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Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies

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X-linked agammaglobulinemia;
Meta-analysis

Abstract Primary immunodeficiency disease (PIDD) associated with hypogammaglobulinemia is typically treated with immunoglobulin replacement therapy. When administered as intravenous immunoglobulin (IVIG), an IgG trough occurs prior to the next replacement dose. While frequently measured, IgG trough levels required to minimize infection risk are not established. To address this question, all available studies evaluating trough IgG and pneumonia incidence in PIDD patients with hypogammaglobulinemia receiving IVIG were quantitatively combined by meta-analysis. Seventeen studies with 676 total patients and 2,127 patient-years of follow-up were included. Pneumonia incidence declined by 27% with each 100 mg/dL increment in trough IgG (incidence rate ratio, 0.726; 95% confidence interval, 0.658–0.801). Pneumonia incidence with maintenance of 500 mg/dL IgG trough levels (0.113 cases per patient-year) was 5-fold that with 1000 mg/dL (0.023 cases per patient-year). This meta-analysis provides evidence that pneumonia risk can be progressively reduced by higher trough IgG levels up to at least 1000 mg/dL.

Introduction

Replacement therapy with IgG is an essential intervention in many primary immunodeficiency diseases (PIDDs) associated with humoral defects [1]. Continual IgG replacement therapy for patients with these types of PIDD reduces the frequency and severity of infections and can lessen morbidity and mortality [2]. The introduction of intravenous immunoglobulin (IVIG) allowed the administration of higher IgG doses than had been possible previously via the intramuscular route. When IVIG therapy was initially approved for clinical use, the recommended replacement dose was 100–200 mg/kg, but this has increased over subsequent decades in light of evolving clinical

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experience [1,3] as studies have shown less frequent bacterial infection and improved outcome with higher doses [4–9]. Doses of IVIG are most commonly provided at monthly intervals [10].

Administration of IVIG results in a rapid peak concentration that decreases over time before the next infusion. The serum IgG concentration immediately preceding the next scheduled IVIG infusion is designated the trough level and is viewed by a majority of immunologists as an important guide to therapy [10]. Trough levels have even been used as a means to evaluate the adequacy of a particular dosage [1,11]. While sufficient trough levels needed for optimal protection of PIDD patients against serious bacterial infections have yet to be established [12], a trough level of 500 mg/dL has in recent years been considered a minimum trough target [3–8,10]. The extent to which trough levels exceeding 500 mg/dL might confer additional benefit has been debated [1]. Resolution of this question has been hampered by the limitations of pertinent clinical data. Since PIDD is rare, the size of reported individual clinical studies has of necessity been small, thus limiting statistical power. Furthermore, different studies assessed disparate infection endpoints, such as total infections, serious bacterial infections or individual infection types. The range of trough levels reported in the individual studies has also often been restricted.

Meta-analysis can allow some of the limitations in existing data to be overcome. By quantitatively combining results from multiple small studies, meta-analysis can increase statistical power and potentially expand the range of trough levels over which infection incidence can be evaluated. A meta-analysis delineating the relationship between trough IgG level and infection incidence during IVIG therapy has not been previously published. Ideally, the primary endpoint for such a meta-analysis would be homogeneous and clinically relevant, with ample event rate data available over a wide range of associated trough levels. Pneumonia fulfills these criteria in patients with PIDD and is one of the primary validated serious bacterial infections used to determine the efficacy of immunoglobulin replacement therapies (www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm072130.htm).[1]

Pneumonia is among the most frequent manifestations of PIDD [13,14]. Between 75 and 84% of patients with common variable immunodeficiency (CVID) were found to have experienced at least one episode of pneumonia before diagnosis, and many had experienced multiple prior episodes [15]. In the US patient registry of X-linked agammaglobulinemia (XLA), 62% of patients had experienced pneumonia [16]. A high pneumonia incidence has also been reported in other PIDDs affecting humoral immunity, including the X-linked hyper-IgM syndrome (81%) [17], NEMO deficiency (31%) [18] and the Wiskott–Aldrich syndrome (45%) [19].

In PIDD patients pneumonia can be severe, frequently requiring intravenous antibiotics and/or hospitalization [20]. Some clinical studies have focused solely on the efficacy of IVIG in preventing pneumonia [21–23], while other studies without such a narrow focus have nevertheless reported pneumonia incidence [4–6,24,25]. Furthermore, pneumonia incidence has been reported for a broad range of trough levels [14,24]. This meta-analysis demonstrates statistically significant progressive decreases in pneumonia incidence associated with trough IgG increases in PIDD patients with antibody deficiency.

[1] This weblink was valid as of July 2010.

Methods

Study selection

Eligible clinical studies must have furnished data on pneumonia incidence in relation to IgG levels among patients receiving IVIG therapy for PIDD with antibody deficiency. Investigations exclusively or predominantly dealing with IgG subclass deficiency or specific antibody deficiency were not eligible. Studies of IgG treatment exclusively via the intramuscular or subcutaneous routes were excluded since these routes of dosing result in a distinct kinetics without comparable trough levels [26]. When more than one route of administration was investigated, only the data pertaining to IVIG were used. No restrictions were placed on study design, time period or reporting language. Final publication was not required, and completed but unpublished studies were sought, for example, through searches of ClinicalTrials.gov. However, studies reported exclusively in abstract form were not sought or included.

