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Pneumococcal Antibody Titers: A Comparison of Patients Receiving Intravenous Immunoglobulin Versus Subcutaneous Immunoglobulin

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Abstract

Purpose: Immunoglobulin replacement is the mainstay treatment in patients with humoral immunodeficiencies, yet a handful of patients continue to develop sinopulmonary infections while on therapy. The objective of our study was to compare immunoglobulin G (IgG) pneumococcal antibody levels in patients with humoral immune deficiencies who have been on intravenous immunoglobulin (IVIG) replacement for at least 1 year to those on subcutaneous immunoglobulin (SCIG) therapy for at least 1 year. **Methods:** A retrospective chart review was completed on 28 patients. These patients' ages ranged between 1 and 61 years. Pneumococcal serotype titers obtained at least 1 year after initiating therapy were compared between patients on IVIG (19 patients) and SCIG (9 patients). **Results:** A comparison between the groups demonstrated that SCIG achieved a higher percentage of serotype titers protective for noninvasive disease (≥1.3) and 100% protection for invasive disease (≥0.2). Our data also demonstrated a similar lack of protection (less than 50% ≥1.3) in 9N, 12F, and 23F on IVIG and 4, 9N, 12F, and 23F on SCIG. **Conclusions:** Our data demonstrated that serotypes 1, 3, 4, 9N, 12F, and 23F exhibited the lowest random IgG means while on IVIG, which was comparable to other published studies that looked at the mean IgG levels. In addition, our retrospective chart review demonstrated a greater number of therapeutic pneumococcal titers with SCIG in comparison to IVIG.

Keywords

allergy/immunology, infectious diseases, medical education, general pediatrics, genetics

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Introduction

Replacement immunoglobulin is the treatment of choice for patients with humoral immunodeficiencies (eg, common variable immunodeficiency, agammaglobinemia, hypogammaglobinemia, combined immunodeficiencies, and specific antibody deficiency), yet a handful of patients continue to develop sinopulmonary infections while on therapy. Monitoring immunoglobulin G (IgG) trough levels has been considered by some as adequate vigilance to ensure proper replacement of antibodies. Pneumococcal antibody titers are generally not followed unless breakthrough infections are demonstrated.

Two routes of immunoglobulin replacement are available for patients with humoral immunodeficiencies, subcutaneous immunoglobulin (SCIG) and intravenous immunoglobulin (IVIG) therapy. Both treatments have their own advantages and disadvantages. IVIG requires intravenous access, but because it was made available for use commercially in the United States in 1984,[1] IVIG has a longer safety profile with relatively faster achievement of therapeutic levels when compared with SCIG. SCIG was Food and Drug Administration approved and available in the United States in 2006 and appears to have lower rates of systemic reactions. SCIG are completed at home by self-injection and is less

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expensive, and patients maintain more consistent IgG trough levels.[2] However, SCIG infusions could be up to 1 to 2 times weekly and needs to be administered at multiple body sites.[3] In a survey on SCIG therapy of primary immunodeficiency (PID) patients in 2008, at least 70% of the patients reported redness or swelling at the infusion site as the most common side effect during or after infusion.[4] This survey also revealed that systemic symptoms such as fever, chills, headaches, muscle aches, wheezing, vomiting, increased blood pressure, anxiety, blood pressure drops, and aseptic meningitis were reported less frequently compared with IVIG.[4]

Only a few studies have investigated pneumococcal titers in patients with humoral immunodeficiencies after at least a year of immunoglobulin therapy in either routes of treatment. Wasserman et al completed an in vivo study that reported the elimination half-life for *Streptococcus pneumoniae* serotypes in 20 PID patients receiving IVIG. The half-life for 3 reported pneumococcal titers from the study were surprisingly different, serotype 14 was reported as 40.77 days, serotype 19A was 60.04 days, and serotype 23F was 29.98 days.[5]

