An Analysis of Intravenous Immunoglobin Site of Care: Home Versus Outpatient Hospital

Rakesh Luthra, MS; Ralph Quimbo, MA; Ravi Iyer, PhD; and Michelle Luo, PhD

Primary immunodeficiency (PI) is a group of congenital disorders characterized by a genetic defect in either the adaptive or innate immune system.[1] Since the first primary immune deficiency (XLA) was defined in 1952, more than 150 other immune disorders have been identified.[1,2] The symptoms associated with PI range from mild to life threatening,[3] and patients with PI-associated conditions such as hypogammaglobulinemia may face substantial risks of contracting severe and even life-threatening infections.[4,5] There are approximately 500,000 cases of PI in the United States, with about 50,000 new cases diagnosed annually.[6-8] The incidence of PI is increasing, which may be partly due to increased awareness and diagnosis of the condition.[9,10]

IVIG, which refers to the intravenous (IV) administration of immunoglobulin (IG), was first approved in the 1980s for the reduction of susceptibility to infections among patients with PI, and later for 5 other indications by the US Food and Drug Administration (FDA).[11,12] Among its approved indications, IVIG is prescribed most commonly for PI. It is viewed as continuous therapy, and in most cases it is not discontinued once it is initiated.[11] IVIG treatment guidelines, labeling, and dosing studies indicate that PI patients should typically receive IVIG therapy once every 3 to 4 weeks at 300 to 600 mg/kg.[13-17]

Currently, IVIG therapies are delivered at different sites of care, including physicians' offices, outpatient departments of hospitals, and at patients' homes. Following the approval of IVIG, patients were typically treated in hospital settings as a precaution against potential safety issues. With increasing knowledge about the safety profile of IVIG, treatment shifted to outpatient settings, which benefited both administration and monitoring. A successful outpatient track record led to the exploration of home-based treatment, and today, a substantial proportion of patients with PI receive their IVIG therapy routinely at home with the assistance of a nurse.[18] An oft-cited benefit of home-based therapy is that it reduces the exposure of immune-compromised patients to pathogens

ABSTRACT

Objectives: To compare treatment outcomes and healthcare costs in a large managed care population for primary immunodeficiency (PI) patients receiving intravenous immunoglobulin (IVIG) in home and outpatient hospital settings.

Study Design: Retrospective observational cohort study.

Methods: This study utilized the HealthCore Integrated Research Database (HIRD) data of nearly 43 million participants in Blue Cross Blue Shield plans. Patients with PI younger than 65 years with at least 1 claim for IVIG between January 1, 2006, and August 31, 2010, with site of care information were identified. Patients with more than 18 IVIG infusions per year or who had evidence of subcutaneous therapy during the study period were excluded. Treatment guidelines and approved dosing recommendations served as proxies for adherence. The differences in adherence levels and costs were examined with a generalized linear model, controlling for baseline Charlson's Comorbidity Index scores.

Results: Patients with PI were identified in the home (165) and outpatient hospital (179) settings. Optimal adherence (13-18 infusions/year) was greater among home-based (47%) versus outpatient hospital (22%). The mean (± standard deviation [SD]) annual IVIG dose fell in line with the recommended dosing window among patients in home 268 (± 221) grams per patient per year (PPPY) compared with patients treated in outpatient hospital 201 (± 217) grams PPPY. The cost per infusion, in 2010 dollars, was significantly lower in patients treated at home ($3293 vs $4745, P <.001). Mean PPPY hospitalization costs trended lower for patients treated at home ($17,538 vs $20,135).

Conclusions: The study found that home-based patients with PI incurred significantly lower costs per infusion; had significantly higher compliance measured by infusion frequency and average dosing according to IVIG treatment guidelines and dosing recommendations; and their hospitalization and pharmacy costs trended lower.