Search strategy

Eligible studies were identified by computer searches of MEDLINE and the Cochrane Library. The searches were conducted between May and September, 2009. Search terms included IVIG; IGIV; intravenous immune globulin; intravenous immunoglobulin; Carimune; Endobulin; Flebogamma; Gamimune; Gammagard; Gammaglobulin; Gammaplex; Gamunex; Intraglobin; Iveegam; Nordimmune; Octagam; Polygam; Privigen; Sandoglobulin; Vigam; primary immunodeficiency; hypogammaglobulinemia; common variable immunodeficiency; agammaglobulinemia; X-linked agammaglobulinemia; and hyper-IgM syndrome. Reference lists of primary study publications and review articles were also examined.

Data extraction

Two investigators independently determined study eligibility and extracted data from the eligible study reports. The κ statistic was 0.68 with a 95% confidence interval (CI) of 0.49–0.86, indicating a high degree of inter-rater agreement. Differences in interpretation were resolved through the intermediation of a third investigator. Data were extracted on study design; geographic study region; IVIG product or supplier; number of patients; mean patient age; gender distribution; clinical diagnosis; numbers of pneumonia episodes; duration of study observation period; IVIG dose and treatment interval; and trough IgG level. In some studies [4–6,22], individual patient trough IgG values were presented as graphical displays in the study reports. Those data were captured from the displays by computer digitization to a precision of ±0.001 mg/dL.

Statistical analysis

Data were analyzed using R version 2.7.2 statistical software (The R Foundation for Statistical Computing, Vienna, Austria). The relationships between pneumonia incidence and either trough IgG or IVIG dose were analyzed by

multilevel overdispersed Poisson metaregression, with observation periods nested in studies. The effect size measure for these analyses was the incidence rate ratio (IRR), defined as the ratio of pneumonia incidence rates corresponding to trough IgG level or IVIG dose increments of 100 mg/dL or 100 mg/kg, respectively. Absence of 1 from the CI surrounding the IRR denotes a statistically significant effect ($p<0.05$). In addition, pneumonia incidence rates were computed for IgG trough levels of 500, 600, 700, 800, 900 and 1000 mg/dL and IVIG doses of 100, 200, 300, 400, 500 and 600 mg/kg. For the meta-analysis of pneumonia incidence in relation to dose, results reported for different attained trough IgG levels at the same nominal IVIG dose were pooled.

In the included study reports, pneumonia incidence was frequently indicated with reference to particular trough IgG cutoff values such as <500 vs. ≥500 mg/dL. In such cases, the mean value within the range designated by the cutoff was used for analysis and plotting [27]. When the means of the values above and below the cutoffs were not reported, those means were directly computed from study reports furnishing individual patient data [27]. For two studies [14,28], neither the means above and below the cutoffs nor individual patient data were available. The means for those two studies were imputed from the distribution of trough IgG values in another included study with extensive sequential individual patient data [4–6].

The relationship between administered IVIG dose and attained trough serum IgG was evaluated by multilevel linear metaregression, again with observation periods nested in studies. The null hypothesis was a slope of zero. Absence of zero from the slope CI indicates significant change in trough as a function of dose ($p<0.05$). The attained trough levels after doses of 100, 200, 300, 400, 500 and 600 mg/kg doses were estimated from the multilevel linear model.

Study quality was assessed by comparison of IRR between prospective and retrospective studies and publication bias by comparison between small and large studies. IRR differences related to PIDD type were also evaluated.

Results

Included studies

The process of study selection is depicted in Fig. 1. After searching and screening, 194 study reports were reviewed in detail and 78 candidate reports identified. Of those, 59 were excluded after detailed examination for reasons detailed in the online supplementary material, most often lack of pneumonia incidence data. Seventeen clinical studies reported from 1982 to 2009 with 676 total patients and 2127 patient-years of follow-up were included in the meta-analysis [4–7,14,20,22–25,28–36]. One of the studies was described in three published reports [4–6]. Eleven of the studies (59%) were published since 2004. All studies involved fewer than 100 patients each. The median number of patients per study was 34 with an interquartile range (IQR) of 29–46. The median total follow-up per study was 49.1 patient-years (IQR, 29.0–163.7 patient-years).

Study characteristics

Table 1 summarizes the characteristics of the included studies, of which 11 were prospective, including two cross-over randomized controlled trials, and 6 retrospective. Six studies were conducted in the United States, more than any other region. Three studies were multinational. Three were conducted in single European countries and three in the Middle East. Canada and Argentina were the sites of one study each. Assorted IVIG products were evaluated in the included studies (Table 1).

