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ORIGINAL ARTICLE

A Systematic Review and Meta-regression Analysis on the Impact of Increasing IgG Trough Level on Infection Rates in Primary Immunodeficiency Patients on Intravenous IgG Therapy

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Abstract

Purpose We conducted a systematic review and meta-regression analysis to evaluate the impact of increasing immunoglobulin G (IgG) trough levels on the clinical outcomes in patients with PID receiving intravenous immunoglobulin G (IVIG) treatment.

Methods Systematic search was conducted in PubMed and Cochrane. Other relevant articles were searched by reviewing the references of the reviewed article. All clinical trials with documented IgG trough levels and clinical outcome of interest in patients receiving IVIG treatment were eligible to be included in this review. Meta-regression analysis was conducted using Comprehensive Meta-analysis Software. Additional sensitivity analyses were undertaken to evaluate the robustness of the overall results.

Results Twenty-eight clinical studies with 1218 patients reported from year 2001 to 2018 were included. The mean IVIG dose used ranges from 387 to 560 mg/kg every 3 to 4 weekly, and mean IgG trough obtained ranges from 660 to 1280 mg/dL. Random-effects meta-regression slope shows that IgG trough level increases significantly by 73 mg/dL with every increase of 100 mg/kg dose of IVIG ($p < 0.05$). Overall infection rates reduced significantly by 13% with every increment of 100 mg/dL of IgG trough up to 960 mg/dL ($p < 0.05$).

Conclusion This meta-analysis concludes that titrating the IgG trough levels up to 960 mg/dL progressively reduces the rate of infections, and there is less additional benefit beyond that. Further studies to validate this result are required before it can be used in clinical practice.

Keywords Primary immunodeficiency · IVIG · IgG trough · infection rates · clinical outcomes

Introduction

Inborn error of immunity (IEI), historically known as primary immunodeficiency (PID), is a heterogeneous group of disorders caused by genetic defects in the cells of the immune system [1]. It has a prevalence of 1:1200 to 1:25,000 depending on the population being studied [2–8]. The most common and clinically significant type of PID, which accounts for 50 to 70% of them, is the predominantly antibody deficiency (PAD) [6, 9, 10]. This group of patients needs regular immunoglobulin G (IgG) replacement, and without it, they could die from simple infection [9, 11]. Hence, providing a balance of safe and cost-effective therapy is important for this life-long condition.

IgG, also known as normal human immunoglobulin, is a treatment of choice for patients with antibody deficiencies. It is made from fractionated blood products from pooled human plasma; hence, each IgG treatment uses a unique biological medicinal product [12]. IgG can be administered via

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intravenous or subcutaneous route. Both routes have been regarded as therapeutically equivalent, and the choice of route depends on several factors including patient's characteristics, venous access, treatment compliance, and patient preference [10]. The route of administration also depends on the availability of the preferred formulation in the center [13].

Although the subcutaneous route is gaining popularity, the intravenous route of administering IgG is still the most common mode of IgG replacement therapy [7, 11]. Intravenous immunoglobulin G (IVIG) replacement doses of 300–800 mg/kg is given every 3–4 weekly at an infusion rate of 0.01–0.08 mL/kg/min as tolerated by the patient [14–16].

Adverse events are common with IVIG treatment, and the incidence rates varied across studies from 2.4 to 12.8% of infusions. The severity also varies from mild reactions, which do not require cessation of therapy to severe reactions requiring stopping the infusion and immediate medical attention [15, 17–20]. Common adverse events that occur with IVIG such as headache, fever, nausea, chills, malaise, and injection site reactions are usually due to fast infusion rate and high dose [17, 18].

According to current practice guideline, the adequacy of IVIG replacement therapy is determined by the IgG trough (pre-infusion level) at steady state in relation with the patients' clinical response [14]. However, the optimal IgG trough level, which is used as a surrogate marker for IgG efficiency, is still not clear. Data from earlier studies have recommended that an IgG trough target of above 500 mg/dL should confer sufficient defense against serious infection [12]. Subsequently, clinical evidence suggested for higher targets; thus, trough levels of 600 to 900 mg/dL [2], 650 to 1000 mg/dL [21], and above 700 mg/dL [22] have been recommended. Meta-analysis performed by Orange et al. (2010) showed that higher IgG trough of up to 1000 mg/dL was associated with lower infection rates [23] while a recent meta-analysis by Shrestha et al. (2019) showed no relationship between IVIG trough and infection rates [24]. These conflicting results as to the actual effectiveness of the higher IgG trough and the reduction of infection rates are likely due to the diverse study inclusion criteria and the use of different routes of administration. Thus, an evidence-based answer to the main question of reduction in infection rates and improved clinical outcome with higher doses of IVIG, like previously reported [23, 25–28], now appears to be controversial [24].

We conducted a meta-analysis to pool data from multiple studies to assess the effect of increasing IgG trough level on the ability to prevent breakthrough infection. We also undertook an additional breakpoint analysis that aim to answer the following question: is there a target IgG trough beyond which additional IgG replacement ceases to provide additional protection against infection?

Methods

We performed a systematic review in accordance with the PRISMA guidelines [29]. A literature search was conducted to find any papers that reported concentrations following IVIG administration in PID patients. Search terms were derived from four main ideas or keywords: "immunoglobulin", "pharmacokinetic", "infection", and "primary immunodeficiency". Then, a list of search terms associated with each key word was generated from the Medical Subject Headings (MeSH) terms in PubMed. Clinical studies from year 2000 to mid-August 2019 were searched from PubMed and Cochrane. Other relevant articles were searched by consulting other reviews and meta-analyses on the subject and reviewing the references of the reviewed articles. We focus our review on studies from year 2000 onwards as this was when the Food and Drug Administration (FDA) Blood Products Advisory Committee (BPAC) outlined and standardized the clinical trial design to evaluate the safety and efficacy of new IVIG product in PID [30]. The standardization of clinical trial protocols enables results from different studies to be compared [31].

Inclusion and Exclusion Criteria

We included studies that (1) involved PID patients on immunoglobulin G therapy; (2) studies that reported any of our a priori outcomes, namely infections, missed school or work days, hospitalizations, antibiotic use for treatment, and adverse drug reactions; and (3) studies published from year 2000 onwards. We excluded studies which (1) did not report the use of IVIG, (2) had no documentation of IgG trough levels, (3) studies that were published other than English, and (4) studies that reported exclusively in abstract form and conference proceedings.

Study Selection/Data Extraction

Initial screening by title and abstract was done by two investigators (LJL and NMS). Irrelevant articles and duplicates were removed. Full-text manuscript of potentially relevant articles was evaluated. Information extracted from full-text article was recorded in a data collection form, which includes information on brand/preparation of IgG, manufacturing and production processes, pharmacokinetic profile, efficacy, and safety assessment by two investigators (LJL and NMS). Any discrepancies observed were resolved through discussion. When discrepancies could not be resolved, a third investigator (SMS) was consulted.

The following study characteristics were extracted: author, year, journal/source, preparation used, total patients enrolled, number of patients enrolled for pharmacokinetic studies, and duration of study. The following summary of patients' characteristics was extracted: mean age, types of PID, mean dose,

and dose intervals. The following outcomes were extracted: summary of pharmacokinetic parameters including IgG trough and peak serum IgG concentration (Cmax); summary of efficacy outcome measures including the rate of serious bacterial infection (event/patient/year), other infection (event/patient/year), missed school/ work (days/patient/year) due to infection, hospitalization (days/patient/year) due to infection and antibiotic use as treatment (days/patient/year); and summary of safety outcomes.