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PRACTICAL IMPLICATIONS

- Site of care for PI patients receiving immunoglobulin therapy should be taken into consideration as a part of the treatment decision making.
- Treatment adherence significantly differs between home and outpatient setting for the PI patients receiving IVIG therapy, suggesting the outcomes benefits of the home care setting.
- The potential economic benefits demonstrated in this study including reduced per infusion costs and trended lower hospitalization and pharmacy costs could also provide useful information to assist payers and policy makers in making IG coverage decisions.

typically associated with hospitals and other public healthcare facilities.[19-22] Furthermore, when patients receive services in the home setting, they have greater control over their living activities, and enhanced options for the resumption of normal activities, including work.[20-22] The decision about site of care also depends heavily on cost reimbursement considerations and patient convenience,[22] in addition to factors such as copay and awareness.

The published literature on infusion therapies in home-based versus outpatient hospital settings is limited. Reduced logistical and travel requirements resulting from home-based delivery of medications such as IVIG could have advantages over outpatient hospital delivery. However, there has been little investigation on site of care, and to the best of our knowledge, none with IVIG. To help address this gap, this retrospective database analysis was conducted to compare real-world treatment outcomes and healthcare costs in a large managed care population of patients with PI receiving IVIG therapy in the home and outpatient hospital settings from a private payer perspective.

METHODS

Data Source and Study Design

Integrated medical and pharmacy data were used to evaluate differences in healthcare utilization and costs among patients with PI who were treated with IVIG either at home or in an outpatient hospital setting. Study data were queried from the administrative claims repository within the HealthCore Integrated Research Database (HIRD), containing fully adjudicated medical and pharmacy administrative claims for over 43 million beneficiaries receiving medical and pharmacy health insurance coverage from Blue Cross Blue Shield plans across 14 states in all geographic regions of the United States. The study period was January 1, 2006, to August 31, 2010. In this longitudinal study, patients were followed from the time they entered the study at the point of initiation of an IVIG therapy (this could be in any calendar year from 2006 to 2010) for the duration of time that they were continuously enrolled.

The researchers only had access to de-identified patient data in this study, and strict measures were observed to ensure that patient anonymity and confidentiality were preserved throughout, in compliance with the Health Insurance Portability and Accountability Act. Current Procedural Terminology (CPT) and Place of Service codes were used to determine the site at which each IVIG treatment was administered—the site was categorized as either home or outpatient hospital, based on their Index IVIG claim. Index IVIG claim was defined as the first claim with evidence of IVIG treatment and site of care information. Index date was defined as the date of first claim for IVIG in the study period. Patient demographics and baseline Deyo-Charlson Comorbidity Index (DCI) were compared in both home and outpatient hospital groups, and results were adjusted for these to avoid any potential biases inherent in the selection of either site of care.

Inclusion Criteria

To be included in this study, patients were required to have a diagnosis for PI and no evidence of IVIG therapy 6 months (clean period) prior to the index date. All patients were required to have continuous medical and pharmacy health plan eligibility at least 6 months prior to and after the index date.

Exclusion Criteria

All patients with PI who received subcutaneous therapy at any time in the course of the study duration and patients with no site-of-care information for the IVIG dispensing were excluded from the study. PI patients with more than 18 mean IVIG infusions per year during the study period were excluded from the analysis to be consistent with the IVIG treatment guidelines and dosing recommendation of 1 infusion every 3 to 4 weeks.[13-17] This exclusion further filtered out any potential subcutaneous immunoglobulin users. Subjects 65 years and older were excluded to remove patients potentially on Medicare. Anomalous patient costs were analyzed with the Walsh test for outliers and were subsequently excluded from the study, as the high costs were related to chemotherapy and organ transplant, and were not related to IVIG costs.[23]

Adherence Measure

Commonly used measures such as the medication possession ratio for measuring prescription adherence

for pharmaceutical prescription refills are not appropriate for IG therapy because of the intravenous infusion of the drug. Instead, a proxy measure for adherence was utilized based on IVIG treatment guidelines and dosing recommendations, which recommend dosing for patients with PI at 300 to 600 mg every 3 to 4 weeks.[13-17] This translates to 13 to 18 infusions per year as the recommended infusion frequency. For the purpose of this study, patients were classified as adherent to therapy if the number of infusions they received per year fell within the recommended infusion frequency. Similarly, dosing compliance was defined as receiving 254 to 507 g/year of IG based on the expected utilization for a 65 kg (143 lb) person receiving 300 to 600 mg/kg every 4 weeks. For pharmacy claims, dose was calculated by multiplying ingredient strength with package size, as obtained from the national drug code description for each IVIG medication. For medical claims, dose was obtained from the CPT code description for each IVIG medication.

