utilization and cost.

Results: A total of 247 eligible patients were included; the majority (75%) had a dose adjustment ratio >1.0. Mean dose adjustment was 1.42 and the median was 1.30 (P <.0001). Patients switching to IGSC 20% required an incremental 126 g Ig per patient per year (PPPY), an amount equivalent to treating an average patient with PI with IGIV for approximately 3.6 months. This increase in Ig utilization could result in an incremental cost of $19,026 PPPY.

Conclusions: Real-world dose adjustments may increase Ig utilization and costs when patients with PI switch from IGIV to IGSC 20%. These changes may potentially impact the payers’ budget for drug costs and burden the available plasma collection and supply.

Primary immunodeficiency (PI) diseases are a group of congenital disorders of the adaptive or innate immune system. The resulting immune dysregulation predisposes affected individuals to an increased rate of infection and autoimmunity.1,2 There are a total of 500,000 estimated cases of PI in the United States and about 50,000 new cases diagnosed annually.3-7 The incidence of PI is increasing, which may in part be due to increased awareness and diagnosis of the condition.8,9

Since the first PI disease was defined in 1952 (X-linked agammaglobulinemia), more than 150 immune disorders have been identified.2,10 Most PIs involve B-cell and/or T-cell defects that lead to some level of antibody loss. For instance, patients with agammaglobulinemia have very low serum immunoglobulin (Ig), whereas patients with severe combined immune deficiency or class switch recombination (formerly called hyper-IgM syndromes) have no functional serum IgG antibodies. Other PIs are associated with more modest degrees of immunodeficiency, leading to hypogammaglobulinemia or IgG subclass defects with varying degrees of antibody production ability.11 The hallmark of PI disorders is recurrent or unusual infections.1,12 These devastating disorders of PI are often associated with decreased health-related quality of life (HRQoL), increased mortality, and high healthcare resource utilization and cost, particularly when left undiagnosed and untreated.6,13

The main treatment for patients with PI is lifelong antibody replacement with Ig therapy.14-16 The goals of treatment are to protect the subject from life-threatening infection, prolong life, and improve HRQoL.17,18 Immunoglobulin concentrate products licensed for PI have been available in the United States since 1981. Approximately 85% of patients with PI are treated with Ig products on a regular basis for their condition.8 These products are prepared by separating the gamma-globulin fraction from plasma pooled from an estimated 3000 to more than 60,000 healthy human donors world-wide.15 Immunoglobulin has become the main plasma product on the global market, with an estimated 12 million liters of plasma utilized from 1992 to 2004.192-22

Ig therapy given intravenously (IGIV) has been a mainstay of treatment for a number of PI disorders since it was first approved in the 1980s. Although the benefits of IGIV include the rapid achievement of normal plasma levels and once-monthly dosing, IGIV does require administration under supervision of a healthcare provider and is associated with systemic adverse events ranging from fever and chills to thrombotic reactions. Introduced in 2000, subcutaneous immunoglobulin (IGSC) offers an alternative option for administering Ig therapy, enabling patients to self-infuse at home. Whereas home administration may provide patients with a greater ease of use, IGSC has several disadvantages, such as the need for administering comparatively larger quantities of fluid than with IGIV, which can be difficult when using a single injection site. As such, IGSC requires once- or twice-weekly infusions.

The reduced bioavailability of IGSC compared with IGIV may also require an upward dose adjustment, resulting in increased Ig utilization in patients who are switching from IGIV to IGSC. The current, conventional IGSC products have a lower bioavailability (as measured by area under the curve [AUC]) than IGIV, possibly due to degradation and/or binding of IGSC in the tissues. As such, the dose of IGSC generally should be increased in order to attain an AUC comparable to that achieved with the prior IGIV dose. Currently, the most commonly used subcutaneous product is immune globulin subcutaneous [human], 20% (IGSC 20%; Hizentra), a 20% human immunoglobulin. Based on the FDA-approved label for IGSC 20% at the time of the analysis, the previous IGIV dose (grams) should be increased by a factor of 1.53 to calculate the initial weekly IGSC 20% adjusted dose.

Whether Ig is administered intravenously or subcutaneously, the drug costs for Ig account for nearly 80% of the total treatment costs. Moreover, the supply of Ig is limited by the complexity of the manufacturing process and the availability of plasma donors; therefore, optimizing the utilization of the available Ig would allow patients with the greatest need to have access to the therapy. As such, the objective of this study was to examine whether dose adjustment occurs in the real world when patients switch from IGIV to IGSC 20% and to evaluate the drug utilization and corresponding increases in drug costs associated with the dose adjustments.

**Data Source**
Pharmacy claims data were abstracted and pooled from 5 electronic, specialty infusion, and pharmacy distribution service databases: BioScrip, BioRx, Caremark, Coram, and Walgreens. These nationwide specialty pharmacy providers render services for a multitude of large health plans across the United States. Of the estimated 256,000 individuals in the United States with a diagnosis of PI, survey data indicate that up to 74% receive Ig therapy. Given the anticipated coverage provided by the specialty pharmacy services and the utilization of Ig, the selected databases were considered to capture data for a representative number of patients with PI in the United States. The dispensing data for analysis covered January 2009 to October 2013 and provided information regarding home care treatment shipments. As patients typically use 1 specialty pharmacy associated with their health plan for drug shipment, the likelihood for duplicate records was low. Further, receiving Ig at a treatment site not covered by the health plan would be unlikely except in the event of an emergency hospitalization.