Quality Assessment

The quality of the included studies were formally assessed by two investigators (LJL and NMS) using the Methodological Index for Non-randomized Studies (MINORS) scale [32] for non-comparative, non-randomized cohort studies. The Methodological Index for Non-randomized Studies (MINORS) scale has eight criteria for non-comparative studies with total score of sixteen. Two points are given for criteria which reported adequate information, one point if reported but inadequate, and no points given if criteria were not reported. The quality score for each study included in this systematic review is shown in Table 1. Any disagreement was resolved by a third investigator (SMS).

Data Syntheses

Due to the unavailability of individual patient data, aggregated data was used in analysis. Only data for total IgG was used for analysis and not the IgG subtypes. Where measures were available only in graphical format, the software WebPlotDigitizer developed by Ankit Rohatgi [61] was used to extract the relevant data. All data were converted to the same units of measurement (i.e., mg/dL, incidence or days per patient per year).

When data were reported in median and range, the mean and standard deviation (SD) (or variance) were calculated according to the method devised by Hozo et al. [60]. When confidence interval for group means is reported, SD was calculated according to the formula given in the Cochrane Handbook for Systematic Reviews of Interventions [62]. When more than one route of administration was investigated, only the data pertaining to IVIG was used. Where studies had more than one intervention group or had analyzed their results in smaller subgroups (i.e., 3 or 4 weekly dose intervals, age group), the data were analyzed separately. Where the information was available, data on doses were normalized to dose per kilogram per 4 weeks.

Statistical Analysis

Meta-analyses for a particular clinical outcome were performed using Comprehensive Meta-analysis software Version 3.0 (trial version) [63]. The event rate of all the clinical outcomes measures (infections, serious bacterial infections, missed school or work days, hospitalization, and antibiotic use for treatment) was pooled. The corresponding 95% confidence intervals (CI) of pooled effect size were also calculated using random-effects model. Random-effects model was applied in our analysis as we assume that there was significant heterogeneity within and between studies [64]. The presence of publication bias was evaluated by visual assessment of funnel plots.

IgG trough was meta-regressed with the five clinical outcomes measured. They were meta-regressed individually and if any of the covariate were found to be significant, they were meta-regressed together. The effect of covariates on the effect size was considered significant when the p value was < 0.05. The random-effects meta-regression used the Method of Moments (DerSimonian and Laird) to measure the true between-study variance (τ^2) with a Knapp-Hartung modification. Statistical significance was set at p value < 0.05.

Additional breakpoint analysis was conducted in all included studies to investigate the influence of increasing IgG trough levels on incidence rate of infection. For this analysis, segmental regression on the rate of infection was plotted against IgG trough levels using GraphPad Prism Version 8 for Windows [65]. The slope of the second line was set to 0 to determine breakpoint (biphasic regression). Data for breakpoint is presented as mean and 95% CI. This method had been described previously by Morton et al. (2018) and Wagner et al. (2002) [66, 67]. After obtaining breakpoint value, it is used as a cutoff IgG trough level and meta-regression was conducted again to determine the impact of increasing IgG trough up to breakpoint value, on the incidence of infection rates. Significance was set at $p < 0.05$.

Subgroup and Sensitivity Analyses

To evaluate the validity and interpretation of the meta-regression analysis, subgroup analyses were performed by comparing (1) studies with small and large sample size (< 40 and ≥ 40 subjects), (2) studies with children only population and mixed population, (3) studies with follow-up period of more and less than 12 months, and (4) studies with specific type of PID or mixed. Sample size of less than 40 is considered small. This is in accordance with the recommendation by the FDA Blood Products Advisory Committee (BPAC), whereby sample size of 40 to 50 subjects would generally prove adequate power for the evaluation of efficacy [30]. The difference in subgroup is considered statistically significant if there is a non-overlap of the confidence intervals of the pooled estimates in the two groups [62].

Subsequently, sensitivity analysis was conducted for the primary outcome (rate of infection with increasing IgG trough levels) if the pooled data from any of the planned subgroup analysis shows significant difference compared to the pooled data of the primary analysis.

Table 1 Characteristics of studies included

Author, year [reference]	Preparation used	Mean age (range)	Subjects in outcome analysis, *n*	Subjects with measured IgG trough, *n*	Types of PID, *n*			Dosing interval		Score*
					CVID	XLA	Others	3 weeks, *n*	4 weeks, *n*	
Eijkhout et al., 2001 [25]	Immunoglobulin I.V., Standard dose	29.9 (1.6–70.3)	41	41	24	19	–	25	8	15
	Immunoglobulin I.V., High dose	29.9 (1.6–70.3)	43	43						
Ochs et al., 2004 [33]	Octagam 5%	31 (6–74)	46	14	28	13	5	19	27	13
Berger et al., 2004 [34]	Flebogamma 5%	38.2 (14–74)	51	21	37	12	2	15	36	14
Church et al., 2006 [35]	Gammagard Liquid 10%	34.0[a] (6–72)	61	57	41	5	15	–	–	15
Berger, 2007 [36]	Flebogamma 5% DIF	38.9 (15–75)	46	20	35	10	1	13	33	14
Berger et al., 2007 [37]	Carimune NF Liquid	32 (4–66)	42	42	32	10	–	19	23	13
Wasserman et al., 2009 [38] and Stein et al., 2009 [39]	Privigen 10%	28 (3–69)	80	25	59	21	–	16	64	16 14
Church et al., 2009 [40]	Privigen 10%	9 (3–15)	31	31	18	13	–	6	25	12
Moy et al., 2010 [41]	Gammaplex 5%	44.0 (9–78)	50	24	46	4	–	22	28	13
Berger et al., 2010 [42]	Flebogamma 10% DIF	36.8 (6–65)	46	19	37	8	1	16	30	14
Wasserman et al., 2010 [43]	Gamunex-C 10%	44[a] (13–68)	32	32	NA	NA	NA	NA	NA	11
Kreuz et al., 2010 [44]	Intratect 5%	15[a] (6–48)	51	17	20	12	19	3	48	14
Jolles et al., 2011 [45]	NA	21.5 (3–60)	27	27	28	17	1	NA	NA	12
van der Meer et al., 2011 [46]	Nanogam 5%	> 18	18	18	12	6	–	NA	NA	13
Wasserman et al., 2012 [47]	Gammagard 10% Liquid/Kiovig 10%	35[a] (4–78)	87	68	49	6	32	NA	NA	15
Wasserman et al., 2012 [48]	Biotest-IVIG/Bivigam 10%	41.2 (6–75)	58	21	51	6	6	17	46	12
Bezrodnik et al., 2013 [49]	NA	11.6 (5.2–17.2)	13	13	5	3	5	NA	NA	11
Melamed et al., 2016 [50]	Gammaplex 5%	10.4 (3–16)	25	23	22	3	–	14	11	14
Ballow et al., 2016 [51]	Flebogamma 5% DIF	9.0 (2–16)	24	19	14	7	3	14	10	14
Borte et al., 2016 [52]	Kiovig 10%	17[a] (2–67)	33	16	32	9	8	0	16	15
Suez et al., 2016 [53]	Gammagard Liquid 10%	36[a] (3–83)	77	69	26	9	42	16	38	14
Wasserman et al., 2016 [54]	Asceniv 10%/ RI – 002	41.8 (3–73)	59	30	46	6	7	10	20	13
Viallard et al., 2017 [55]	Tegeline 5%	41.9 (22.9–61.6)	22	22	18	3	1	7	15	14
	ClairYg 5%	41.9 (22.9–61.6)	22	22	18	3	1	7	15	14
Krivan et al., 2017 [56]	IqYmune 10%	27.4 (2–61)	62	28	42	20	–	5	57	14
Borte et al., 2017 [57] and Melamed et al., 2018 [58]	Panzyga 10%	26.8 (2–75)	51	51	43	8	–	21	30	15 13
Ochs et al., 2018 [59]	Panzyga 10%	< 16 (2–15)	25	25	20	5	–	13	12	13