Lejtenyi and Mazer tested antibody titers for 14 pneumococcal serotypes (1, 3, 4, 6B, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19F, 23F, and 33F) in IVIG products provided by CSL Behring. The authors reported that 44 sets of IVIG products demonstrated differences in achieved levels of pneumococcal antibodies (with serotypes 14 and 19F achieving the highest levels).[6] Since immunoglobulin replacement therapy is processed from 40,000 or more liters of plasma, each with their own variety of immunologic antibody protection against a variety of known pathogens from vaccine or infectious exposures, the higher levels of serotypes 14 and 19F could be a reflection of natural infections from those serotypes in the donor pool. They concluded that the range in levels achieved by each pneumococcal titer were most likely a reflection of the population the IVIG therapy was being produced from because there was no difference in the manufacturing process of each product.[6]

To date, only a few small studies have been performed in human subjects including one from Belgium that investigated pneumococcal levels in 22 children with PID on IVIG therapy.[7] Based on the World Health Organization reference range of 0.2 to 0.35 μg/mL for protection against invasive pneumococcal disease,[8] 89% to 100% of the patients achieved trough levels ≥0.2 μg/mL for serotypes except 4, 9V, and 12F.[7] However, for protection against noninvasive pneumococcal infections, only 4 pneumococcal serotypes (6B, 14, 19A, and 19F) achieved the majority of trough levels >1.3 μg/mL and this was evident in only 65% to 93% of patients.[7,8] In Lejtenyi's study, all 14 tested pneumococcal serotypes in the actual IVIG product achieved levels consistent with therapeutic protection; however, the data have not been compared clinically.[6] None of the previous studies provided information regarding pneumococcal titers in patients on SCIG therapy.

The objective of our study was to compare IgG pneumococcal antibody levels in patients with humoral immune deficiencies who have been on IVIG for at least 1 year with those on SCIG therapy for at least a year. These levels were obtained at routine follow-up appointments, in our laboratory or outside laboratories, as part of their standard of care and not timed based on infusion schedule. We hypothesized, based on incidental findings of low pneumococcal titers in several immunodeficiency patients, that there will be lower pneumococcal titer levels after at least 1 year of SCIG compared with IVIG.

Methods

Retrospective chart review was performed on 28 humoral immunodeficiency patients who have been receiving immunoglobulin replacement for at least 1 year and had serum pneumococcal antibody titers levels evaluated. From each patient one random blood sample was collected, and 14 pneumococcal serotypes were measured from each sample. These 14 different pneumococcal serotype antibody titers (1, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 12F, 14, 18C, 19F, and 23F) were obtained from the participants at random intervals, not timed based on infusion schedule, and were assessed by standard ELISA method. A total of 392 total pneumococcal titer values were collected for analysis. However, 3 pneumococcal titer values had to be removed from the database because they were reported as <0.3 from an outside laboratory and were not compliant with statistical analysis. Based on the article by Orange et al and the World Health Organization reference range (0.2-0.35 μg/mL), we established our cutoff for protection against invasive and noninvasive pneumococcal disease.[8,9] Pneumococcal titer levels ≥0.2 μg/mL were considered as protective against invasive pneumococcal disease, and levels ≥1.3 μg/mL were considered protective against noninvasive pneumococcal disease.

Statistical Analyses

Continuously scaled data were reported using means, standard deviations, and median values. A parametric independent sample *t* test was employed to examine mean pneumococcal titer values by 2 types of immunoglobulin therapy. If assumptions of normality and/or homogeneity of variance (Levene's test for equality of variance) were violated a nonparametric Mann-Whitney

Table 1. Demographics of Patients.

	N (%)	On IVIG	On SCIG
Age (years)			
1-18	13 (46%)	9	4
19-30	10 (36%)	8	2
31-50	3 (11%)	1	2
51-70	2 (7%)	1	1
Gender			
Female	7 (25%)	5	2
Male	21 (75%)	14	7
Race			
Caucasian	18 (64%)	12	6
African Americans	7 (25%)	4	3
Arabic	2 (7%)	2	0
Hispanic	1 (4%)	1	0

Abbreviations: IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.