Healthcare Cost Analysis

IVIG-related, non–IVIG-related, hospitalization, emergency department (ED), and pharmacy costs were examined specifically. All costs were based on paid claims and were adjusted to 2010 US dollars. Pharmacy costs included paid costs of all drugs received by the patient. IVIG-related costs represented the aggregate of the cost of IVIG drug therapy plus the cost of administration during the study period. We adjusted for comorbidity burden in our analysis of healthcare cost and utilization. Literature shows that patients with comorbidities at baseline typically use more healthcare resources and incur higher costs,[24-26] so additional adjustment for baseline costs were not done in the analysis. Non-IVIG costs were assessed as total healthcare costs, less all IVIG-related costs. Hospitalization cost included costs associated with inpatient hospitalization, while pharmacy cost reflected the cost of prescription medication through pharmacy benefits. All costs were annualized by dividing the total costs by the follow-up time for each patient.

Statistical Analysis

All outcome measures were compared between the home-based and outpatient IVIG treatment groups and designed to avoid any potential biases inherent in the selection of either site of care. Study metrics included both descriptive statistics—continuous variables represented by means and standard deviations; and categorical variables represented as percentages—and adjusted results, controlling for baseline DCI scores. The mean DCI scores, an established method used to capture baseline comorbidities, were calculated. The DCI consisted of 17 diagnoses identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes. The Index assigns a weight from 1 through 6 for each comorbid condition diagnosed. The final DCI score represents the sum of the weighted values of the comorbidities that are present; higher scores indicate greater comorbidity burden.[27] Significant differences in outcomes were determined with the use of appropriate statistical comparison tests—*t* test, χ^2, and analysis of variance. Generalized linear models were used as the basis of regression analyses to assess differences in healthcare resource utilization and costs after controlling for baseline DCI score. Differences in healthcare resource utilization were evaluated with negative binomial distribution fitted with a log link function, while healthcare costs were assessed with Gamma distribution with log link function. All statistical analyses were conducted with SAS 9.2 (Cary, North Carolina) software. Alpha was set at .05 for each test.

RESULTS

Patient Disposition

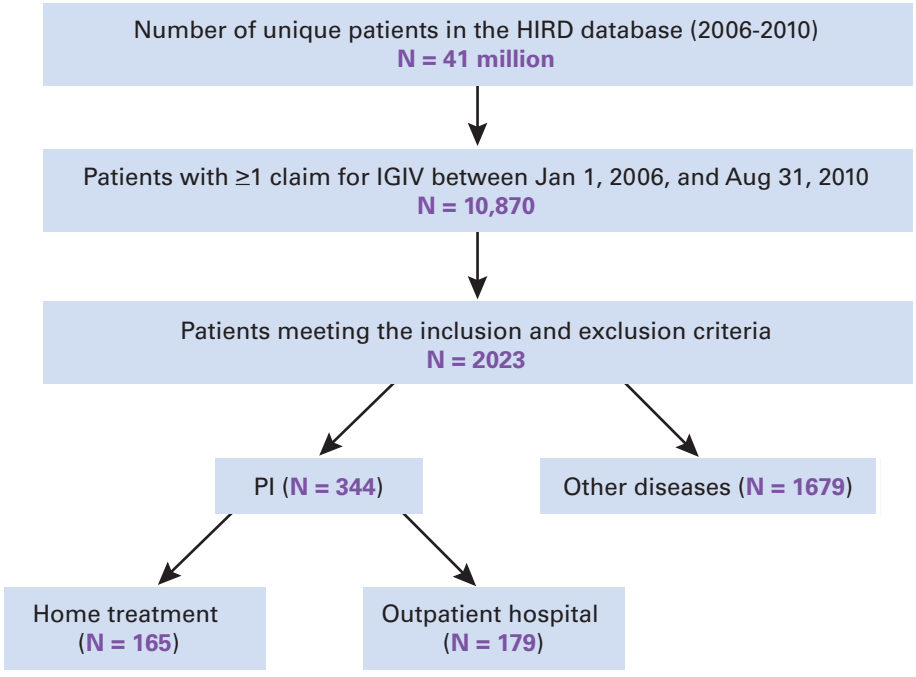
Medical and pharmacy claims identified 2023 patients with at least 1 claim for IVIG during the study period of January 1, 2006, to August 31, 2010. A total of 344 patients identified with PI met the inclusion and exclusion criteria as shown in **Figure 1**. Analysis of the data demonstrated that >75% of the study population overall did not change site of care for IVIG therapy administration during follow-up, indicating that there was limited switching between sites of care following the index date.

