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A Comparative Study of Intravenous Immunoglobulin and Subcutaneous Immunoglobulin in Adult Patients with Primary Immunodeficiency Diseases: A Systematic Review and Meta-Analysis

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Abstract

Objectives: subcutaneous immunoglobulin (SCIG) is a new therapeutic procedure for patients with primary immunodeficiency (PI). This research is a systematic review of studies on the efficacy and safety of intravenous immunoglobulin (IVIG) and SCIG in adult patients with PI. Methods: this study includes a systematic review of cohorts and randomized clinical trials (24 articles) from 5 databases with no time limits. Random effects meta-analysis was performed for outcomes such as efficacy and safety.

Results: standard mean difference (SMD) of serum immunoglobulin level was equal to 0.336 (P <0.01; 0.205-0.467) and the odds ratio (OR) of side effects was 0.497 (P=0.1; 0.180-1.371). The results indicate that SCIG leads to a higher level of immunoglobulin and a reduction in side effects but shows the same infection rate as IVIG.

Conclusion: our analysis shows that shifting from IVIG to SCIG therapy can have clinical benefits for PI patients.

Keywords: Subcutaneous immunoglobulin, Intravenous immunoglobulin, primary immunodeficiency, efficacy, safety.

Introduction

Rapid advances and extensive developments in immunology in recent decades have provided new treatments for primary immunodeficiency (PI). PI is caused by genetic or developmental defects in the immune system. Due to these defects, the body cannot protect itself against viral, bacterial, or fungal infections [1]. Thus PI diseases are characterized by recurrent or persistent infections that cause serious complications or death [2, 3]. The prevalence of PI diseases is estimated at one in 10000 people [4]. Immunoglobulin was used for different groups of patients, while the highest volume of it was administered in patients with PI [5]. Exogenous antibody therapy to protect patients against infections and toxins goes back to 100 years ago, but there is increasing in the manufacturing, administration, and application of this type of immunotherapy, which is known as therapeutic human immunoglobulin [6].

The goal of Ig replacement therapy is to reduce the severity and frequency of infections and prevent long-term complication [7]. Human Ig can be administered by the intramuscular, subcutaneous, or intravenous routes to prevent infections in patients with primary antibody deficiency [8].

Intravenous immunoglobulin preparations have improved over the years evolving from immune serum globulin that is injected intramuscularly at relatively low doses [9]. IVIG was the most common PI therapy during 1980-1990 [10]. Since the 1990s, subcutaneous IgG (SCIG) administration for replacement therapy in patients with primary immunodeficiencies (PID) became an increasingly more common practice in some Scandinavian countries [11-13] and SCIG has recently been established as the preferred, more effective, and more tolerable therapy [14-16]. For choosing the best treatment method for PI patients we should consider some important variables such as monthly IgG dose, administration frequency and route, device used for administration, infusion rate & volume, number of infusion sites, product and formulation, site of care, patient/caregiver education and training, occurrence and management of adverse effects. These variables and treatment approaches may vary over time depending on

such factors as living conditions, infections and complications which can affect treatment methods [17].

So far, two systematic reviews have been conducted to compare the IVIG and SCIG for treatment of primary immune deficiency [8, 18]. Because of the limitations of these studies (such as considering all kinds of studies, the small number and low quality of included primary studies) and recent publication of primary studies [19-23], implementing new secondary study is essential. The aim of this study was to conduct a systematic review to compare the safety and efficacy of IVIG and SCIG and explain their advantages and disadvantages for PI patients.

Methods

Protocol

This study is a systematic review that includes all forms of clinical trial (RCT, CCT, and cohort) and aims to compare IVIG and SCIG treatments with respect to certain outcomes. This review was done according to the PRISMA[1] guidelines and based on a predetermined protocol.

Search Method

The most relevant and important sources of medical databases were systematically searched: SCOPUS, CRD (DARE, NHS EED, HTA), MEDLINE via the OVID interface, PUBMED and Cochran. Other relevant articles were searched by reviewing the references of founded articles. Searching lasted until March 16, 2015. In order to find related studies, we searched appropriate keywords (primary immunodeficiency, antibody deficiency, subcutaneous immunoglobulin, intravenous adjacent with immunoglobulin, antibody and gammaglobuline) both MeSH terms and free text in databases.