Mean patient age was <18 years in 8 studies (47%) and ≥18 years in 9 studies (53%). Young children, with mean baseline age ranging from 2.3 to 3.5 years, were the subjects of three studies. Although age exceeded 70 years in individual patients of 4 studies, none of the included studies was specifically

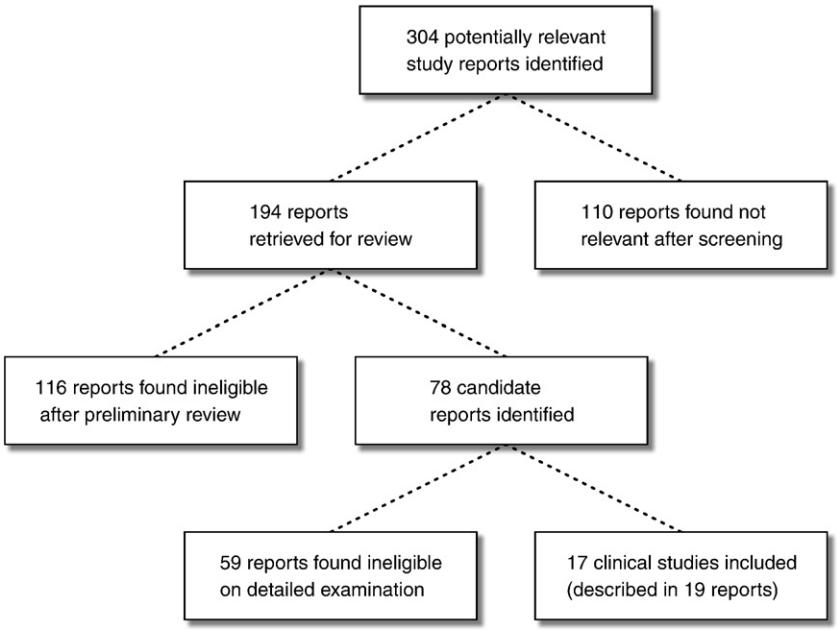

Figure 1 Process of clinical study selection.

focused on an elderly population. Males comprised the majority of patients in 15 studies (88%). The types of PIDD evaluated among included studies are indicated in Table 2. Patients exclusively with XLA were enrolled in 3 studies and exclusively with CVID in one. More than one PIDD was represented in the remaining 13 studies. Across all 17 studies, CVID and XLA were the most frequent PIDD, accounting respectively for 49% and 37% of all 676 patients in the meta-analysis (Table 2). CVID was the predominant PIDD in 4 studies, comprising over 75% of all patients in each of those studies [4–6,23,34,35]. No patients with subclass deficiency were enrolled in 14 studies, while two studies included one patient each with subclass deficiency (Table 2). In one study, 10 patients comprising 33% of the total enrollment exhibited subclass deficiency [31].

Information concerning previous pneumonia or pre-existing chronic lung disease was reported for 7 of the 17 included studies. In 5 of those studies the proportions of patients who had experienced one or more prior episodes of pneumonia were 48% [14], 78% [28], 81% [23], 83% [22] and 100% [4–6]. In the two remaining studies, 21% [20] and 53% [36] of patients had presented with pre-existing chronic lung disease. In none of those 7 studies were data for pneumonia incidence in relation to trough IgG or IVIG dose stratified according to previous pneumonia or pre-existing chronic lung disease. Consequently, it was not feasible to analyze the impact of previous pneumonia or pre-existing chronic lung disease.

Reported details on criteria for diagnosing pneumonia during the course of IVIG therapy were limited. In one included study [23], pneumonia was diagnosed on the basis of history, chest X-ray, physical examination and need for hospitalization. Bacterial pneumonia was reported in 6 studies [24,25,32,34–36], while the diagnostic criteria for pneumonia were unspecified in the remaining 10 studies.

In 10 studies (59%), pneumonia incidence and trough IgG levels were reported for a single cohort receiving a particular IVIG dosage over one observation period. Four studies documented pneumonia incidence before and during therapy with one IVIG dosage [14,22,23] or two different dosages [7]. In two of those studies [14,22], patients receiving the same nominal IVIG dosage were stratified into groups according to attained IgG trough levels of <500 vs. 500–800 vs. >800 mg/dL or of <500 vs. ≥500 mg/dL. Of the three remaining studies, two [4–6,30] involved sequential treatment with two different IVIG dosages and one [28] a single nominal dosage with stratification according to IgG trough levels <300, 300–500 and >500 mg/dL. In one of the two studies with sequential treatment [4–6], patients crossed over in randomized order between low and high IVIG dosages; however, pneumonia incidence was only reported for periods during which trough IgG was <500 vs. ≥500 mg/dL, regardless of dosage. Hence, in the meta-analysis, pneumonia data from that study could only be assessed with reference to trough IgG but not IVIG dose.

As a result of the multiple comparisons made in 7 included studies, the total number of distinct observation periods with pneumonia and trough IgG data was 29. Since data from multiple groups receiving the same nominal dosage were pooled in the analysis of pneumonia incidence with respect to dose and since one study was excluded for that analysis [4–6], the number of distinct observation periods with pneumonia and dose data was 22. For analysis of the relationship between administered IVIG dose and attained serum IgG trough level no study needed to be excluded, and the distinct observation periods available for this analysis totaled 24.

