Published in final edited form as:

J Clin Immunol. 2013 January ; 33(1): 49–54. doi:10.1007/s10875-012-9776-y.

Home Care Use of Intravenous and Subcutaneous Immunoglobulin for Primary Immunodeficiency in the United States

Faith Huang,

Division of Clinical Immunology, Department of Medicine, The Mount Sinai School of Medicine, Icahn Medical Center, 1425 Madison Avenue, Room 11-20, New York, NY 10029, USA

Elizabeth Feuille, and

Division of Clinical Immunology, Department of Medicine, The Mount Sinai School of Medicine, Icahn Medical Center, 1425 Madison Avenue, Room 11-20, New York, NY 10029, USA

Charlotte Cunningham-Rundles

Division of Clinical Immunology, Department of Medicine, The Mount Sinai School of Medicine, Icahn Medical Center, 1425 Madison Avenue, Room 11-20, New York, NY 10029, USA

Charlotte Cunningham-Rundles: charlotte.cunningham-rundles@mssm.edu

Abstract

Purpose—Utilization reports on immunoglobulin (Ig) use for immunodeficiency in the United States (U.S.) have focused on prescribing practices in hospitals. There have been no large-scale reports on Ig use for immune deficiency in the home. We investigated the use of Ig in 3,187 subjects diagnosed with primary immunodeficiency.

Methods—Cross-sectional data on 4,580 subjects in the U.S. receiving Ig in 2011 was obtained from a major home care provider. Demographics, route, dose, and frequency of Ig use by subjects with ICD-9 coded primary immunodeficiencies were analyzed.

Results—Of 4,580 subjects, 3,187 had ICD-9 codes suggesting primary immunodeficiencies; 1,939 (60.8 %) were females and 1,248 (39.2 %) were males, with age ranging from 0 to 95 years. The predominant diagnoses were: common variable immunodeficiency (279.06; $n=1,764$; 55.3 %), hypogammaglobulinemia (279.00; $n=635$; 19.9 %), unspecified immunity deficiency (279.3; $n=286$; 9 %), other selective Ig deficiencies (279.03; $n=171$; 5.4 %), and agammaglobulinemia (279.04; $n=127$; 4 %). 54 % of subjects received Ig by the subcutaneous (SC) route, and 46 % by intravenous (IV) route, with more SC use by older subjects. The mean dose prescribed was 483 mg/kg/month, but less Ig was ordered for subjects on SCIg (409 mg/kg/month), as compared to subjects on IVIg (568 mg/kg/month). A highly significant inverse correlation between increasing age and dosage of Ig ordered was found ($P<.0001$).

Conclusion—Analysis of home care use of Ig in primary immune deficiency revealed that the SC route was prescribed more than the IV route, especially for older patients. By either method of administration, less immunoglobulin was prescribed for older subjects.

Keywords

Intravenous immunoglobulin; subcutaneous immunoglobulin; primary immunodeficiency disease

Introduction

While human immunoglobulin (Ig) has been increasingly used for many disease states, antibody replacement in primary immune deficiency (PID) states was its first established use and still constitutes one of the main indications for this therapy [1–3]. The clinical benefits of Ig include decreased incidence of upper and lower respiratory tract bacterial infections, reduced antibiotic use, fewer hospital admissions, improved growth, maintenance of normal pulmonary functions, and improved quality of life [4, 5].

The intravenous (IV) and subcutaneous (SQ) routes are both effective methods of administration of Ig for PID [6–8]. While earlier reports suggested that lower doses were satisfactory, the current trend is to give increased amounts, with attention paid to trough IgG levels as well as the health of the patient [4, 5, 9]. However, there are still substantial differences in the amounts of Ig prescribed by individual practitioners, and it is important to understand the utilization of Ig in the treatment of PID in the United States. Most previous publications on the use of Ig have focused on global Ig use in hospital settings [1, 10–12]. As 45.1 % of all subjects with PID are likely to receive Ig treatment [13], and in most cases in the home, we examined the demographics, products, and dosing of Ig used in the home care setting for a large cohort of subjects with PID in the United States.