Eligibility Criteria

Every Controlled Clinical Trial (CCT), Randomized Clinical trial (RCT), and cohort study were included, while studies on animal samples and healthy subjects were excluded. Moreover, we included studies only adults and excluded children's groups (under 12 years old) from selected studies. It must be noted that there was no time limit in inclusion criteria and only articles in English language were included.

[1] Preferred Reporting Items for Systematic Reviews

Study Selection

Title and abstract of studies were examined by a reviewer based on predetermined criteria (study design, language of study and human studies only) and in case of ambiguities a second reviewer reexamined the studies. The complete text of eligible articles were acquired and data extraction form was applied to each study based on the Centre for Reviews and Dissemination (CRD) checklist. This process was repeated by a second reviewer in case of ambiguities. Finally, the number of patients having experienced a certain outcome, the total number of patients assessed for dichotomous outcomes, and mean and standard deviation for continuous outcomes were obtained. In order to eliminate overlapping studies age category was used in selected studies. Otherwise, we should corresponded with the author to insure if sources of data had not overlapped with other studies.

Quality Assessment

The quality of included studies were assessed according to Jadad scale for rating the quality of clinical trials. This scale allocates a score to each trial, ranging from 0 for very poor to 5 for high quality studies. Critical Appraisal Skills Programme (CASP) checklist was used to assess the quality of cohort studies. Accordingly, any study with 7 positive responses to the 12 CASP questions was considered as high quality, while studies with 5-7 positive responses were regarded as average quality and with less than 5 positive responses as poor quality.

Outcome Measurement

- Efficacy outcomes: Serum immunoglobulin (Ig) level (mean and standard deviation) and infection rate (frequency per year).
- Safety outcomes: Side effects. Results are reported in terms of the total number of side effects and the number of side effects per infusion.

Statistical Analysis

Random-effects meta-analysis and Mantel–Haenszel test were used in Stata 12 to combine the results of studies investigating serum immunoglobulin level and its side effects. Dichotomous data were extracted from the studies to calculate OR for side effects at the 95% confidence interval (CI). Also fixed-effects model was used for data related to serum Ig levels and Standard Mean Differences (SMD) were taken to measure the efficacy of Ig therapy methods. For comparing the difference infection rate of two methods we synthesized the results.

Results

212 articles were obtained by searching the databases, and after excluding repeated cases 56 articles were examined. Moreover, the results of 24 articles were subjected to meta-analysis. The data from these studies are the result of clinical trials as well as prospective and retrospective cohort studies. The study selection process based on the PRISMA guidelines is shown in Figure 1.

Characteristics of Eligible Studies

The studies included in this research had efficacy and safety implications for the outcomes of interest, serum Ig level, infection rate, and side effects. 945 patients were included in our analysis (446 for efficacy assessment through serum Ig levels and 376 through infection rate and antibiotics use, and 431 for safety assessment through side effects). All the patients were diagnosed with some type of primary immunodeficiency disease and they belonged to different age groups. It must be noted that in studies which examined both children and adults, only results belonging to adults were used in meta-analysis. Individual characteristics of each study are shown in Table 1.

Quality of Studies

For assessing the quality of studies, different types of bias (selection, performance, attrition, and detection) were examined. There was no blinding in clinical trials and the majority of the studies were not randomized. Also cohort studies had not been controlled for confounding factors or blinding; thus, there is the chance of bias in these studies. Generally 6 studies had high quality, 8 studies had moderate quality and 10 studies had poor quality among selected studies.

Serum Ig Levels

Most of the eligible studies (18 out of 24 with 446 patients) have measured and compared serum Ig levels in SCIG and IVIG treatments. Data from replacing SCIG with IVIG and changes in serum Ig levels were meta-analyzed and the results are shown in Figure 2. Since mean values were used in meta-analysis, the final result is expressed in SMD which is equal to 0.336 (CI: 0.2 – 0.47) indicating that SCIG Compared with IVIG has higher efficacy in increasing serum Ig levels. (Mean IVIG=8.54/Mean SCIG=9.59).