Demographic Characteristics at Baseline

Of the 344 patients included in this study, 165 received their IVIG treatment at home and 179 in outpatient hospital settings. Of the patients who initiated therapy at home, 87% continued therapy in the home setting for the duration of the study. A lower proportion (69%) continued therapy in the outpatient hospital setting after therapy was initiated in an outpatient hospital. Less than 2% of patients who received IVIG either at home or at an outpatient hospital in this database had a pharmacy claim for IVIG.

Table 1 shows the demographic characteristics of the study population. Females made up 58.8% of the home-based and 49.2% of the outpatient hospital treatment groups. The mean (± standard deviation [SD]) age in the home-based group was 38.5 (± 17.5) years and 39.5 (± 20.8) years in the outpatient hospital group. Preferred provider

Figure 1. Patient Disposition



HIRD indicates HealthCore Integrated Research Database; PI, primary immunodeficiency.

organizations (PPOs) represented more than two-thirds of the patients in either cohort, followed by health maintenance organizations (HMOs), which covered about one-fifth of the patients in either cohort. The mean (± SD) DCI score was 1.4 (± 1.9) in outpatient hospital group versus 1.1 (± 1.4) in the home-based group; the difference was not statistically significant. The baseline characteristics of patients in the home and outpatient hospital settings suggested that the patients in the 2 settings were relatively comparable.

Adherence

Optimal adherence was examined based on a proxy of recommended 13 to 18 infusions per year, according to IVIG treatment guidelines and dosing recommendations.[13-17] As shown in **Figure 2**, overall, a significantly higher proportion of patients treated at home (47%) received infusions that were within the optimal frequency of 13 to 18 infusions per year, compared with only 22% of the patients treated in outpatient hospital settings (P <.001). Conversely, 39% of the patients who were treated in outpatient hospital settings received suboptimal infusion frequency (7-12 infusions per year) compared with only 22% of patients in the home setting in the course of study period. A greater proportion of patients with the furthest departure from the optimal infusion frequency (<7 infusions per year) were in the outpatient hospital setting (39% in outpatient hospital setting versus 29% in home setting (P <.0001). In addition, the mean (± SD) IVIG annual dose fell in line with the recommended dosing window among patients in the home-based cohort, 268 (± 221) grams per patient per year (PPPY) compared with 201 (± 217) grams PPPY (P <.005) in patients in the outpatient hospital cohort.

Costs

Healthcare costs, based on paid claims costs, were first examined as cost per infusion, including IVIG drug and administration costs between the 2 settings, and reported in 2010 dollars throughout. The unadjusted mean cost per IVIG infusion was significantly lower in the home-based treatment group—$3290 (median: $2948)—versus $4784 (median: $3612) in the outpatient cohort (P <.0001). This significant difference was consistent after adjusting for baseline DCI score. The adjusted mean cost per infusion was $3293 per patient in the home setting versus $4745 in the outpatient cohort, or 31% lower in the home setting group (P <.0001) (**Figure 3**).