PID primary immunodeficiency, *XLA* X-linked agammaglobulinemia, *CVID* common variable immune deficiency, *NA* not available

[a] Calculated mean using the formula by Hozo et al. [60]

*MINORS score for quality assessment of non-randomized studies

Results

The study selection process was based on PRISMA guidelines as depicted in Fig. 1. A total of 191 studies have been identified. Twenty-eight were duplicate articles, 163 articles have been screened for title and abstract, and 80 deemed to be potentially eligible. We excluded 51 studies for the following reasons: no data on population of interest, no IVIG data, review articles, no documentation on IgG trough, and no clinical outcome of interest and conference proceedings. Another one study was excluded because of different methods of reporting outcomes, i.e., authors reported as monthly rates instead of annualized rates [68]. Data of 1218 patients from 28 articles were included in the systematic review analysis.

The meta-analysis included data from adult and pediatric patients with various types of PID for example X-linked agammaglobulinemia (XLA) and common variable immunodeficiency (CVID). Summary of the characteristics of studies included is shown in Table 1. Twenty-eight clinical studies reported from year 2001 to 2018 were included (Tables 1 and 2). The sample size ranges from 13 to 87 patients. All, except 5 studies [43, 46, 47, 52, 55], had an observational period of 12 months to avoid seasonal bias, as it has been shown that the rate of infections is the highest in the winter months [30]. Most of the patients received 4-weekly dosing (Table 1).

The types of PID included in each study are shown in Table 1. Across all the studies, common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA) were the most frequent type of PID, accounting for 65.9% (775/1176) and 18.7% (220/1176), respectively, of all the patients included in the analysis. Other types of PID account for 15.4% (181/1176) of the study population.

IgG Trough on Clinical Outcomes

This systematic review included data from 1218 patients with outcome analysis (i.e., serious bacterial infections, other infections, missed school or work days, hospitalization, and antibiotic use) of which, 818 (66.8%) of them have documented IgG trough levels. The mean (± standard deviation) dose used in the clinical studies ranges from 387 ± 88 to 560 ± 170 mg/kg. The mean IgG trough and Cmax gathered from all the clinical studies in this systematic review ranges from 660 ± 160 to 1280 ± 320 mg/dL and 1010 to 2709 ± 552.7 mg/dL. Random-effects linear regression slope showed that IgG trough level increases significantly by 73 mg/dL with every

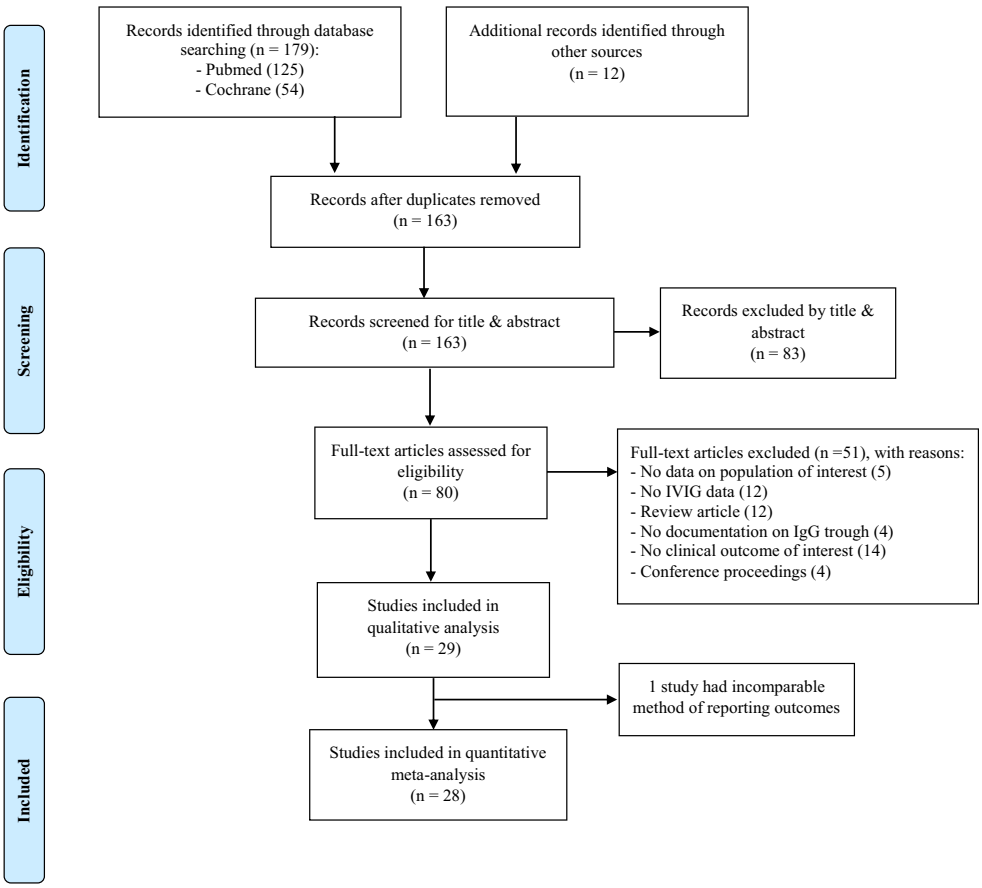

Fig. 1 Flow chart of study selection process (flow chart adapted from PRISMA) [29]

Table 2 Summary of eligible studies with the corresponding pharmacokinetic parameters and outcomes measured