Examined data show no significant difference between SCIG and IVIG in the amount of Ig required for a given period. Also monthly Ig dose was not significantly different between these two methods. (The mean doses used for SC 150 mg/kg per week and 600 mg/kg per month for IV)

Side Effects

To examine this outcome, 13 articles (431 patients) were examined to compare side effects during treatment with SCIG and IVIG in PI patients. The Odds ratio which was calculated through meta-analysis indicated the superiority of SCIG due to fewer side effects (OR = 0.497; P=0.1; 0.180-1.371). Our analysis clearly showed that SCIG (regardless of its method of delivery) had fewer side effects. On the other hand, systemic complications such as headache, fever, and anaphylactic reactions can occur in IVIG, which can be reduced by changing treatment to SCIG [15, 24, 25]. This change can also improve tolerability in patients who previously had systemic reactions to IVIG. PI patients who switch from IVIG to SCIG require medical care only during the first six months after treatment change, while treatment with IVIG requires more medical care.

Infection Rate and Antibiotics Use

In selected studies, 14 studies (376 patients) have examined infection rate (severe infection in respiratory system) as a measure of treatment efficacy. However, due to differences in measurement of data, the results of the studies were synthetized.

Trials performed in one Swedish and two American centers showed there are 163 and 121 incidences of moderate infections in treatment periods in IVIG and SCIG respectively, which predominantly (>85%) occur in the upper or lower respiratory tract. However, the studies showed that the differences between treatment methods were not statistically significant [15].

Another recent study indicated that severe bacterial infection was observed with an annual infection rate of 0.06 per patient. Days off work/school significantly decreased with SCIG therapy. A small insignificant reduction was also observed in the number of hospitalization days (1.93 ± 4.08 vs. 0.64 ± 2.94), using SCIG method [23].

Kenagane et al. observed no serious bacterial infections in PI patients treated with SCIG, while 52.4% of these patients had infectious episodes [21]. However, in another clinical trial by Bezrodnik et al. no serious infection was observed during the SCIG treatment period, and only 2 cases of non-invasive pneumonia were reported with no need for hospitalization. The annual infection rate was 1.4 infections per subject/year during the IVIG administration period compared with 0.4 infections per subject/year during the SCIG period [19].

In a similar study, the annual rate of serious bacterial infections was reported to be 0 during a 12-month SCIG therapy (upper 99% CI 0.133). Also, the annual rate of hospitalization was 0.56 per patient [26]. Another study reported that during a six-month period of IVIG therapy, 15 patients experienced 42 infections (an annual infection rate of 4.73 per patient). During the

study (SCIG therapy), 10 patients experienced 34 infections (an annual infection rate of 3.95 per patient), and overall 44% of the patients received antibiotics in 267 days of 3145 days of the study [27].

Discussion

The present study is a systematic review that examines the safety and efficacy of subcutaneous versus intravenous immunoglobulin therapy in patients with primary immunodeficiency using a systematic review of indicators such as serum Ig levels, infection rate, and side effects. Our meta-analysis of serum Ig levels as an efficacy indicator suggests more efficacy of SCIG compared to IVIG (SMD = 0.336; P < 0.01; 0.205-0.467). However, because of the limitations of studies that were used in our systematic review, we cannot be definite about the more effectiveness of SCIG than IVIG. Moreover, the results of current study clearly indicate that SCIG (regardless of its method of delivery) is associated with fewer side effects. On the other hand, IVIG is associated with systemic complications such as headache, fever, and anaphylactic reactions, which can be reduced by switching to SCIG. Overall, the results suggest the superiority of SCIG in comparison with IVIG due its association with fewer side effects (OR = 0.497; P=0.1; 0.180-1.371).