**Sample Selection**
All patients with an International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code of 279.x (disorders involving the immune mechanism) for the maximum available time period were identified from the databases. In order to evaluate dose adjustments, patients were required to have at least 2 continuous claims for both IGIV and IGSC 20%. To ensure a clean dataset, only patients with an IGIV dosing frequency of 21 to 30 days and an IGSC 20% dosing frequency of 3.5 to 7 days were retained for inclusion in the analysis. Patients whose first dispensed Ig therapy was via subcutaneous route were excluded to focus on patients switching from IGIV to IGSC 20%. The route of Ig therapy, when not available, was identified by a combination of prescribed product brand name and dosing frequency. Weekly dosing (every 3.5 to 7 days) of Ig was considered to represent subcutaneous administration; monthly dosing (every 21 to 30 days) was considered to represent intravenous administration. If the product was IGSC 20%, it was assumed that the product was administered via the subcutaneous route, since IGSC 20% is indicated for subcutaneous administration only. Otherwise, if dosing frequency was not
available to determine the route of administration, patients were excluded. The index date for patients was the date of the switch to a subcutaneous administration of Ig within the study period.

Analysis of Outcomes

The average Ig doses for IGIV and IGSC 20% were calculated for the continued stable infusion periods and standardized to grams per 30 days for each patient. The average Ig dose was calculated based on the dispensed dose. If a patient received multiple products with the same route during the time period, a weighted average of the dose was calculated based on the number of days on each product. The primary outcome of interest was the dose adjustment ratio, calculated by dividing the dispensed IGSC 20% dose in grams per 30 days by the dispensed IGIV dose in grams per 30 days for each patient. Wilcoxon signed rank test was used to test the research hypothesis that the median dose adjustment ratio was different from 1.0. The same analysis was also conducted separately for each specialty pharmacy database.

Cost Analysis

A cost analysis was performed to estimate the economic impact of dose adjustments in patients switching from IGIV to IGSC 20%. For this analysis, the incremental IGSC 20% drug use in grams per 30 days and per year, if any, was calculated. The incremental cost was estimated by multiplying the unit cost of IGSC 20% and incremental gram utilization per 30 days. The 2014 wholesale acquisition cost (WAC) obtained from Red Book was used to determine the unit cost of IGSC 20%. One-way and 2-way sensitivity analyses were conducted to examine the impact of varying the dose adjustment ratio and the WAC of IGSC 20% on the incremental Ig drug utilization and the incremental per person per year (PPPY) costs.

RESULTS

During the study time period, there were 16,065 unique patients with PI with 289,921 claims in the pooled data. Of these patients, 247 were identified who switched from any IGIV product to IGSC 20% and met the inclusion criteria. Forty-two patients were pediatric and adolescent patients (aged 0-16 years) and 205 were adult patients (>16 years). The median age of this group was 44 years (mean ± SD, 40 ± 20 years). The median weight was 68 kg (mean ± SD, 74 ± 35 kg). The median duration of therapy was 351 days (mean 442 days) for IGIV and 345 days (mean 406 days) for IGSC 20%.

Dose Adjustment

Of the 247 patients identified with a switch from IGIV to IGSC 20%, the majority (75%) had a dose adjustment ratio greater than 1.0. As shown in Figure 1, the pooled data indicated a median dose adjustment of 1.30 (mean ± SD, 1.42 ± 0.90; P < .0001), indicating the dose adjustment ratio is significantly different from 1.0.

Drug Utilization and Cost Analysis

First, the impact of dose adjustment on drug utilization when patients switched from IGIV to IGSC 20% was modeled per the product label for IGSC 20%. For a hypothetical patient weighing 70 kg dosed at 0.5 g/kg/month, a dose increase by a factor of 1.53 would result in an additional 223 g of Ig PPPY. This is equivalent to treating an average patient PI with IGIV for approximately 6.4 months. Similar results were found for the pediatric and adolescent group and the adult group. Four of the 5 median dose adjustment ratios (switched patients ≥ 5) were statistically significant and different from 1.0 (P < .001), confirming consistent actual dose adjustment in the real world.
an incremental cost of $33,613 PPPY. Similarly, when the dose adjustment ratio of 1.30 from the real-world data analyses is used, the additional IgG utilization required for patients switching from IGIV to IGSC 20% translates to an incremental cost of $19,026 PPPY (Figure 2b).

**Sensitivity Analysis**

One-way and 2-way sensitivity analyses were conducted to examine the robustness of the estimates by varying the observed dose adjustment ratio and the unit drug cost of IGSC 20%. In a 1-way sensitivity analysis varying the observed dose adjustment ratio over a range of –15% to 15%, the resulting incremental additional Ig utilization ranged from 44 to 208 g PPPY (Figure 3) and the incremental cost ranged from $6659 to $31,393 PPPY. This additional Ig utilization could be expected to cover between 1.3 and 5.9 additional months of IGIV treatment.