U test was substituted. A series of 2 × 2 Fisher's exact χ^2 tests were performed to examine proportional differences between invasive and noninvasive infections by dichotomizing different titer-level cutoff values for therapeutic and nontherapeutic levels. All statistical procedures were conducted using SPSS Version 22.0 (IBM Inc, Chicago, IL). Statistically significance differences in means or proportions were considered significant at $P \leq .05$.

Results

Demographics

Tables 1 and 2 summarizes demographics, diagnoses, immunoglobulin brands and chronic conditions of our patients. The majority of our patients were ≤30 years and most were on IVIG. A higher percentage of our patients were Caucasian and were male gender. The most common diagnosis was common variable immune deficiency and the second most common was agammaglobulinemia. More patients on IVIG had comorbidities related to the gut which could contribute to a secondary loss of IgG and effect levels even further. Patients on IVIG had around double the number in each category vs patients on SCIG. Immunoglobulin therapy were initially dosed at 0.5grams/kg and adjusted based on trough IgG levels. The trough IgG levels on our patients ranged from 671-1560 with an average IgG level of 1049.

All mean values of pneumococcal titers except serotype 4 were above the therapeutic level for noninvasive infections, and all mean values were above the therapeutic level for invasive infections. Pneumococcal titer serotype values were separated based on the type of immunoglobulin therapy each patient was receiving in order to determine the individual means and standard deviations. Both sets of geometric mean values including the standard deviation are demonstrated in Table 3. The pneumococcal titers 23F in IVIG, 19F in SCIG, and 5 in IVIG and SCIG (Table 3) have mean values associated with large standard deviations that were related to outliers present in the titer values. Both methods of immunoglobulin replacement demonstrated that the means for serotypes 1, 3, 4, 9N, 12F, and 23F fell below the cutoff of protection from noninvasive infection.

A Mann-Whitney *U* test was completed, which revealed no significant differences for any of the 14 pneumococcal serotypes.

Crosstabs analysis was completed in order to illustrate the percent distribution between therapeutic and nontherapeutic levels for invasive (< and ≥0.2) and noninvasive (< and ≥1.3) infections (Tables 4 and 5). For invasive pneumococcal disease (≥0.2), SCIG achieved 100% protection, while IVIG had gaps in coverage in all but 2 serotypes (5 and 19F). For noninvasive pneumococcal disease (≥1.3), both types of immunoglobulin therapy had gaps in achieving protection levels. SCIG achieved 100% protection of noninvasive disease with 5 different serotypes (5, 7F, 14, 18C, and 19F) as opposed to IVIG, which did not achieve 100% protection with any of the measured pneumococcal serotypes. Last, SCIG had 0% protection in serotype 4 for noninvasive disease, whereas IVIG had 82.40% coverage in the same serotype.

Fisher's exact test revealed no statistical significance among any of the individual serotypes in the crosstab analysis for invasive (≥0.2) and noninvasive (≥1.3) pneumococcal disease.

Discussion

Our data demonstrates that there are gaps between adequate IgG trough levels and antibody titer protection against several pneumococcal serotypes that are known to cause invasive pneumococcal diseases (serotypes 4, 6B, 8, 9V, 14, and 23F) specifically with IVIG. Overall, SCIG appeared to have a higher total percentage of therapeutic pneumococcal titer levels than IVIG despite the smaller sample size. For protection from invasive disease (≥0.2 μg/mL), patients on SCIG therapy achieved 100% protection. For noninvasive disease (≥1.3 μg/mL) 10 out of 14 pneumococcal titers had the majority of coverage while patients were on either type of therapy. This was comparable to Pieretti et al, who found that 55% of their patients evaluated achieved protective levels of ≥1.3 in ≥7 out of 14 serotypes tested.[10] SCIG,

Table 2. Diagnosis, Brands of Immunoglobulin Replacement, and Comorbidities That Can Influence IgG Levels.