Author, year [reference]	Mean dose ± SD (mg/kg/dose)	Infusion rate, mean ± SD (mL/kg/h, range)	IgG trough, mean ± SD (mg/dL)	Cmax, mean ± SD (mg/dL)	Efficacy					Overall adverse event [related to treatment], mean (UCI)
					Serious bacterial infection	Other infection	Missed school/ work	Hospitalization	Antibiotic use	
Eijkhout et al., 2001 [25]	Standard dose: Adult: 300 mg/kg/4 weeks Children: 400 mg/kg/4 weeks	NA	660 ± 160	NA	NA	4.67	NA	NA	78.05% of patients	[4.40%]
Eijkhout et al., 2001 [25]	High dose: Adult: 600 mg/kg/4 weeks Children: 800 mg/kg/4 weeks	NA	940 ± 270	NA	NA	3.33	NA	NA	60.47% of patients	[6.49%]
Ochs et al., 2004 [33]	300–450 mg/kg/3 weeks 400–600 mg/kg/4 weeks	NA	871 766	1489[a] 1815[a]	0.1 (98% CI 0.033–0.279)	NA	5.29	0.32	NA	23% [5%]
Berget et al., 2004 [34]	583.33 mg/kg/4 weeks	NA	700[a]	1844.5 (SE 583.7)	0.061	NA	7.83	0.87	NA	[8.2% (10.1%)]
	427.0 mg/kg/4 weeks		866[a]	1900.0 (SE 572.3)						
Church et al., 2006 [35]	455 ± 112 mg/kg[b]/ 3–4 weeks	4.3 [4.0–5.0]	1009 ± 206.4[a]	2050[b] (95% CI 1980, 2200)	0 (95% CI from 0 to 0.060/year)	3.46	NA	0	NA	20.72%
Berger et al., 2007 [36]	598.67 mg/kg/4 weeks	NA	951 ± 132	1929 ± 441 (range 1300–2420)	0.021	1.96	12.95	0.77	55.52 (Treatment)	[11.6% (15.6%)]
	449 mg/kg/4 weeks		900 ± 92	2069 ± 338 (range 1590–2800)						
Berger et al., 2007 [37]	682.27 ± 161.67[c] mg/kg/4 weeks	Mean infusion time: 3.1 h (range 1.9–5.4)	1155[a]	NA	0	3.65	5.61	0.85	93.0 (treatment + prophylaxis)	32.5% (39.45) [21.7% (27.5%)]
	478.2 ± 130.55[c] mg/kg/4 weeks		870[a]	NA						
Wasserman et al., 2009 [38] and Stein et al., 2009 [39]	450.7 ± 128.5[b] mg/kg/4 weeks	Starting 4th infusion onwards, 86% of the infusions were given at the maximum rate of 8 mg/kg/min	1023 ± 223[b]	2295 ± 605[b] Median: 2340 (range 1040–3460)	0.08 (upper one-sided 97.5% CI = 0.182)	3.55	7.94	2.31	87.4 (treatment + prophylaxis)	21.8% [9%]
Church et al., 2009 [40]	Children 3–11 years old 487.8 ± 135.2[b] mg/kg/4 weeks	Maximum infusion rates of 8 mg/kg/min were use in 30/31 patients	910 ± 221[b]	NA	0.12 (upper one-sided 97.5% CI = 0.429)	4.63 (upper one-sided 97.5% CI = 5.78)	11.51	0.53	47.88 (treatment + prophylaxis)	22.1% (26.2%) [suspected to be product related: 6% (8.9%)]
	Adolescent 12–15 years old 465.8 ± 100.3[b] mg/kg/4 weeks		1042 ± 165[b]		0.10 (upper one-sided 97.5% CI = 0.539)	2.42 (upper one-sided 97.5% CI = 3.57)	4.83	0	56.64 (treatment + prophylaxis)	
		NA	1071[a]	1892.3 ± 267.7	0	3.28 (SD 3.024)				

Table 2 (continued)

Author, year [reference]	Mean dose ± SD (mg/kg/dose)	Infusion rate, mean ± SD (mL/kg/h, range)	IgG trough, mean ± SD (mg/dL)	Cmax, mean ± SD (mg/dL)	Efficacy					Overall adverse event [related to treatment], mean (UCI)
					Serious bacterial infection	Other infection	Missed school/ work	Hospitalization	Antibiotic use	
Moy et al., 2010 [41]	625.33 ± 121[c] mg/kg/4 weeks 466.2 ± 116[c] mg/kg/4 weeks		904[a]	1892.3 ± 267.7			8.73 (SD 34.41)	4 patients were hospitalized	108 courses of therapeutic antibiotics in 33 patients	19.5% (22.1%) by 48 h and 23.9% by 72 h
Berger et al., 2010 [42]	614.68 mg/kg/4 weeks 461 mg/kg/4 weeks	0.08 mL/kg/min (4.8 mL/kg/h)	976 ± 165 877 ± 126	1950 ± 283 2092 ± 366	0.025	2.2	3.0	0.6	56.4 (treatment)	27.6%
Wasserman et al., 2010 [43]	200–600 mg/kg/ 3–4 weeks	NA	960 ± 210	2110 ± 390	0	2.0	N/A	N/A	N/A	25%
Kreuz et al., 2010 [44]	387 ± 88 mg/kg/ 3–4 weeks	2.4 mL/kg/h (1.0–5.9)	854[a]	1510 ± 310 Median (range): 1480 (1040–213-0)	0.02 (one-sided 99% confidence interval (CI) = 0·00–0·11)	2.0	3.92 (SD 7·04)	0.35 (SD 1·47)	32.12 (SD 47·17) (treatment)	13.1% (15.48%)
Jolles et al., 2011 [45]	N/A	NA	678 ± 132.9	NA	0 (upper 99% confidence limit 0.351)	3.35 (95% CI 2.435–4.499)	4.58	1.70	22.17 (treatment)	NA
van der Meer et al., 2011 [46]	150–400 mg/kg/ 2–5 weeks	6.8 mL/kg/h	680 ± 120	1010	0.60	3.11	N/A	1.43	35 antibiotic courses (in 14 patients)	24.7%
Wasserman et al., 2012 [47]	N/A	Median (range): 246 mL/h (60–668) 3.86 mL/kg/h	1040 ± 365.6[b]	2190[b] (95% CI 2070–2390)	0	4.51 (95% CI, 3.50–5.69)	0.23	0.06	3.15 (treatment + prophylaxis)	20.7% (25%)
Wasserman et al., 2012 [48]	666.67 ± 258.33 mg/kg/4 weeks 500 ± 193.75[c] mg/kg/4 weeks	> 80% of patients able to tolerate at a rate of ≥ 3.0 mL/kg/h 49.6% able to tolerate at a rate of ≥ 3.5 mL/kg/h	1076 ± 254 943 ± 215	2184 ± 4293 2122 ± 425	0.035	2.6	2.28	0.21	39.1 (treatment)	27.7% (30.6%)
Bezrodnik et al., 2013 [49]	556 mg/kg/4 weeks	NA	960.2 ± 542.4	NA	0	1.4	NA	NA	NA	7.69%
Melamed et al., 2016 [50]	545 ± 65[c] mg/kg (429–689)/3 weeks 521 ± 121[c] mg/kg (316–800)/4 weeks	NA	953 ± 65	NA	0.09 (upper one-sided 99% CI = 0.36)	3.2 (SD 2.7)	4.2 (SD 8.28)	0.45	32.0 (SD 28.28) (treatment)	26.4% (30.4%)
Ballow et al., 2016 [51]	471.8 ± 99.7 mg/kg/3 weeks 432.8 ± 97.9 mg/kg/4 weeks	NA	800–1000	NA	0.051 (one-sided 99% upper confidence interval 0.0526)	1.4 (SD 3.0)	6.2 (SD 17.7)	0.2 (SD 1.1)	19.6 (SD 35.1) (treatment)	(30.3%)

Table 2 (continued)