Table 1 Characteristics of clinical studies included in meta-analysis.

Study	Design	Region	IVIG product or supplier	Age[a], years	% Male
Ammann et al., 1982 [29]	P	United States	Cutter	32.2 (1.5–63)	79.4
Schiff et al., 1984 [30]	P	United States	Intraglobin	17 (3.5–29)	75.0
Roifman et al., 1987 [4–6]	C-RCT	Canada	Sandoglobulin	24[b] (7–50)	66.7
Liese et al., 1992 [7]	R	Germany	Unspecified	2.3 (2–5)	100.0
Quartier et al., 1999 [14]	R	France	LFB, Sandoglobulin or Endobulin	3.0 (0.6–9.7)	100.0
Chapel et al., 2000 [31]	C-RCT	Sweden and UK	Endobulin	44 (18–67)	33.3
Plebani et al., 2002 [20]	R	Italy	Unspecified	3.5 (0.3–17)	100.0
Aghamohammadi et al., 2004 [22]	R	Iran	Unspecified	5.2 (0.8–14.1)	100.0
Berger and Pinciaro, 2004 [32]	P	United States	Flebogamma 5%	38.2 (14.0–74.0)	60.8
Ochs and Pinciaro, 2004 [33]	P	United States	Octagam	31 (6–74)	60.9
Bayrakci et al., 2005 [28]	R	Turkey	Unspecified	5.1[b] (0.8–13.9)	84.8
Church et al., 2006 [24]	P	United States	Gammagard Liquid 10%	34[b] (6–72)	46.0
Pourpak et al., 2006 [23]	R	Iran	Sandoglobulin or Nordimmune	8.1 (2.5–16.0)	53.8
Berger, 2007 [34]	P	United States	Flebogamma 5% DIF	38.9 (15.0–75.0)	63.0
Berger et al., 2007 [35]	P	United States and Canada	Carimune NF Liquid	32 (4–66)	69.0
Krasovec et al., 2007 [36]	P	Argentina	Inmunoglobulina G Endovenosa UNC	10.1 (2–18)	70.0
Stein et al., 2009 [25]	P	United States and Europe	Privigen	28 (3–69)	57.5

Abbreviations: C-RCT, crossover randomized controlled trial; IVIG, intravenous immunoglobulin; P, prospective; R, retrospective.
[a] Mean (range) at baseline except as otherwise indicated.
[b] Median; assumed equal to mean for classification of mean age as <18 year vs. ≥18 years.

Table 2 Types of PIDD in included clinical studies.

Study	CVID	XLA	AGG	HIM	SD	Other	Total
Ammann et al., 1982 [29]	24	7		3			34
Schiff et al., 1984 [30]	12	2		2			16
Roifman et al., 1987 [4–6]	10	2					12
Liese et al., 1992 [7]		29					29
Quartier et al., 1999 [14]		31					31
Chapel et al., 2000 [31]	18				10	2 [a]	30
Plebani et al., 2002 [20]		73					73
Aghamohammadi et al., 2004 [22]		5	18				23
Berger and Pinciaro, 2004 [32]	37	12	1	1			51
Ochs and Pinciaro, 2004 [33]	28	13		2	1	2 [b]	46
Bayrakci et al., 2005 [28]	20	19		7			46
Church et al., 2006 [24]	22	5		1	1	32 [c]	61
Pourpak et al., 2006 [23]	26						26
Berger, 2007 [34]	35	10				1 [d]	46
Berger et al., 2007 [35]	32	10					42
Krasovec et al., 2007 [36]	10	14	1 [e]			5 [f]	30
Stein et al., 2009 [25]	59	21					80
Total	333	253	20	16	12	42	676

Abbreviations: AGG, agammaglobulinemia; AT, ataxia telangiectasia; CVID, common variable immunodeficiency; HIM, hyper-IgM; PIDD, primary immunodeficiency disease; SD, subclass deficiency; XLA. X-linked agammaglobulinemia.

[a] Specific antibody deficiency.

[b] One each hypogammaglobulinemia and functional immunodeficiency.

[c] Nineteen hypogammaglobulinemia; 10 unspecified PIDD; one each AT, severe combined immunodeficiency, and hyper-IgE syndrome.

[d] AT with hypogammaglobulinemia.

[e] Autosomal recessive.

[f] Four AT; one hyper-IgE syndrome.

IVIG dose vs. IgG trough

Across all included studies, with diverse diagnoses and IVIG products represented, linear increases in trough IgG level were attained with increments in IVIG dose administered (Fig. 2). As shown by the slope of the dose-response curve, trough IgG increased 121 mg/dL with each additional 100 mg/kg in IVIG dose.

Trough IgG and pneumonia

Data on trough IgG levels prior to commencement of IVIG therapy were available for four of the included studies. Three of those studies concerned patients with XLA or agammaglobulinemia, and mean pretreatment trough IgG ranged from 42 to 90 mg/dL. Patients with CVID were the subject of the fourth study, and pretreatment trough IgG averaged 210 mg/dL. During the 25 observation periods after the start of IVIG treatment median trough IgG was 650 mg/dL (IQR, 320–840 mg/dL). Individual study trough IgG and pneumonia incidence data are presented in the online supplementary material.