Diagnosis	N (%)	On IVIG	On SCIG
Common variable immune deficiency	12 (43%)	8	4
Agammaglobinemia	8 (29%)	5	3
Specific antibody deficiency	4 (14%)	3	1
Good syndrome	1 (3.5%)	1	0
Ectodermal dysplasia/NEMO	1 (3.5%)	1	0
Immunodeficiency centromeric instability and facial anomalies syndrome	1 (3.5%)	1	0
Severe partial DiGeorge syndrome	1 (3.5%)	0	1
Total	28 (100%)	19 (68%)	9 (32%)
Brands of Immunoglobulin Replacement Therapy	IVIG	SCIG	
	Gammagard Gammunex Privigen	Hizentra	
Chronic Conditions in Addition to Immunodeficiency	On IVIG	On SCIG	
Chronic renal disease	1	0	
Chronic Gut disease	5	2	

Abbreviations: IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.

Table 3. Comparison of the Geometric Means and Ranges for Each Type of Pneumococcal Antibody Titer From Patients on IVIG or SCIG.

Pneumococcal Serotype (IgG)	Geometric Mean (Range) on IVIG	Geometric Mean (Range) on SCIG
1	1.25 (0.08-4.67)	1.29 (0.59-2.15)
3	1.20 (0.14-3.74)	1.27 (0.5-2.16)
4	0.41 (0.04-1.39)	0.38 (0.2-0.58)
5	5.93 (0.61- 31.32)	8.97 (3.78-24.65)
6B	1.51 (0.11-3.16)	1.48 (0.7-2.81)
7F	2.52 (0.1-6.6)	3.41 (1.63-11.25)
8	1.32 (0.1-4)	1.71 (0.93-3.03)
9N	0.96 (0.08-4.96)	1.14 (0.52-2.5)
9V	1.41 (0.08-8.6)	1.40 (0.51-2.37)
12F	0.93 (0.12-6.15)	1.18 (0.56-2.34)
14	2.92 (0.11-8.93)	4.1 (2.06-7.5)
18C	2.46 (0.1-10.58)	4.87 (2.32-7.32)
19F	3.91 (0.29-11.98)	5.45 (1.65-18.97)
23F	1.25 (0.03-17.7)	1.00 (0.6-1.64)

Abbreviations: IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.

Table 4. Distribution of Pneumococcal Titers for Invasive Disease[a].

Pneumococcal Serotype (IgG)	≥0.2 (SCIG)	≥0.2 (IVIG)
1	100.00%	94.70%
3	100.00%	94.70%
4	100.00%	82.40%
5	100.00%	100.00%
6B	100.00%	94.70%
7F	100.00%	94.70%
8	100.00%	94.70%
9N	100.00%	94.70%
9V	100.00%	94.70%
12F	100.00%	88.90%
14	100.00%	94.70%
18C	100.00%	94.70%
19F	100.00%	100.00%
23F	100.00%	94.70%

Abbreviations: IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.
[a]Crosstabs analysis demonstrating the percent distribution of serotype titer levels based on protection against invasive (≥0.2) infections.

however, demonstrated a higher majority percentage value of serotype titers ≥1.3 μg/mL (Table 5).

Our data demonstrated that serotypes 5, 7F, 14, and 19F maintained the majority of titer levels of ≥1.3 μg/mL on IVIG product. This data are comparable to the Belgian study by Tuerlinckx et al, who discovered higher trough values (≥1 μg/mL) for serotypes 6B, 14, 19A, and 19F in patients receiving IVIG, and the highest percentages of patients lacking invasive disease protection were found

Table 5. Distribution of Pneumococcal Titers for Noninvasive Disease[a].