Methods

Patients, Diagnoses, and Ig Products

A national home care supplier of IV and SC Ig provided cross-sectional data on 4,580 subjects who received Ig in the U.S. in one calendar year, 2011. Demographics and route of administration, for subjects given the main PID diagnoses as captured by 17 ICD-9 codes were analyzed. (Table I) The dose of Ig prescribed was calculated for 1,639 subjects for whom data were available, using the number of grams of product, frequency of administration, and weight of the patient. Subjects were excluded from these analyses if data were unavailable ($n=1,281$), or if the frequency of dosing was unclear ($n=267$). The Ig products were categorized as follows: IV or SC administration, lyophilized or liquid.

Statistical Analyses

Descriptive statistics are presented as median (inter-quartile range) for non-normally distributed continuous variables and as mean $\pm$ standard deviation (or standard error) for those normally distributed. Associations between categorical data were assessed using the Fisher's exact test. Unpaired t -test was used to compare means for continuous variables. The one-way ANOVA test was used to compare the means of multiple groups. Spearman's rank correlation coefficient was used to assess how well the relationship between two variables can be described using a monotonic function.

Results

Population

Among the 4,580 subjects receiving Ig home care, 3,187 had ICD-9 codes used for PIDs, including the following diagnoses: common variable immunodeficiency (279.06; $n=1,764$; 55.3 %), hypogammaglobulinemia (279.00; $n=635$; 19.9 %), unspecified immunity deficiency (279.3; $n=286$; 9 %), other selective Ig deficiency (279.03; $n=171$; 5.4 %), agammaglobulinemia (279.04; $n=127$; 4 %), and combined immunity deficiency (279.2; $n=105$; 3.3 %). Eighteen (0.6 %) subjects were diagnosed with selective IgA deficiency (279.01), and 9 with selective IgM deficiency (279.02, $n=9$, 0.3 %). (Table I) The age range

for these subjects was between birth and 95 years of age; 1,339 were female (60.8 %) and 1,248 were male (39.2 %).

Products Administration and Dosing of Ig Prescribed

There were 12 IV products and 2 SC products in use for this cohort in 2011. In 2011, 54 % of the PIDD subjects were given SC Ig, and 46 % were given IV Ig. The IV forms were mostly liquid products ($n=1,328$, 42 %) but lyophilized products were also given to a small number of patients ($n=122$, 4 %). IV Ig and SC Ig were prescribed at intervals of 2 to 8 weeks, but most commonly at four-week intervals for IV and at one-week intervals for SC Ig. The dose of Ig, in mg/kg/month was calculated for 1,639 subjects for whom the number of grams ordered, patient's weight, and frequency of administration was available. Of these, the mean dose of Ig for either form was 483 mg/kg/month (standard error, SE, 0.5). However, for the 761 subjects receiving IV Ig, the mean dose of 568 mg/kg/month (SE 17.5) was significantly higher than the mean dose prescribed for 878 subjects on SC Ig, 409 mg/kg/month (SE 11.9) ($P<.0001$, unpaired two tailed t test).

Doses and PIDD Diagnoses

When comparing dosages for patients with the 5 most common PIDD diagnoses (Table II), the dose prescribed for the IV route did not differ significantly (one way ANOVA $P=0.3151$). However, for subjects given SC, the amounts ordered were quite different. (One-Way ANOVA, $P<.0001$).