Author, year [reference]	Mean dose ± SD (mg/kg/dose)	Infusion rate, mean ± SD (mL/kg/h, range)	IgG trough, mean ± SD (mg/dL)	Cmax, mean ± SD (mg/dL)	Efficacy					Overall adverse event [related to treatment], mean (UCI)
					Serious bacterial infection	Other infection	Missed school/ work	Hospitalization	Antibiotic use	
Borte et al., 2016 [52]	Pre-study dose every 3–4 weeks	NA	720 ± 175.6	NA	0	6.29 (95% CI 4.20–8.99)	10.69 (95% CI 5.34–18.78)	0.12 (95% CI 0.04–0.26)	19.59 (95% CI 12.59–28.80) (treatment + prophylaxis)	Rate of AE/infusion: 0.712 event/infusion
Suez et al., 2016 [53]	3 weeks	NA	1158 ± 267.6	2709 (95% CI 2430–3019)	0	3.86 (95% CI 2.77–5.22)	3.20 (95% CI 1.88–5.03)	0.20 (95% CI 0.08–0.42)	63.2 (95% CI 43.39–88.29) (treatment + prophylaxis)	NA
	4 weeks		1019 ± 233.9	2485 (95% CI 2318–2664)						
Wasserman et al., 2016 [54]	3 weeks	95.8% of the infusions administered at the maximum allowed rate of 8 mg/kg/min. Infusion rate ranges from 0.5 to 13.3 mg/kg/min	1152 ± 308	2427 ± 452	0	3.584 (one-sided 95% 4.417)	1.56 (one--sided 95% 2.14)	0	41.2 (treatment)	12.2% (15.6%)
	4 weeks		954 ± 245	2227 ± 584	0	3.370 (one-sided 95% 3.893)	1.71 (one--sided 95% 2.09)	0.026	29.2 (treatment)	15.4 (18.2%)
Viallard et al., 2017 [55]	Tegeline 444.5 ± 80.5 mg/kg every 3–4 weeks	2.46 mL/kg/h	802 ± 131	NA	0	4.35	8.8 (95% CI 6.4, 11.9)	0	27.3% of patients	Rate of AE/infusion: 0.080 event/infusion
	ClairYg 444.5 ± 80.5 mg/kg every 3–4 weeks	2.65 mL/kg/h	912 ± 170	NA	0	4.3	0.3 (95% CI 0.1, 0.9)	0	59.1% of patients	Rate of AE/infusion: 0.090 event/infusion
Krivan et al., 2017 [56]	560 ± 17 mg/kg/4 weeks	4.88 ± 1.89 mL/kg/h	773 ± 236	1810	0.017	3.79 (SD 3.62)	1.01 (SD 3.6)	0.89 (SD 3.3)	19.5 (SD 26.8) (treatment)	15.5% (18.3%)
Borte et al., 2017 [57] and Melamed et al., 2018 [58]	693.33 mg/kg/4 weeks 453 mg/kg/4 weeks 485 mg/kg/3–4 weeks	Maximum infusion rate of 0.08 mL/kg/min was used in 90.1% of infusions	1280 ± 320[b] 820 ± 320[b] 930 ± 355[b]	NA	0.080 (one-sided 99% CI, upper limit 0.503)	3.68 (one-sided 95%CI, upper limit 0.5.12)	3.64	0.080	Overall: 82.4% of patients	5.1%
Ochs et al., 2018 [59]	Children 2–5.9 years old Mean dose: 535 mg/kg/3–4 weeks	0.136 mL/kg/min	820–990	1610–1930	0	6.7 (range 2.3–19.4)	7.4	0	24.5 (treatment + prophylaxis)	TAAE reported by 84% of patients
	Children 6–11.9 years old Mean dose: 497 mg/kg/3–4 weeks				0.1 (0.0098–1.0240)	3.8 (range 2.1–7.0)	3.2	0	121.3 (treatment + prophylaxis)	

Table 2 (continued)

Author, year [reference]	Mean dose ± SD (mg/kg/dose)	Infusion rate, mean ± SD (mL/kg/h, range)	IgG trough, mean ± SD (mg/dL)	Cmax, mean ± SD (mg/dL)	Efficacy					Overall adverse event [related to treatment], mean (UCI)
					Serious bacterial infection	Other infection	Missed school/work	Hospitalization	Antibiotic use	
	Adolescent 12–15.9 years old Mean dose: 484 mg/kg/3–4 weeks				0	3.7 (range 1.8–8.0)	6.7	0	151.8 (treatment + prophylaxis)	

Cmax: peak serum concentration, serious bacterial infection measured in mean event per patient-year, other infection measured in mean event per patient-year, missed school/work days measured in mean days per patient-year, hospitalization measured in mean days per patient-year, antibiotic used measured in mean days per patient-year

SD standard deviation, *NA* not available, *UCI* upper one-sided confidence interval

[a] Data extracted using WebPlotDigitizer [61]

[b] Calculated mean using the formula by Hozo et al. [60]

[c] Calculated SD using the formula by Higgins and Green [62]

increase of 100 mg/kg/4 weeks dose of IVIG (95% CI 11.090, 135.337) ($p = 0.02$) (Fig. 2).

According to FDA's requirement, the main evidence of efficacy of IgG therapy is less than one serious bacterial infection per patient-year [30]. Most if the clinical studies had less than one-tenth of the targeted rate. The pooled annual rate of serious bacterial infections was 0.023 (95% CI 0.013, 0.033). The annual rate of the other outcomes, i.e., other infections, days missed from school or work, and days of hospitalization, was also reviewed, and the pooled effect sizes with the 95% confidence intervals were 3.322 (2.964, 3.680), 5.180 (4.098, 6.261), and 0.346 (0.253, 0.439), respectively. Meta-regression analysis was applied to determine the effect of increasing IgG trough levels on effect size (i.e., other infections, missed school/work days, hospitalization days). Each plot in the graphs (Fig. 3) represents a single group of patients in a study. Note that 80% of the studies included have one group of patients per study for analysis. Random-effects meta-regression analysis showed declining trend of overall infection rates ($p = 0.21$), missed school or work days ($p = 0.08$), and hospitalization days ($p = 0.02$) with the increase of IgG trough (within the range of 6.8 to 12.8 g/L) (Fig. 3). Only hospitalization days were significant. The incidence of serious bacterial infection was too small to be evaluated statistically. Days on antibiotic use could not be analyzed because of inconsistency in reporting method. It was unclear if the reported data was antibiotic used as treatment or treatment and prophylaxis.

Segmented regression explained more variations between the measured infection rates and IgG trough levels. As in Fig. 4, the break point was identified to be at 960 (95% CI 826–1094) mg/dL, slope = − 0.006, $R^2 = 0.176$, df = 26. Using this break point value, random-effects meta-regression for all studies with IgG trough levels of 960 mg/dL and below showed a statistically significant decline in infection rates with increasing IgG trough levels from 660 to 960 mg/dL with p value of 0.018 (Fig. 5). Incidence rate ratio was 0.866 (95% CI, 0.862, 0.870), which implies a statistically significant 13% reduction in infection rates for each 100 mg/dL increment in IgG trough. The robustness of this observed outcome was assessed by performing subgroup analysis, followed by sensitivity analysis.

Subgroup analyses were performed separately for studies with small [40, 43, 45, 46, 49–52, 55, 59] and large sample sizes, children only population [40, 49–51, 59] and mixed age population, and studies with follow-up period of less [43, 46, 47, 52, 55] and more than 12 months (Table S1 in Online Resource). Subgroups on the types of PID could not be analyzed as all of the studies included were combined data of all types of PID. Among the 28 studies, 5 studies with a follow-up duration of less than 12 months [43, 46, 47, 52, 55] showed to have a significant difference on the pooled event rate across the outcomes analyzed compared to the primary analysis.