Across all included studies, pneumonia incidence progressively declined with increasing trough IgG. IRR was 0.726 (CI, 0.658–0.801), implying a statistically significant 27% reduction in pneumonia incidence for each 100 mg/dL increment in trough IgG (Fig. 3). Pneumonia incidence with maintenance of 500 mg/dL IgG trough levels was 5-fold that with 1000 mg/dL. The data points in Fig. 3, which are scaled in proportion to log-transformed patient-years of observation, did not display any systematic change in size over the range of evaluated IgG trough levels. Hence, there was no indication that the available data were more sparse for any particular trough levels, for example those at the highest end of the range. It should be noted that the dispersion of data points in Fig. 3, based on Poisson metaregression and plotted on a log scale, cannot be directly compared with that in Fig. 2, derived from linear metaregression and displayed on a linear scale.

IRR for pneumonia in relation to trough IgG was similar between prospective and retrospective studies and among differing PIDD types (Table 3). IRR in small studies also differed little from that in large, and hence there was no evidence of publication bias (Table 3). Excluding the single study [31] with a sizeable minority of subclass deficiency patients (33%) showed negligible effect (IRR, 0.727; CI, 0.655–0.808).

In the earliest reported study of the meta-analysis, a prospective multicenter investigation published in 1982 [29], no cases of pneumonia were observed despite a comparatively low IVIG dose (93 mg/kg) and IgG trough level (283 mg/dL). Active monitoring for infection was performed at hospital visits every 4 weeks, and other types of infections were frequent, including bronchitis in half the patients. Thus, there was no apparent basis other than sampling variation for the comparatively low incidence of pneumonia in that study.

IVIG dose and pneumonia

The median treatment interval between IVIG infusions among the included studies was 24.6 days (IQR, 24.5–

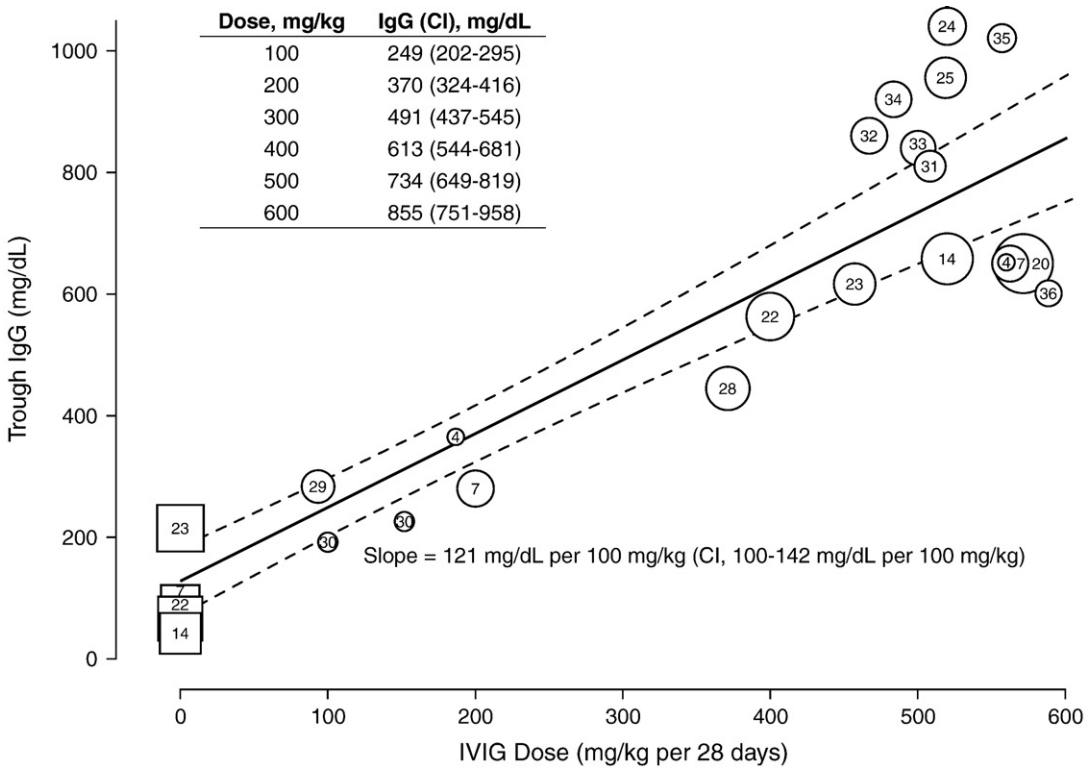

Figure 2 Effect of IVIG dose (mg/kg per 28 days) on trough IgG level (mg/dL). Each data point corresponds to a single observation period in a patient group of a particular study. Data points labeled by reference citation and scaled in proportion to log-transformed patient-years of observation. Observations before start of IVIG therapy shown as squares and after start as circles. Solid line shows multilevel model predictions, and dashed lines indicate CI of metaregression. Abbreviations: CI, 95% confidence interval; IVIG, intravenous immunoglobulin.