Age of the Patient, Route of Administration and Doses Prescribed

SC Ig was more commonly prescribed for the 413 subjects 65 years and older (66 %) than it was for the 1,323 subjects younger than this age (52 %) ($P=.0001$, Fisher's exact test). However, with increasing age, the Ig dose prescribed for either route decreased inversely, ($r=-0.2709$, 95 % confidence interval (CI): $[-0.3165$ to $-0.2240]$, $P<.0001$) (Fig. 1). This trend was especially apparent for subjects receiving SC Ig ($r=-0.3609$, 95 % CI: $[-0.4188$ to $-0.3002]$, $P<.0001$), but was true for subjects given IV formulations. ($r=-0.1486$, 95 % CI: $[-0.2194$ to $-0.0763]$, $P<.0001$) (Fig. 2).

Discussion

We report here nationwide data on the home use of Ig for a large number of subjects diagnosed with humoral defects using ICD-9 diagnosis codes, generally in accordance with published evidence [2], although Ig was also prescribed for a few subjects with selective IgA and IgM deficiency. A previous European study reported that 73.2 % of patients received Ig via the IV route and 26.7 % via the SC route [13]. Perhaps due to the passage of time, the growing acceptance of this route, and the emergence of new SC products, our study showed that the use of the SC formulations in the home in the U.S is now more common, at least with regard to this home care provider. As Medicare covers the cost of IV Ig in the home, but none of the related professional services such as nursing or supplies, it is not surprising that this study shows that subjects older than 65 were being given SC in greater numbers than subjects younger than this age.

The prescribed doses, calculated with the number of grams of Ig ordered, the patient's weight, and the frequency of administration, were generally in accordance with the recommended dose of 400 to 600 mg/kg/month [8, 14–17]. The most common frequency of IV Ig dosing was every 4 weeks, consistent with the survey by Yong et al., which reported that 87 % of surveyed allergist/immunologists initially prescribed this frequency [18]. This study also showed that subjects with agammaglobulinemia were also were given more IV and SC Ig (566.7 mg/kg/mo and 615.4 mg/kg/mo) than subjects with CVID (534.4 mg/kg/

mo and 345.7 mg/kg/mo), in accordance with other work which showed that these subjects may need higher doses [4, 15].

The total monthly dose of SC Ig required to give the same “area under the curve” of serum IgG over time has been calculated at 1.37 to 1.53 times the dose of IV Ig [19–23], thus current package inserts for SC products recommend higher doses of Ig for subjects given SC forms. However, for this home care provider, the mean Ig dose was actually lower for patients receiving SC Ig (408.5 mg/kg/month) than it was for patients receiving IV Ig formulations (568.3 mg/kg/month), suggesting that common use in the U.S. has not reflected the higher doses suggested. At this point in time, it is unclear whether or not an increased SC dose results in clinical differences in terms of infections for patients [5–7].

We found a statistically significant inverse correlation between the dose ordered and the age of the patient. We have no explanation for this; no studies suggest that less Ig is needed in older subjects. This difference was not due to the inclusion of 127 younger subjects with agammaglobulinemia (who as noted above received higher doses). However, higher dosing in children could reflect the clinical practice of specialized immunologists seeing infants and younger children with PIDDs. In addition, younger PIDD patients may have closer follow-up than older patients, leading to more frequent dose escalation with changing weight. Perhaps equally, as the older population ages, weight gains might not be taken into account with increased dosing.

The diagnosis of the subjects investigated here are based on the physician assigned ICD codes used to obtain Ig therapy, and are likely to contain an unknown degree of error. In addition, as one major home infusion company provided the data analyzed here, it is possible that data from other home care providers would show different trends. Additionally, due to incomplete data capture, we were only able to calculate the doses of Ig ordered for about half of this patient group. We calculated the dose based on Ig prescribed, and, although the prescribed and delivered doses are generally considered to be the same, we cannot confirm that these prescribed doses were actually infused.

Conclusion

For this provider, the subcutaneous route was used in the home more than the IV route, with a trend towards increased SC administration in older subjects. The estimated dosage was found to be in line with general treatment recommendations. The mean dose was significantly higher for subjects receiving IV Ig when compared to the mean dose for subjects receiving SC Ig. A statistically significant inverse correlation was found between the dose ordered and the subjects' age.