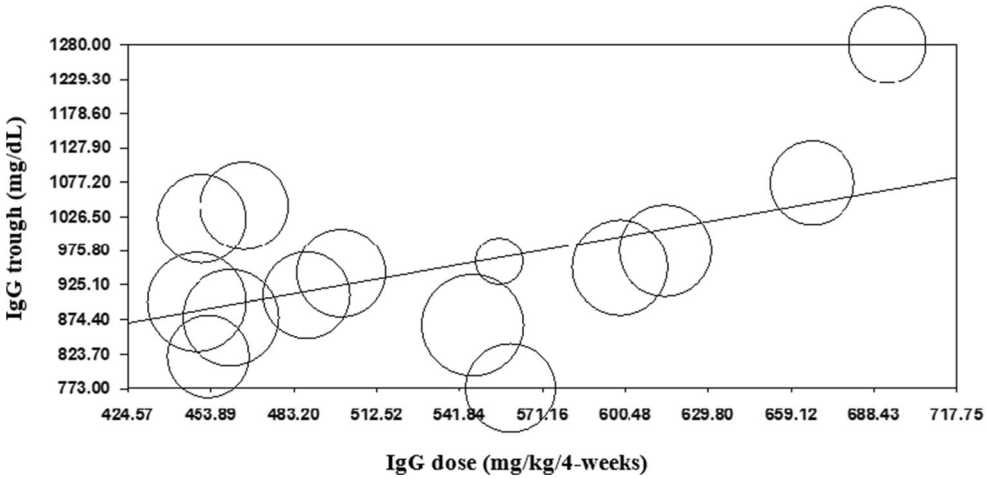

Fig. 2 Effect of IVIG dose (mg/kg/4 weeks) on IgG trough level (mg/dL). Each circle represents an aggregated data in a group of patients in an included study and the size of the circle is proportional to the study weights. Slope, $y = 0.73213x + 558.49$ ($p = 0.021$) (95% CI 0.11090, 1.35337). Trough IgG increase by 73 mg/dL with every increase of 100 mg/kg/4 weeks) of IVIG

Therefore, sensitivity analysis was performed by removing the 5 studies with less than 12 months of follow-up period. The exclusion of the 5 studies did affect the results in the primary analysis. Using the same break point value of 960 mg/dL, random-effects meta-regression showed a non-statistically significant decline in infection rates with increasing IgG trough levels from 660 to 960 mg/dL with p value of 0.0632. However, when applying fixed effect model for the same subset of data, the decline of infection rates with increasing IgG trough levels from 660 to 960 mg/dL was significant ($p < 0.001$) (Figure S1 in Online Resource).

The pooled event rate for adverse events is 0.22 (95% CI 0.192, 0.251) per infusion. Majority of the adverse events, such as headache, flushing, chills, fever, malaise, and pain at injection site, are transient and mild. Random-effects meta-regression also showed that increasing IgG trough, Cmax, and infusion rates did not significantly increase the risk of adverse events ($p = 0.58$, $p = 0.40$ and $p = 0.21$, respectively) (Fig. 6).

Discussion

IgG trough levels have been used to measure the adequacy of IgG replacement therapy in patients with PID [14]. With the current trend of using larger doses in order to attain higher IgG trough levels with the hope of reducing the rate of breakthrough infections to as minimum as possible, it is not clear what level of IgG trough to aim for in order to obtain maximal benefit with minimal risk. In this study, meta-regression analysis shows that clinical outcomes improved with increasing IgG trough. Importantly, we identified that the mean number of overall infection per patient-year has progressively reduced with increasing IgG trough up to 960 mg/dL and it reached a plateau beyond this level.

Overall, there was a decline in the rate of infections, acute serious bacterial infection, missed school or work days, and hospitalization days with increasing IgG trough levels (range 660 to 1280 mg/dL). However, the decline was not statistically significant for all outcomes except for hospitalization days. A meta-analysis by Orange and colleagues showed that the risk of pneumonia was significantly reduced with higher IgG trough levels up to 1000 mg/dL [23]. The difference in findings may be due to the inclusion of IgG levels before the commencement of IVIG therapy; hence, larger improvement was observed. Since then, many have aimed for higher IgG trough levels (above 1000 mg/dL) with the hope to minimize infection rates [47, 48, 53, 58]. In a recent meta-analysis conducted by Shrestha et al. (2019), they found no significant association between the IVIG trough range and infection rate [24]. Therefore, it remained unclear of the impact of increasing IgG trough on rate of infection. Given this observation, we applied a two-segment regression approach on the rate of infection against IgG trough to obtain a break point hypothetical IgG trough value which is able to give a significant reduction in infection rates. Using the data of 19 clinical studies which reported IgG trough of up to 960 mg/dL, it was found that increasing IgG trough from 660 to 960 mg/dL is able to reduce infection rates significantly ($p < 0.05$). Above that level, reduction in infection rates was not significant (Fig. 5). This observation is in agreement with Lucas et al., (2010), where the overall pooled data collected over two decades initially showed a reduction in infection rates from 2.8 ± 3.0 to 1.9 ± 1.9 infections per patient-year when the mean IgG trough was increased from 6.44 ± 2.02 to 8.28 ± 2.35 g/L, but later in the following decade, the infection rates remained constant (2.3 ± 2.0 g/L) despite higher mean trough obtained (10.06 ± 2.46 g/L). However, they also reported that their subgroup of patients with XLA did benefit from higher IgG trough [69].

The subgroup analysis showed that sample size of more and less than 40 subjects had the similar impact of IgG trough