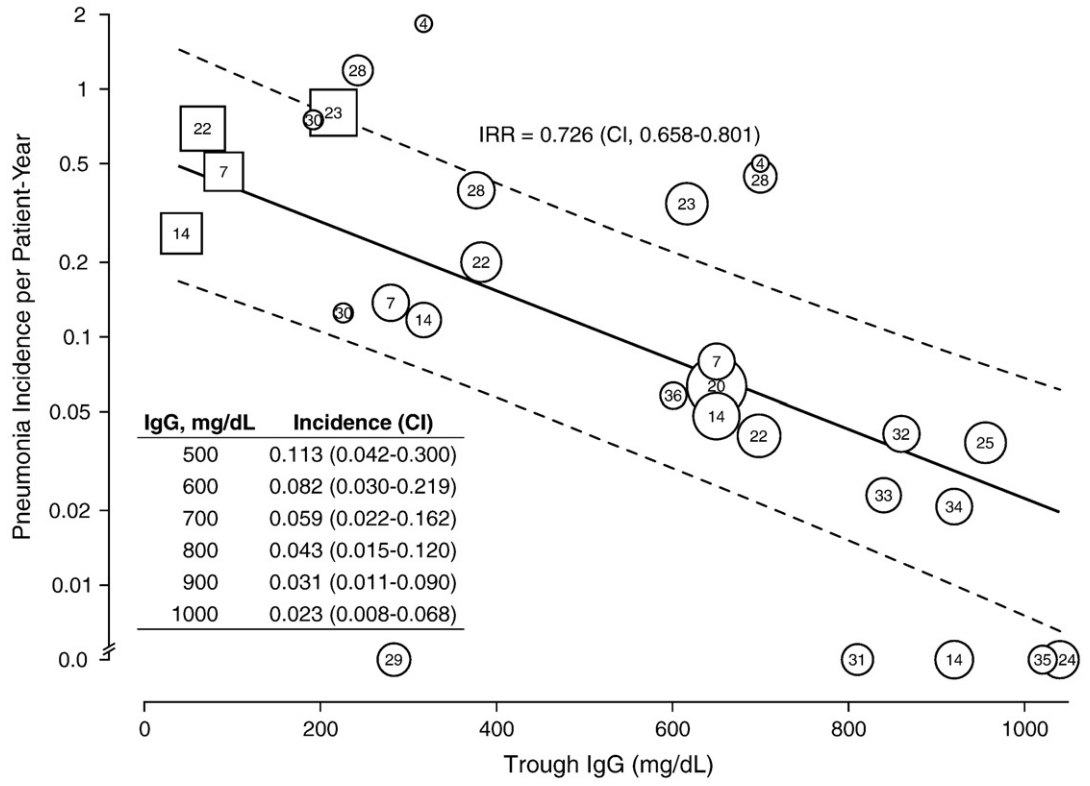

Figure 3 Effect of trough IgG level (mg/dL) on pneumonia incidence per patient-year. Graphic conventions as in Fig. 2. Abbreviations: CI, 95% confidence interval; IRR, incidence rate ratio per 100 mg/dL increase in trough IgG level.

Table 3 Effects of study design and PIDD type on pooled IRR for pneumonia.

Category	Studies	Pooled IRR (CI)	
		Trough IgG [a]	IVIG dose [b]
Study design			
Prospective [c]	11	0.662 (0.544–0.806)	0.615 (0.414–0.914) [d]
Retrospective	6	0.735 (0.597–0.907)	0.734 (0.519–1.037)
Study size (patients)			
≤30	7	0.719 (0.608–0.851)	0.722 (0.571–0.913) [d]
>30	10	0.755 (0.661–0.862)	0.726 (0.639–0.825)
PIDD type			
CVID [e]	4	0.785 (0.697–0.885)	0.826 (0.772–0.883) [d]
XLA or AGG	4	0.690 (0.602–0.791)	0.679 (0.535–0.862)
Mixed	9	0.785 (0.627–0.984)	0.598 (0.310–1.152)

Abbreviations: AGG, agammaglobulinemia; CI, 95% confidence interval; IRR, incidence rate ratio; IVIG, intravenous immunoglobulin; PIDD, primary immunodeficiency disease; XLA, X-linked agammaglobulinemia.

[a] IRR per 100 mg/dL increment in trough IgG.

[b] IRR per 100 mg/kg increment in IVIG dose.

[c] Including crossover randomized controlled trials.

[d] One study without evaluable data for IVIG dose as related to pneumonia not included in this pooled estimate [4–6].

[e] >75% of patients in study with CVID.

27.9 days). With adjustment for treatment interval, the median administered dose of IVIG was 492 mg/kg (IQR, 328–529 mg/kg) per 28 days. Individual study IVIG dose and pneumonia incidence data are presented in the online supplementary material.