Acknowledgments

We gratefully acknowledge the help of Keith Crawford, Senior VP, Medical Marketing, Manufacturer Affairs, & Clinical Trials at Coram Specialty Infusion Services for giving us access to this data.

References

1. Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature. *Transfusion*. 2006; 46(5):741–753. [PubMed: 16686841]
2. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*. 2006; 117(4 Suppl):S525–S553. [PubMed: 16580469]

3. Shehata N, Palda V, Bowen T, Haddad E, Issekutz TB, Mazer B, et al. The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. *Transfus Med Rev.* 2010; 24(Suppl 1):S28–S50. [PubMed: 19962579]
4. Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immuno-deficiency disorders: relationship to immunoglobulin therapy over 22 years. *J Allergy Clin Immunol.* 2010; 125(6):1354.e4–1360.e4. [PubMed: 20471071]
5. Berger M. Incidence of infection is inversely related to steady-state (trough) serum IgG level in studies of subcutaneous IgG in PIDD. *J Clin Immunol.* 2011; 31(5):924–926. [PubMed: 21643892]
6. Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. *J Clin Immunol.* 2000; 20(2):94–100. [PubMed: 10821460]
7. Gardulf A, Nicolay U, Asensio O, Bernatowska E, Bock A, Carvalho BC, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies—a prospective, multi-national study. *J Clin Immunol.* 2006; 26(2):177–185. [PubMed: 16758340]
8. Maarschalk-Ellerbroek LJ, Hoepelman IM, Ellerbroek PM. Immunoglobulin treatment in primary antibody deficiency. *Int J Antimicrob Agents.* 2011; 37(5):396–404. [PubMed: 21276714]
9. Bonagura VR, Marchlewski R, Cox A, Rosenthal DW. Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection. *J Allergy Clin Immunol.* 2008; 122(1):210–212. [PubMed: 18602574]
10. Gajewski LK, Bailey EM, Brown PD, Chandrasekar PH. Immune globulin use at a multihospital medical center. *Am J Hosp Pharm.* 1994; 51(6):801–805. [PubMed: 8010320]
11. Chen C, Danekas LH, Ratko TA, Vlasses PH, Matuszewski KA. A multicenter drug use surveillance of intravenous immunoglobulin utilization in US academic health centers. *Ann Pharmacother.* 2000; 34(3):295–299. [PubMed: 10917372]
12. Frauger E, Grassi J, Pradel V, Bornet C, Rouby F, Delorme J, et al. Use of intravenous immunoglobulins in clinical practice: data from three French university hospitals. *Fundam Clin Pharmacol.* 2011; 25(6):753–761. [PubMed: 21219439]
13. Gathmann B, Grimbacher B, Beaute J, Dudoit Y, Mahlaoui N, Fischer A, et al. The European internet-based patient and research database for primary immunodeficiencies: results 2006–2008. *Clin Exp Immunol.* 2009; 157(Suppl 1):3–11. [PubMed: 19630863]
14. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. *Lancet.* 1987; 1(8541):1075–1077. [PubMed: 2883406]
15. Liese JG, Wintergerst U, Tymptner KD, Belohradsky BH. High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. *Am J Dis Child.* 1992; 146(3):335–339. [PubMed: 1543181]
16. Eijkhout HW, van Der Meer JW, Kallenberg CG, Weening RS, van Dissel JT, Sanders LA, et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. *Ann Intern Med.* 2001; 135(3):165–174. [PubMed: 11487483]
17. Nelson RP Jr, Ballow M. 26. Immunomodulation and immunotherapy: drugs, cytokines, cytokine receptors, and antibodies. *J Allergy Clin Immunol.* 2003; 111(2 Suppl):S720–S743. [PubMed: 12592317]
18. Yong PL, Boyle J, Ballow M, Boyle M, Berger M, Bleesing J, et al. Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies: a working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology. *Clin Immunol.* 2010; 135(2):255–263. [PubMed: 19914873]
19. Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol.* 2006; 26(3):265–273. [PubMed: 16783465]
20. Hagan JB, Fasano MB, Spector S, Wasserman RL, Melamed I, Rojavin MA, et al. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in