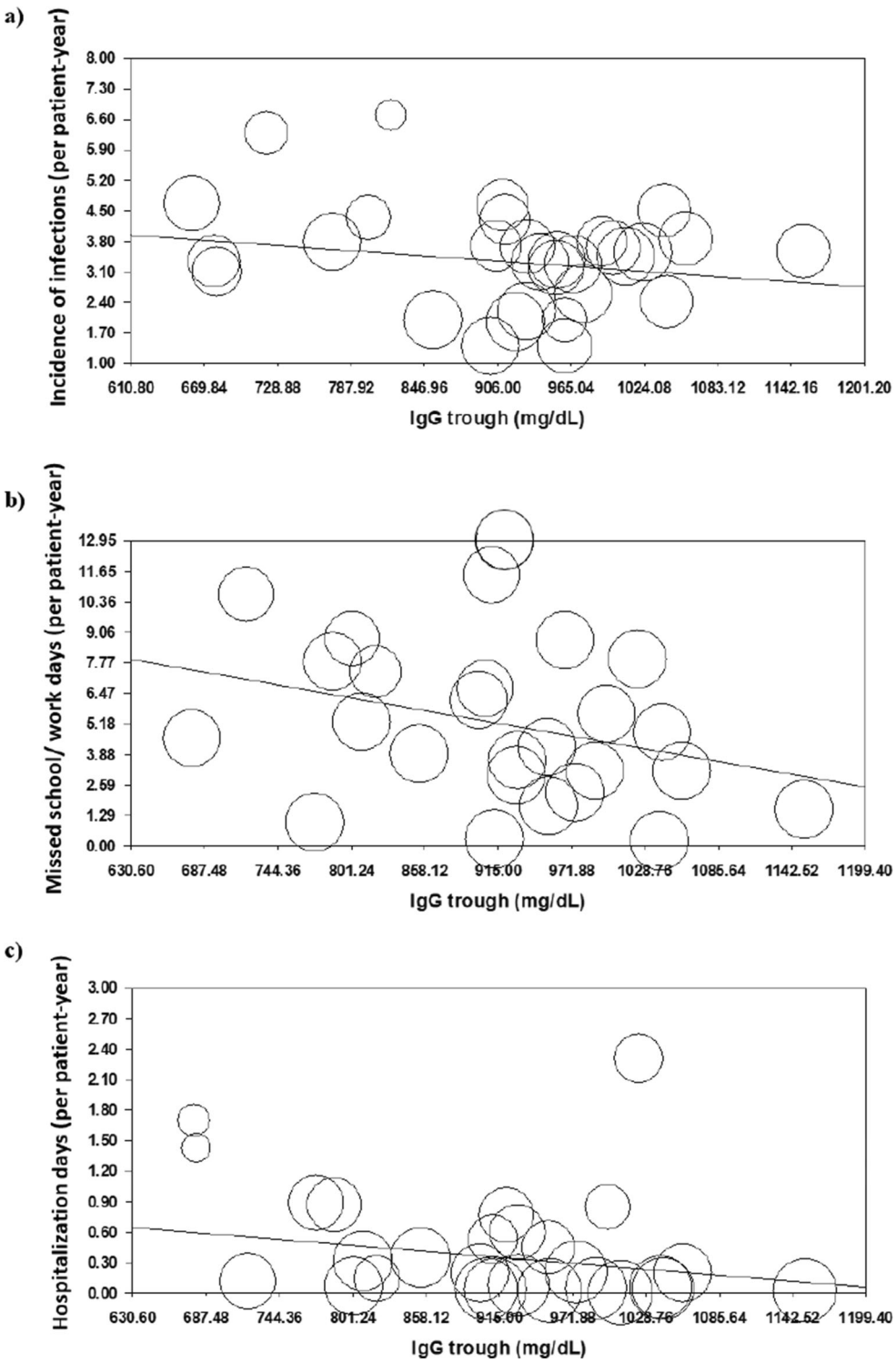

Fig. 3 **a** Effect of increasing IgG trough level on the incidence of overall infection rate per patient-year. Slope, $y = -0.00202x + 5.18482$ ($p = 0.211$). **b** Effect of increasing IgG trough level on the rate of missed school or work days per patient-year. Slope, $y = -0.00952x + 13.92669$ ($p = 0.081$). **c** Effect of increasing IgG trough level on the rate of hospitalization days per patient-year. Slope, $y = -0.00103x + 1.29897$ ($p = 0.016$). Each circle represents an aggregated data of a group of patients in an included study, and the size of the circle is proportional to the study weights

on rate of other infection (refer Table S1 in Online Resource). The pooled event rate of other infection was also comparable among studies with children only and those with mixed age groups. Differing types of PID could be a potential source of heterogeneity; however, this could not be analyzed due to unavailability of required data. Furthermore, meta-analysis, reported by Orange and colleagues (2010), showed that the impact of IgG trough on pneumonia rates was comparable among the differing types of PID [23]. In this study, the only factor that gives significantly different results compared to the primary analysis was the duration of follow-up of less than 12 months, in which all measured

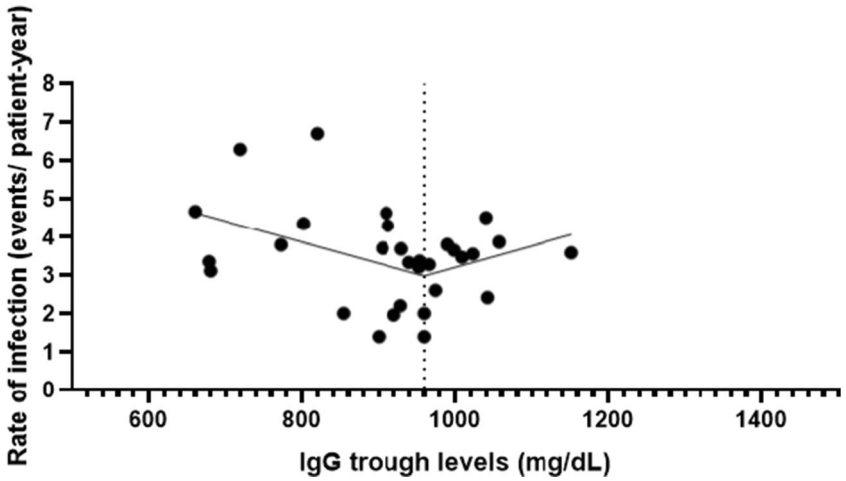

Fig. 4 Segmental linear regression between rate of infection (events per patient-year) and IgG trough levels (mg/dL). Each plot represents a data from a group of patients in a study. Dash line indicates the break point = 960 mg/dL, 95% CI 826–1094

outcomes (i.e., serious bacterial infections, other infections, missed school or work days, and hospitalization) could be affected by seasonal bias [30].

The primary analysis of this study suggests that for patients with PID on IVIG therapy, titrating the IgG trough level up to 960 mg/dL progressively improves clinical outcomes and levels beyond which may fail to provide additional protection against infection. It is known that the dose-response relationship is only approximately linear in the central portion (20–80% of the maximum response) of the dose-response curve [70]. It is therefore possible that there are diminishing returns in the response at higher IgG concentrations as the IgG concentration reaches the non-linear portion of the dose-response curve. However, sensitivity analysis showed that the impact of increasing IgG trough level from 660 to 960 mg/dL on the decreasing infection rate was not significant (Figure S1 in Online Resource). Therefore, further studies to validate this result are required before it can be implemented as a clinical guide.

Meta-regression analysis showed that with every increase in 100 mg/kg dose of IVIG, trough IgG increased by 73 mg/dL (Fig. 2). Similar results were reported by investigators from India where in their cohort of patients, increase in 100 mg/kg of IVIG dose resulted in an increase in serum IgG level of 53.6 mg/dL [71]. An earlier meta-analysis by Orange and colleagues showed a steeper increase in trough IgG level with dose, whereby with every increase in 100 mg/kg, trough IgG increased by 120 mg/dL [23]. This may be because our analysis only included clinical studies from year 2000 onwards, where most clinicians have started practicing a dose initiation of 400–600 mg/kg every 3–4 weekly. Meta-analysis done by Orange and colleagues included studies from years 1982 to 2009, in which they also analyzed data from earlier studies which used doses less than 200 mg/kg and also data from patients who have not started replacement therapy [23, 26, 28]. Both of their estimates fall within the 95% confidence interval of our analysis.

In this study, we found that increasing IgG trough, Cmax, and infusion rates does not significantly increase the risk of adverse reactions. This agrees relatively well with the report of considerable reduction of infusion related adverse reaction in

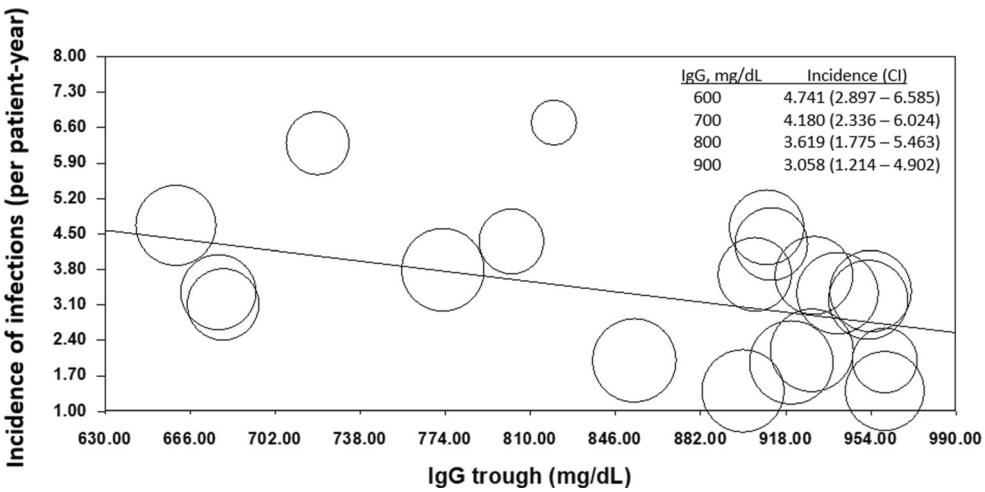

Fig. 5 Effect of increasing IgG trough level on the incidence of overall infection rate per patient-year. Slope, $y = -0.00561x + 8.10703$ ($p = 0.018$). Each circle represents an aggregated data of a group of patients in an included study, and the size of the circle is proportional to the study weights. CI confidence interval