Each additional 100 mg/kg dose increment was associated with a significant reduction in pneumonia incidence (IRR, 0.726; CI, 0.649–0.812), as displayed in Fig. 4. No trend toward sparser data was apparent within any part of the IVIG dose range covered in Fig. 4.

IRR for pneumonia in relation to IVIG dose was comparable between study designs and sizes and PIDD types (Table 3). The impact of excluding the study with 10 subclass deficiency patients [31] was negligible (IRR, 0.727; CI, 0.642–0.823).

Discussion

The long-term goal of IVIG replacement therapy in PIDD is to reduce the incidence of infection and prevent as many serious infections as possible. By preventing pneumonia, IVIG therapy can also reduce its attendant complications, such as bronchiectasis and progressive lung disease.

This is the first meta-analysis to quantify the relationship between pneumonia incidence and IgG trough levels in PIDD patients with antibody deficiency. A progressive decline was shown in pneumonia incidence with increasing IgG trough levels up to at least 1000 mg/dL. Dose increments up to at least 600 mg/kg were also associated with diminished pneumonia incidence.

A common clinical approach is to individualize treatment, identifying the IgG trough level or "biological IgG level" that is effective for a given patient [12]. After attaining the general target trough levels that have been recommended [1], dosage can be adjusted upward as needed to minimize infection in that patient [9,37]. Ultimately, immunoglobulin replacement therapy for a given patient needs to be individualized.

Despite more than 30 years of experience with IVIG, the optimal range of IgG trough levels needed to minimize infection in most patients has remained uncertain. While 500 mg/dL emerged from early studies as an appropriate initial minimum trough target, subsequently accumulated clinical evidence has prompted recommendations for higher targets, generally to levels approaching or exceeding the lower limit of IgG concentration for normal healthy adults, which is approximately 700 mg/dL [38]. Thus, target trough levels of >800 mg/dL [1] and 650–1000 mg/dL [11] have been recommended in contemporary clinical guidelines. An expert panel convened by the European Medicines Agency recognized the value of 600–900 mg/dL trough levels compared with 550–650 mg/dL in preventing infection (www.emea.europa.eu/pdfs/human/bpwg/36185706en.pdf)[2]. In a recent evidence-based practice guideline from Canada, maintenance of a 700 mg/dL minimum trough level was the consensus recommendation [39]. These recommendations of higher trough levels are supported by this meta-analysis, since the incidence of pneumonia associated with 500 mg/dL trough levels was 5-fold that with 1000 mg/dL.

Clinical strategies to minimize pneumonia are expected to help in preventing pulmonary morbidity. A feared complication of recurrent pneumonia is bronchiectasis, a major cause of progressive chronic lung disease in PIDD patients [40]. Higher IgG trough levels may be of value in preserving lung function even in the absence of overt infections, particularly in patients with existing chronic lung disease and detectable structural damage to the lung [13]. Forced vital capacity and forced expiratory volume in 1 s (FEV_1) have been shown to be significantly greater in PIDD patients with chronic lung disease receiving high dose IVIG (600 mg/kg) vs. low dose (200 mg/kg) [6]. In a study of serial lung function tests among PIDD patients, changes in FEV_1 increased linearly with IgG trough level over the evaluated range of 800–1100 mg/dL [41].

While in the present study only the incidence of pneumonia was analyzed, the advantages of higher trough levels do not appear to be restricted to one particular type of infection. For example, in a retrospective study of 31 agammaglobulinemia patients, the annual incidence of bacterial infections requiring hospitalization was zero when the IgG trough exceeded 800 mg/dL compared to ~0.05 at 500–800 mg/dL and ~0.2 for <500 mg/dL [14]. In a randomized trial of two IVIG products, the incidence of validated infections during maintenance of IgG trough levels >900 mg/dL was 13.6%, compared with 18.6% at 700–900 mg/dL and 20.9% with <700 mg/dL [42]. At the present time, pneumonia is the only type of serious infection for which available data allow a meta-analysis on the impact of IgG trough levels. Further clinical data are needed to delineate that impact on other infection endpoints.

[2] This weblink was valid as of July 2010.