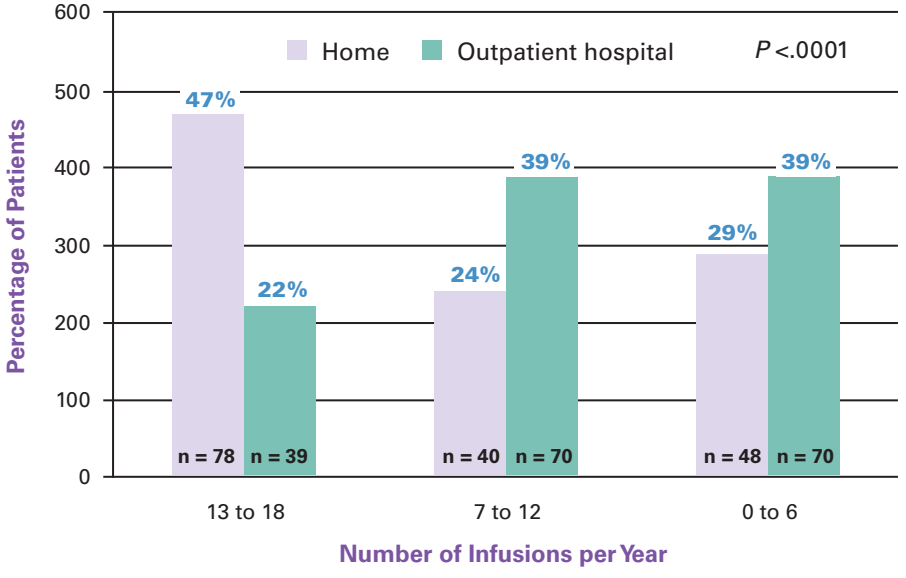
A comparison of the total non-IVIG costs (total cost excluding IVIG cost) between the 2 settings showed that the mean (± SD) PPPY non-IVIG costs were lower in the home-based cohort—$47,077 (± $84,479)—compared with $58,515 (± $90,329) for the outpatient hospital

Table 1. Demographic Characteristics at Baseline

Baseline Characteristics, Stratified by Setting	PI (N = 344)				P[a]
	Home (N = 165)		Outpatient Hospital (N = 179)		
Gender, N (%)					
Male	68	41.2	91	50.8	.0736[a]
Female	97	58.8	88	49.2	
Age, mean (SD)	38.5	17.5	39.5	20.8	.6207[a]
Health plan, N (%)					
HMO	35	21.2	39	21.8	.3916[a]
POS	9	5.5	10	5.6	
PPO	111	67.3	125	69.8	
FFS	0	0	1	0.6	
Other	10	6.1	4	2.2	
DCI score, mean (SD)	1.1	1.4	1.4	1.9	.0688[a]

DCI indicates Deyo-Charlson Comorbidity Index; FFS, fee for service; HMO, health maintenance organization; PI, primary immunodeficiency; POS, point of service; PPO, preferred provider organization; SD, standard deviation.
[a]Not significant (alpha set at .05).

Figure 2. Treatment Frequency Adherence in Primary Immunodeficiency Patients by Setting

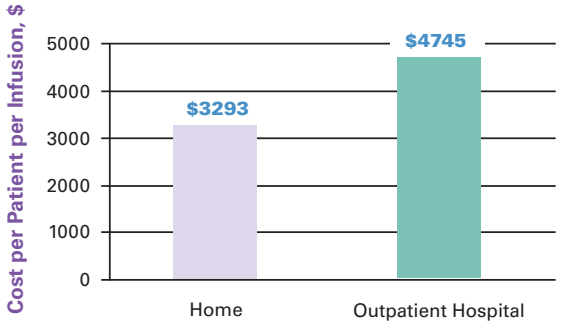


category (median: $17,764 vs $27,356). However, the difference was not statistically significant. After adjusting for baseline DCI scores, the trend toward lower non-IVIG costs PPPY for home-based patients compared with outpatient hospital persisted. The adjusted non-IVIG cost PPPY was $43,131 in the home-based group versus $50,289 ($P$ = .2128) among the outpatient hospital group.