- patients with primary immunodeficiency. *J Clin Immunol.* 2010; 30(5):734–745. [PubMed: 20454851]
21. Wasserman RL, Irani AM, Tracy J, Tsoukas C, Stark D, Levy R, et al. Pharmacokinetics and safety of subcutaneous immune globulin (human), 10 % caprylate/chromatography purified in patients with primary immunodeficiency disease. *Clin Exp Immunol.* 2010; 161(3):518–526. [PubMed: 20550549]
 22. Berger M, Rojavin M, Kiessling P, Zenker O. Pharmacokinetics of subcutaneous immunoglobulin and their use in dosing of replacement therapy in patients with primary immunodeficiencies. *Clin Immunol.* 2011; 139(2):133–141. [PubMed: 21353644]
 23. Bonilla FA. IgG replacement therapy, no size fits all. *Clin Immunol.* 2011; 139(2):107–109. [PubMed: 21420364]

Fig. 1.
Ig dosing for all patients receiving either IV or SC Ig was plotted against age in years.
Spearman's rank correlation coefficient: -0.2709 , $P < .0001$

Fig. 2.

IV: Ig dosing for all patients receiving IVIg was plotted against age in years. Spearman's rank correlation coefficient: -0.1486 , $P < .0001$. SC: Ig dosing for all patients receiving SCIg was plotted against age in years. Spearman's rank correlation coefficient: -0.3609 , $P < .0001$

Table I

Patients with PIDD diagnosis

PIDD ICD-9 Code	PIDD diagnosis	Number of patients	Percentage
279.06	Common variable immunodeficiency	1,764	55.3
279.00	Hypogammaglobulinemia unspecified	635	19.9
279.3	Unspecified immunity deficiency	286	9.0
279.03	Other select immunoglobulin deficiency	171	5.4
279.04	Congenital hypogammaglobulinemia (agammaglobulinemia)	127	4.0
279.2	Combined immunity deficiency	105	3.3
279.05	Immunodeficiency with hyper IgM	34	1.1
279.01	Selective IgA immunodeficiency	18	0.6
279.09	Other deficiency humoral immunity	12	0.4
279.02	Selective IgM immunodeficiency	9	0.3
279.10	Immune T cell deficiency unspecified	7	0.2
279.11	DiGeorge syndrome	6	0.2
279.8	Other disorders immune mechanism	4	0.1
279	Disorders immune mechanism	3	0.1
279.12	Wiskott Aldrich syndrome	3	0.1
279.0	Deficiency humoral immunity	2	0.06
279.19	Other deficiency cell-mediated immunity	1	0.03
Total number of patients with PIDD		3,187	

Table II

Mean Ig dose for patients with specific PIDD diagnoses

ICD-9 code	Diagnosis	IV dose, in mg/kg/month (number of patients)	SC dose, in mg/kg/month (number of patients)
279.00	Hypogammaglobulinemia unspecified	587.7 (<i>n</i> =210)	569.8 (<i>n</i> =117)
279.03	Other select immunoglobulin deficiency	616.5 (<i>n</i> =34)	380.8 (<i>n</i> =47)
279.04	Congenital hypogammaglobulinemia (agammaglobulinemia)	566.7 (<i>n</i> =38)	615.4 (<i>n</i> =40)
279.06	CVID	534.4 (<i>n</i> =336)	345.7 (<i>n</i> =562)
279.3	Unspecified immunity deficiency	652.5 (<i>n</i> =84)	480.7 (<i>n</i> =67)
One way ANOVA		<i>P</i> =.3151	<i>P</i> <.0001