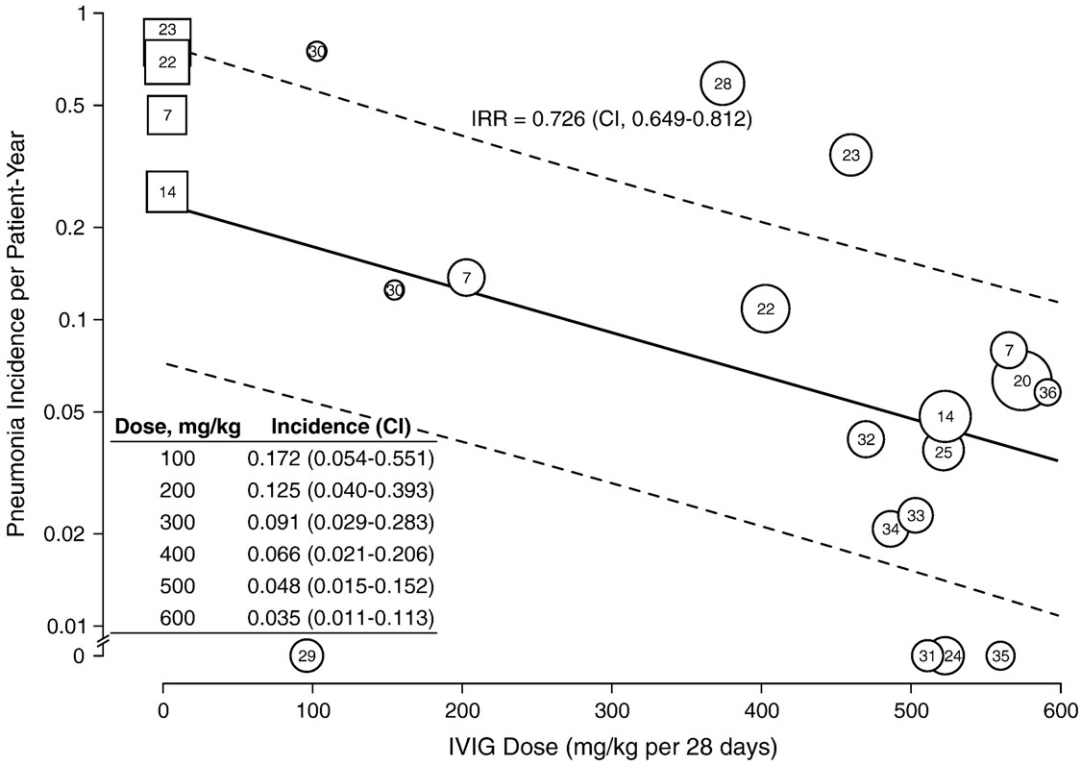

Figure 4 Effect of IVIG dose (mg/kg per 28 days) on pneumonia incidence per patient-year. Graphic conventions as in Fig. 2. Abbreviations: CI, 95% confidence interval; IRR, incidence rate ratio per 100 mg/kg increase in IVIG dose; IVIG, intravenous immunoglobulin.

The validity and interpretation of a meta-analysis depend in part on the quality and homogeneity of the included studies. Table 3 presents sensitivity analyses that provide reassurance in both respects. In higher quality studies, as judged by prospective design, the magnitude of reduction in pneumonia incidence with increments in IgG trough and IVIG dose was similar to that in retrospective studies. Differing PIDD types could be a potential source of heterogeneity; however, the impact of trough and dose on pneumonia was also comparable among patient populations predominantly with CVID vs. exclusively with XLA or other hypogammaglobulinemia, as well as mixed PIDD types.

Although inter-individual variation is noteworthy among patients with CVID, average pretreatment trough IgG levels in CVID populations are generally higher than those in XLA or agammaglobulinemia. It is possible that the incremental response to IVIG therapy might differ between patients with higher vs. lower pretreatment IgG trough levels. As indicated in Table 3, however, the meta-analysis did not support that proposition. Thus, among CVID patients the rates of decrease in pneumonia incidence in relation both to increasing trough IgG level and IVIG dose, as quantified by IRR, were comparable to those in studies of XLA or agammaglobulinemia.

This meta-analysis was designed to determine the relationship between trough IgG level and pneumonia incidence rather than possible differences in effectiveness between IVIG products. Examples of product differences that could theoretically affect efficacy include the many different manufacturing methods used to isolate IgG, or the geographic origin of plasma donors. It was assumed that the trough IgG-pneumonia relationship would be independent of product differences. However, it was not feasible to test this assumption directly, since there have been neither head-to-head comparison trials of different IVIG preparations (with reported product-specific trough levels) evaluating pneumonia as an efficacy endpoint nor multiple studies of the same products with pneumonia and trough data (Table 1).

Unexpectedly, the meta-analysis failed to reveal a threshold IgG trough up to at least 1000 mg/dL above which patients were completely protected against pneumonia. This finding supports the clinical observations that in general higher trough levels well into the normal range for IgG continue to provide significant added protection against serious infections. Hence, increasing the trough level either by decreasing the dosing interval or increasing the dose size until a patient is no longer experiencing pneumonia would be an evidence-based practice. Additional research, however, is needed to determine whether a general threshold trough of optimal protection against pneumonia may exist above 1000 mg/dL. Given the higher trough levels that are becoming commonplace in contemporary immunoglobulin replacement therapy, it is likely that such additional data may be available in the future. The present observations, however, do allow the conclusion that PIDD patients receiving IVIG therapy and experiencing pneumonia are likely to be helped by increasing the IgG trough levels to at least the mid-normal range of IgG.

Conflict of interest statement

J.S.O. is a consultant to Baxter Healthcare Corp as well as to other major manufacturers of polyclonal immunoglobulin including Talecris Biotherapeutics and CSL Behring. He is also on the research grants review panel for Octapharma and the scientific advisory board for IBT reference laboratories. W.J. G. is presently a full-time employee of Baxter Healthcare. R. J.N. and M.M.W. received funding from Baxter Healthcare for this meta-analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clim.2010.06.012.

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