An examination of the relationship between adherence and non-IVIG costs (**Figure 4**) indicated that total non-IVIG costs were lowest among patients receiving infusions within the optimal IVIG treatment guidelines and dosing recommendations (recommended treatment frequency of 13-18 infusions per year).[13-17] The non-IVIG costs trended higher as treatment deviated from the recommended treatment frequency.

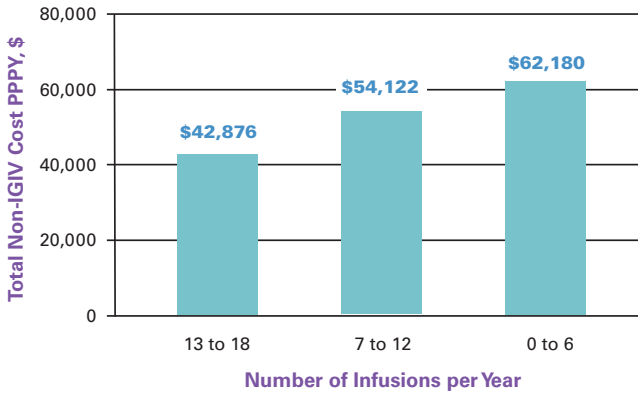
An analysis of specific components of healthcare costs, such as hospitalization, ED, and pharmacy costs (**Figure 5**) showed that mean hospitalization costs were $17,538 in patients treated in home settings, relative to $20,135 in patients treated in outpatient hospital settings.

Figure 3. Mean Cost[a] per Patient per Infusion by Setting



[a]Cost adjusted for baseline Deyo-Charlson Comorbidity Index score, and converted to 2010 US dollars.
P <.0001 home vs outpatient hospital.

Figure 4. Relationship Between Adherence to IG Therapy and Non-IGIV Cost[a]



IG indicates immunoglobulin; IV, intravenous; PPPY, per patient per year.
P = .1128. Not significant (alpha set at .05).
[a]In 2010 US dollars.

The mean pharmacy costs PPPY were $7091 and $9663 (median: $3013 vs $3931). The costs associated with ED visits were low in both settings ($589 in home settings vs $438 in outpatient hospital settings) and costs for office visits, though statistically insignificant, were lower for home settings compared with outpatient settings ($3277 in home vs $4523 in outpatient setting) (**Table 2**); however, the results were not found to be statistically significant.

DISCUSSION

This observational study utilized one of the largest samples of PI patients available within a real-world managed care database to assess potential differences in adherence outcomes and costs among patients infused with IVIG at different sites of care; specifically, at home and outpatient hospital settings. The study results indicated that IVIG treatment in the home setting was associated with better adherence within the treatment guidelines and dosing recommendations in terms of infusion frequency and dosing levels.[13-17] The difference in cost per IVIG infusion per patient was statistically significant: $1452 (31%) less among home-based patients relative to those treated in outpatient hospitals. Such differences in direct costs between the 2 settings are of considerable importance to payers who must evaluate data across large numbers of patients in their membership. Based on the difference in the cost per infusion, it was estimated that IVIG treatment delivered in the home setting could result in annual savings of $18,876 to $26,136 for 1 patient receiving 13 to 18 infusions per year. These findings may also have implications for patients, who typically bear a portion of their healthcare costs through copays, coinsurance, and out-of-pocket costs. However, such costs were not included in the current study; but this area is worthy of future research.

When non-IVIG costs were considered, patients treated at home trended toward lower total non-IVIG costs versus outpatients. Key healthcare cost components such as hospitalization and pharmacy costs trended lower in patients treated in the home setting compared with patients treated in outpatient hospital settings.