Pneumococcal Serotype (IgG)	≥1.30 (SCIG)	≥1.30 (IVIG)
1	66.70%	47.40%
3	55.60%	53.60%
4	0.00%	82.40%
5	100.00%	89.50%
6B	55.60%	68.40%
7F	100.00%	89.50%
8	77.80%	63.20%
9N	44.40%	31.60%
9V	55.60%	57.90%
12F	44.40%	38.90%
14	100.00%	89.50%
18C	100.00%	73.70%
19F	100.00%	89.50%
23F	22.20%	47.40%

Abbreviations: IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.
[a]Crosstabs analysis demonstrating the percent distribution of serotype titer levels based on protection against noninvasive (≥1.3) infections.

in serotypes 4 and 12F while on IVIG.[7] Our data demonstrated similar lack of protection (less than 50% ≥1.3) in 9N, 12F, and 23F on IVIG and 4, 9N, 12F, and 23F on SCIG. In addition, Pieretti et al discovered similar results with a lack of coverage in serotypes 4, 9N, and 12F.[10] Knutsen et al demonstrated that antibody trough levels for serotypes 1, 4, 9V, 18C, and 23F while on IVIG were lower than the other serotypes.[11] This is complementary to our data in Table 3 with serotypes 1, 3, 4, 9N, 12F, and 23F exhibiting the lowest random IgG means while on IVIG. This suggested that regardless of timing in drawing blood to analyze serotypes (trough vs non-trough), there are some pneumococcal serotypes titers that will not achieve complete protection.

Knutsen et al also demonstrated that IgG trough levels while on IVIG and IgG levels while on SCIG were comparable at 965 ± 278 mg/dL and 945 ± 237 mg/dL.[11] This was comparable to our results for IVIG versus SCIG at 999.5 ± 219.95 and 1153.67 ± 301.1.

The nonsignificant difference with the crosstab analysis for the therapeutic and nontherapeutic pneumococcal titers between IVIG and SCIG could be related to unequal sample size between both immunoglobulin types of therapy and overall small sample size. Although there was no statistical significance among the data, these values potentially suggest a clinical significance in immunity protection against pneumococcal disease in patients on immunoglobulin therapy. These findings go against our original hypothesis and could be related to frequency of administration because of more consistent troughs achieved with SCIG or the type of patient donor pool that SCIG's brand is using. However, our IVIG products ranged in brands due to insurance reasons and could also be contributing to discrepancy in coverage. Further analysis into the actual product's pneumococcal antibody titer levels is warranted to support this potential explanation. Findings have suggested that monitoring pneumococcal antibody titers in patients who receive immunoglobulin replacement therapy, in particular, IVIG, rather than monitoring only trough IgG levels, may be necessary, and future study in this area is required. Changing the dose of immunoglobulin replacement or switching immunoglobulin replacement products may also be necessary, especially if patients continue to have breakthrough infections or are unable to achieve pneumococcal titers at the therapeutic levels.

Limitations to our study included but were not limited to a small sample size, in particular the SCIG group. Future multicenter studies are warranted to increase statistical power analysis and to reduce bias. The other limitation of our study was that not all of our pneumococcal antibody titers were obtained as trough levels, although published literature regarding the necessity in obtaining the trough pneumococcal antibody titers is very limited. Our primary analysis obtained levels at random intervals due to patients' schedules, outside infusion facilities, and home infusions, which did not make timed blood draws always feasible. Obtaining the pneumococcal antibody titers before and after the immunoglobulin replacement therapy may provide us more information with regard to fluctuation of titer levels. Further research and analysis are also needed regarding pneumococcal titers in each individual IVIG/SCIG product brands. Information regarding pneumococcal serotypes or other bacteria that causes breakthrough infections in patients on immunoglobulin replacement therapy would be helpful for further analysis and has not been analyzed within our patient population at this time. A portion of our patients on immunoglobulin replacement therapy suffer from comorbidities that can affect the metabolism of the newly replaced immunoglobulin. These comorbidities are listed in Table 2; however, they were not controlled in our analysis because of the small sample size. Larger and multicenter studies are required to evaluate primary immune deficient patients that are on immunoglobulin therapy, their comorbidities, infection types and rates, and the role of using pneumococcal titers as another marker to monitor the immunoglobulin replacement therapy in PID disorders.

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Author Contributions

PFA: Contributed to conception and design; contributed to analysis; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

PP: Contributed to conception and design; contributed to analysis; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

ES: Contributed to conception and design; contributed to analysis; critically revised the manuscript; gave FINAL approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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