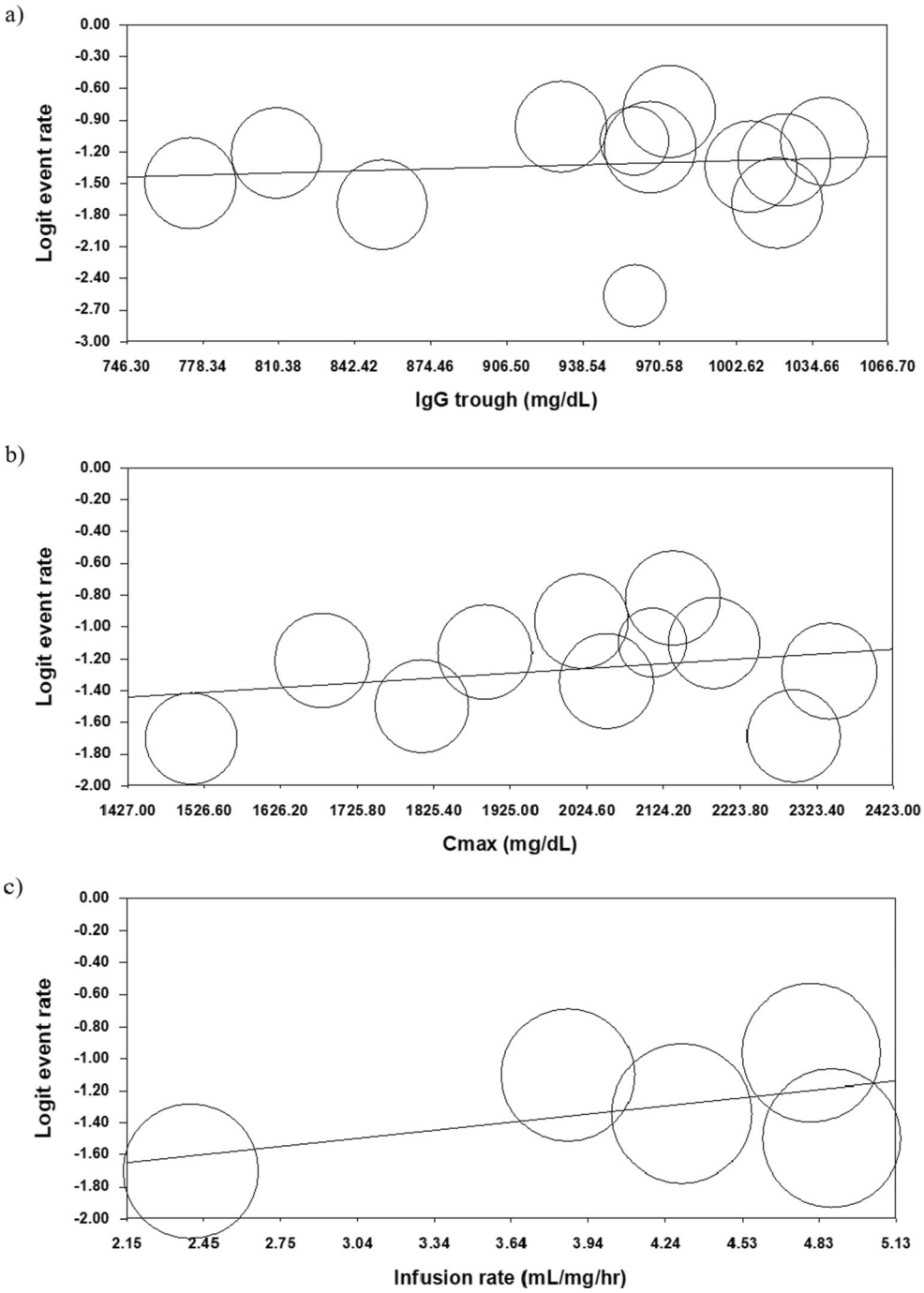

Fig. 6 Effect of increasing IgG trough, maximum serum concentration (Cmax) and infusion rates, on the incidence of adverse events. Slopes, **a** $y = 0.00060x - 1.88931$ ($p = 0.581$), **b** $y = 0.00030x - 1.87277$ ($p = 0.402$), and **c** $y = 0.17211x - 2.02137$ ($p = 0.205$). Each circle represents the available aggregated data of a group of patients in an included study, and the size of the circle is proportional to the study weights

the past two decades due to the improved manufacturing processes [2] and more stringent guidelines to adhere to before the marketing of an IVIG product [30]. Aghamohammadi and colleagues reported about 40% of adverse reactions occurred with rapid infusion and all symptoms improved with reduced infusion rate. Therefore, to avoid unnecessary risk of adverse reaction, it is recommended to initiate the infusion rate of IVIG at a rate not faster than 0.01 mL/kg/min for 30 min and to increase gradually every 15 to 30 min to a maximum rate of 0.08 mL/kg/min as tolerated by the patient [15].

Since IgG trough remains to be a common guide for treatment, this study provides a general guide to an upper limit of target trough. In patients with persistent infections despite optimal immunoglobulin G replacement, antibiotic chemoprophylaxis could be considered [71, 72]. Many researchers suggest for personalized treatment as they found that IgG levels that prevent infection among patients varied widely [69, 73]. This may be due to the difference in baseline endogenous IgG level at diagnosis for each patient. For example, patients with XLA at diagnosis usually have profound

hypogammaglobulinemia with serum IgG level of less than 200 mg/dL [74, 75], whereas patients with CVID have a relatively higher pre-treatment IgG level of less than 450 mg/dL [76–78]. As suggested by Cunningham-Rundles, for patients with higher residual IgG, a higher trough levels should be targeted. The author also suggested that the increment in the serum IgG level was more important than the trough level [79]. Therefore, future research should look into alternate methods of measuring exogenous IgG efficiency, such as measuring the increment in serum IgG from baseline, rather than IgG trough.

The strength of this meta-analysis is that it included a large group of studies to quantify the relationship of increasing IgG trough levels with its clinical outcomes in patients with PID on IVIG therapy. However, there are a few limitations of this study. Studies included were all cohort studies, which limits the overall strength of evidence due to population heterogeneity. Heterogeneity may also be contributed by subjective assessment of outcomes measured. However, these risks are reduced by only including studies after year the 2000 when the guidelines on the clinical studies for the marketing of IVIG were implemented. This guideline not only has a predetermined criteria in patient selection, but it also has a rigorous criteria for defining "serious bacterial infections" and a general guideline for clinical trial investigators to further pre-define their definition and diagnostic criteria for the other outcome measured [30]. This study may also have been confounded by the variation of timing in measuring IgG trough levels (21 days versus 28 days post dose), which may be different among patients included. To address this, doses were normalized prior to analysis. Product variation could also result in difference in efficacy due to the difference in manufacturing methods and geographic origin of plasma donors [13]. However, it is not feasible to test this assumption as there is neither direct comparison between products used nor multiple studies using the same product to measure the impact of IgG trough and its outcome. Therefore, in this meta-regression analysis, we assume that the measured clinical outcomes are independent of product difference [31].

Conclusion

This study suggests that for patients with PID on IVIG therapy, titrating the IgG trough level up to 960 mg/dL progressively improves clinical outcomes and levels beyond that provide less additional protection against infection. However, due to inconsistent results, the value of 960 mg/dL, being an estimated guide to an upper limit of target IgG trough, may serve as potential hypothesis for the design of future studies and interventions. Further studies to validate this result is required before it can be implemented and be used in managing individual patient.

Authorship Contributions LJL, NMS, and SMS contributed to the conception and design and conducted the systematic search of the study. All authors contributed to data analysis, drafting, and revising the article. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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