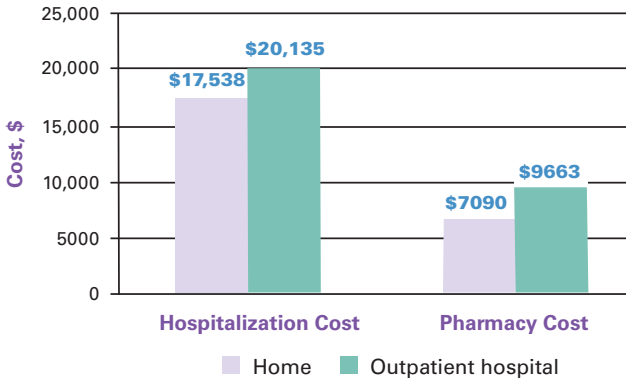
The better adherence to optimal frequency in the home setting observed in the study may be due to patient convenience factors such as privacy, comfort, and the flexibility of scheduling infusions. Research has shown that many patients prefer to receive IV therapy in the privacy and comfort of their own home, and around their own schedules.[20] The difficulty of scheduling IVIG infusions around patients' work and activity schedules, as well as the reduced flexibility of scheduling outpatient hospital appointments for an IVIG visit, may have contributed to these differences in adherence. Also, repeated journeys to the hospital or outpatient offices for IG therapy may pose a potential inconvenience and expense to patients, and negatively affect adherence. The impact of medication adherence on clinical, economic, and humanistic outcomes has been well demonstrated. Findings in various therapeutic areas demonstrate decreased medication adherence resulting in increased hospitalizations, nursing home admissions, physician visits, and potentially avoidable healthcare costs.[28-33] The results of this study, showing that non-IVIG costs trended higher when patients did not comply with the recommended treatment frequency, were consistent with the results of those prior studies.

The reduction in costs in the home setting was in line with previous published studies. A Swedish study examining direct costs in 165 patients with PI showed that the hospital administration of IVIG is more expensive than administration at home.[34] Studies with cancer chemotherapy and antibiotic infusion therapy, which also utilized both home-based and outpatient service settings, might be useful proxies for comparison, given the paucity of such studies for IVIG. One small French study that compared the cost of home-based and outpatient chemotherapy for small-cell lung cancer showed a 16% cost reduction in the home-based setting.[35] A similar comparison involving 80 colorectal cancer patients in South Korea found that home-based infusion was associated with cost savings of 16.6% versus hospital infusion.[36] The findings in this study were consistent with this overall trend.

This study examined the differences in direct costs between treating patients with PI at home or in an outpatient hospital. Other comparisons such as productivity and quality of life could not be undertaken due to lack of data availability within the administrative claims database used for this study. Indirect costs, such as patients' and possibly caregivers' travel time, time lost from work or educational activities, and reduced daily activity levels could be substantial for patients receiving IG therapy in outpatient hospitals. Lucas et al reported that findings from a subcutaneous immunoglobulin therapy program that has been in operation since 1992 at Oxford Radcliffe Hospitals in the United Kingdom, indicated that home-based infusion programs improved both the convenience and feasibility of the therapy.[37] Another study showed that receiving IG therapy at home could improve the quality of life for both the patient and the family or caregiver.[38]

The findings in this study point to the overall viability and benefits of the home-based setting in the treatment of PI patients with IVIG. However, IG therapy in the home setting may not be suitable for all the patients and should be evaluated by patients and their treating physicians based on individual needs.

Figure 5. Mean Hospitalization Costs and Pharmacy Costs[a] per Patient per Year



[a]In 2010 US dollars.
Hospitalization cost: $P = .6716$; pharmacy cost: $P = .1816$. Not significant (alpha set at .05).