Similarly, varying the IGSC 20% WAC over a range of –15% to 15%, while keeping the dose adjustment ratio constant at 1.30, resulted in an incremental cost PPPY ranging from $16,172 to $21,880. As would be expected, a 2-way sensitivity analysis varying both the observed dose adjustment ratio and IGSC 20% WAC simultaneously resulted in the greatest range of incremental costs PPPY. The incremental cost PPPY ranged from $5660 to as high as $36,102 (Figure 4).

**DISCUSSION**

The use of IGIV and IGSC are well established and accepted modes of Ig delivery in patients with PI. To our knowledge, this is the first time an analysis has been undertaken using dispensing records to evaluate the real-world dose adjustment patterns in patients with PI switching from IGIV to IGSC 20%. This retrospective database analysis of real-world claims data found that dose increases frequently occurred (75% of the patients who switched from IGIV to IGSC 20%) and resulted in substantial increased Ig utilization. In these patients, the dose adjustment ratio was 1.30, translating to an additional 126 g of Ig PPPY. This increase is both statistically significant and clinically meaningful, as this excess Ig utilization is equivalent to treating a patient with IGIV for an additional 3.6 months. The median duration of therapy of 351 days for IGIV and 345 days for IGSC 20% shows that the patients were followed longitudinally for a significant and similar period of time and were not acute/one-time users.

The observed dose adjustment is valid and relevant to clinical practice. It has been previously reported that the lack of dose adjustment in patients who switched from IGIV to IGSC 20% was associated with worse outcomes (higher infections, days of hospitalization, days of antibiotic use, and days of missed activities), resulting in increased resource utilization.32

The increased Ig dose required to attain an equivalent systemic Ig exposure of the prior IGIV dose also has substantial societal and economic implications. As Ig therapy is manufactured from large pools of human plasma, there is a finite amount of Ig product globally that can be produced. The plasma supply is intrinsically limited by donor availability.33,34 Without sufficient quantities of plasma, which often represent pooled blood from 3000 to 60,000 individuals,15 the manufacturing process cannot begin. Thus, dose increases of 126 g PPPY of treatment, as observed in this study, can represent a potential impact on the plasma donor pool and manufacturing resources.

Clearly, the dose adjustment observed has financial implications, as well. Results of this analysis estimated that the cost of the additional Ig utilization might exceed $19,000 PPPY, based on the published drug WAC of IGSC 20%. Even when the drug cost of IGSC 20% is varied ±15% in order to account for actual price differences, and the
dose adjustment ratio is varied ±15% as the dose is highly individualized, the cost impact still exceeds $5600 PPPY and may exceed $36,000 PPPY. Although this represents the potential cost to the healthcare payer, the patient may also incur costs via higher out-of-pocket coinsurance or other patient cost-sharing schemes.

**Limitations**

This study represents the first analysis of real-world treatment patterns and cost implications in patients with PI switching to subcutaneous products; however, there are several limitations that should be addressed. First, the sample size of the 247 unique patients with PI who switched from IGIV to IGSC 20% was relatively small. This may limit the generalizability of the study results, depending on whether this sample is representative of the larger PI population. However, it should be noted that this sample size is not unexpected in this orphan disease; large sample sizes are, in general, difficult to obtain for conditions such as PI. Additionally, in January 2015, the FDA revised the approved label for IGSC 20% (Hizentra), whereby the factor used to calculate the initial weekly IGSC 20% dose was reduced from 1.53 to 1.37. While this change does not affect the interpretation of this analysis, future analyses should account for the revised dose adjustment factor in order to determine whether this label change impacts physician prescribing practices. There are also inherent limitations to using pharmacy claims data. Pharmacy claims reflect dispensing information, but may not accurately measure the timing, site, and actual receipt of therapy. Additionally, other factors beyond bioavailability may have influenced the dose adjustment ratio, including patient disease profile, comorbid conditions, and infusion history.

Finally, the cost analysis was intended to provide only estimates of the potential costs of the incremental Ig drug utilization. Sensitivity analyses were undertaken to test the estimated costs to potential changes that may be observed in the real world, and these analyses found similar trends for substantial Ig utilization and associated drug costs. However, a more comprehensive pharmacoeconomic analysis could consider a wider scope of treatment costs, such as nursing time for Ig administration, infusion chair/equipment costs, physician supervision, personnel and time required for training on the administration of IGSC, treatment monitoring, and costs for managing potential treatment-related complications. The additional costs for using these resources should also be considered to confirm and extend the findings of our empirical cost analysis.

**CONCLUSIONS**

For patients who elect to switch from IGIV to IGSC, the dose should be individualized. A majority of patients (75%) switching from IGIV to IGSC 20% show evidence of dose adjustment. In the real world, a median dose adjustment of 1.30 was observed, representing an incremental consumption of 126 g of Ig and cost of $19,206 PPPY. This dose increase may place a substantial burden on drug expenditures for payers, as well as potentially impact the available plasma collection and supply.

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