Limitations

One of the inherent limitations of claims-based analysis of observational data is the generalizability of the results to the overall population. While this study drew from a large managed care database, the final samples of home-based and outpatient hospital subjects were relatively small. Even though there is little reason to doubt that the 344 patients with PI included in this study share disease symptoms, clinical, and demographic characteristics with the overall PI population, the small sample size may limit the generalizability of the study results, depending on whether this sample is representative of the larger PI population. The small sample size also precluded the use of more robust comparison methodologies, such as propensity score matching, which may have necessitated additional patient exclusions. Nonetheless, the size of our patient sample is reflective of the relatively rare nature of this condition. For this analysis, we utilized the HIRD, which is one of the very few data repositories capable of facilitating the assessment of such rare conditions among working-age and pediatric patients differentiated by treatment settings.

Table 2. Mean Costs, by Setting

	Home		Outpatient Hospital		
Cost Category	Mean	Median	Mean	Median	Statistical Testing
IVIG	$29,779	$24,877	$31,626	$19,095	0.5994
Inpatient Visits	$17,538	$0	$20,135	$531	0.6716
ED Visits	$589	$0	$438	$0	0.2981
Office Visits	$3277	$1689	$4523	$1662	0.1187
Pharmacy	$7091	$3013	$9663	$3931	0.2560

ED indicates emergency department; IVIG, intravenous immunoglobulin.

The necessity for a small proportion of patients to switch sites during the study period represented another important challenge. The site of care was identified based on the initiating IVIG claim with site of care information. It is possible that some patients may have initiated treatment in a hospital and switched to home-based treatment later, potentially leading to home-based treatments being classified as outpatient hospital treatment. Our analysis showed that once patients were classified as receiving treatment in a particular site, they remained largely stable in that site for the duration of the study. Such stability was especially better in patients initiating treatment in the home setting compared with the outpatient hospital setting (87% vs 69%). Also, any potential misclassification would be conservative and, in fact, any bias would favor the outpatient-hospital cohort and reduce the magnitude of the difference in costs.

Though this study used a rich repository of medical, pharmacy, and laboratory data, it was still subject to the limitations associated with the use of administrative claims data for research purposes. While it is desirable to follow a patient longitudinally, there are limitations associated with it. Patients with PI identified and included in our analysis were followed for a fairly long period of time (between 6 months and 5 years), during which many factors (eg, treatment guidelines, patient preference, treatment pattern) could have changed. However, our review of literature did not suggest such changes in treatment guidelines during the study period. Further, patient preference cannot be measured in a retrospective administrative claims database. As usual, unobservable factors capable of influencing outcomes cannot be meaningfully included in claims-based analyses. Nonetheless, claims provide a good starting point for the establishment of some key differences between these 2 sites of care, and add a solid base of knowledge on a largely understudied subject.

Lastly, claims data have inherent limitations, such as the possibility of incompleteness and reduced specificity, and may be affected by coding, sequencing, and routine handling errors, all of which were carefully managed and mitigated in this study. The study sample was drawn from a large managed care database of largely working-age adults. As a consequence, it could prove challenging to generalize or replicate these findings across other demographics.

CONCLUSIONS

This study found that PI patients treated at home had significantly greater compliance in infusion frequency and average dosing according to the treatment guidelines and approved dosing recommendations, and they incurred significantly lower cost per infusion, while their hospitalization and pharmacy costs trended lower. This appears to be the first comparison of these 2 types of sites and PI patients in an empirical managed care population. Additional comparison studies of this kind will be useful in the further exploration of any additional benefits that may be associated with the home-based delivery of IVIG therapy for PI.

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Author Affiliations: HealthCore, Inc, Wilmington, DE (RL, RQ); Medical Outcomes Research and Economics, Baxter Healthcare Corporation, Deerfield, IL (RI, ML).

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Authorship Information: Concept and design (RL, RAQ, RGI, ML); acquisition of data (RL, RAQ); analysis and interpretation of data (RL, RAQ, RGI, ML); drafting of the manuscript (RL, RGI, ML); critical revision of the manuscript for important intellectual content (RL, RAQ, RGI, ML); statistical analysis (RL); supervision (ML).

Address correspondence to: Michelle Luo, PhD, Baxter Healthcare Corporation, 1 Baxter Pkwy, Deerfield, IL 60015. E-mail: Michelle_Luo@baxter.com.

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