Subcutaneous immunoglobulin has been used to treat patients with PI diseases who experience severe adverse effects in IVIG or have problem in venous access [28]. Standard IVIG therapy usually involves 1 infusion per month and a maintenance dose of 400-600 mg/kg [29]. However, SCIG is administered weekly or biweekly with a maintenance dose of 100 mg/kg, the cumulative monthly dose is similar to that of IVIG therapy [30]. Patients reporting less satisfaction with subcutaneous therapy cite the frequency of injections and local site reactions as their primary reasons. However, the method of delivery, injection volume, and rapidity of infusion, number of sites, and number of infusions per week can be adjusted to meet specific patient needs as long as the prescribed weekly amount of immunoglobulin is being administered. Moreover the results of studies about the costs of these two treatments and their role in improving patients' quality of life indicate that in most countries SCIG is used for a large number of patients, as it is associated with less costs, increased patient autonomy, and enhanced quality of life [8, 31-34]. It has been estimated that the annual cost of SCIG per

patient is less than IVIG [14]. In addition, all estimates indicate the preference of home-based therapy compared to office-based or hospital-based therapy [35].

While the current study shows the more efficacy of SCIG, a systematic review and Meta-analysis that was done in 2012 demonstrates that SCIG replacement therapy achieved serum IgG through levels that are comparable with those obtained with IVIG therapy [odds ratio (OR=1.00, range:0.84–1.15; p<0.01). On the other hand, the side effects results of this systematic review with odds ratio of 0.09 (0.07– 0.11; p<0.001) are the same as our study that indicates a significant preference of SCIG over IVIG because of a decrease in systemic adverse events. Although the systematic review confirms that few studies have compared SCIG and IVIG in a randomized controlled design, the majority of studies are (retrospective or prospective) cohort studies and in most cases the patient is given the chance to choose between these methods [18]. Infection rate analysis of the results showed the lack of serious bacterial infections in most cases, and annual infection rate has been estimated to be very low in SCIG [36, 37], which indicates this method is effective in protecting patients against infections [38, 39].

SCIG has emerged as an alternative to IVIG and is currently adopted in many countries due to having the same efficacy, safety, and tolerability as IVIG, while being associated with less costs and higher quality of life. However, the patients are given the right to choose between these methods. A systematic review and economic evaluation conducted in Canada showed that SCIG leads to an acceptable serum Ig level, but due to limited evidence it cannot be recommended as a replacement for IVIG [40]. However, it can be a suitable intervention for patients who have problem with IVIG or prefer home-based therapy. A concern for physicians is the precise SCIG dose that should be prescribed, as there are pharmacokinetic differences between IVIG and SCIG.

The present research was conducted to provide new insights into the efficacy and safety of SCIG and IVIG. Patients that benefit from SCIG therapy include those with poor venous access, those experiencing systemic adverse reactions to IVIG, and patients with anti-IgA antibodies thought to be a risk factor for systemic reactions. In spite of the result of our systematic review which indicates higher level of serum Ig and lower systemic side effects, more studies are required to make decision about replacing IVIG with SCIG.

Key Issues

- Primary immunodeficiency is caused by genetic or developmental defects in the immune system. The prevalence of PI diseases is estimated at one in every 10,000 people.

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- Human Ig can be administered by the intramuscular, subcutaneous, or intravenous routes and to prevent infections in patients with primary antibody deficiency. Exogenous antibody therapy to protect patients against infections and toxins is over 100 years old, but there has been an increase in the manufacture, administration, and application of this type of immunotherapy.

- IVIG was the most common PI therapy during 1980-1990. Since the 1990s, subcutaneous IgG (SCIG) administration for replacement therapy in patients with PID became an increasingly more common practice.

- Examined data show no significant difference between SCIG and IVIG in the amount of Ig needed for a given period. Also monthly Ig dose was not significantly different in these two methods. SCIG compared with IVIG was shown to have higher efficacy in increasing serum Ig levels.

- SCIG leads to an adequate and acceptable level of immunoglobulin (regardless of its method of delivery) while IVIG had more side effects. However, SCIG was associated with mild and tolerable localized reactions. On the other hand, systemic complications such as headache, fever, and anaphylactic reactions can occur in IVIG, which can be prevented by changing treatment to SCIG.

- SCIG is currently adopted in many countries due to having the same efficacy, safety, and tolerability as IVIG. Patients are given the right to choose between these methods.

Financial and competing interests disclosure

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Reference annotations

** Of interest*

*** Of considerable interest*

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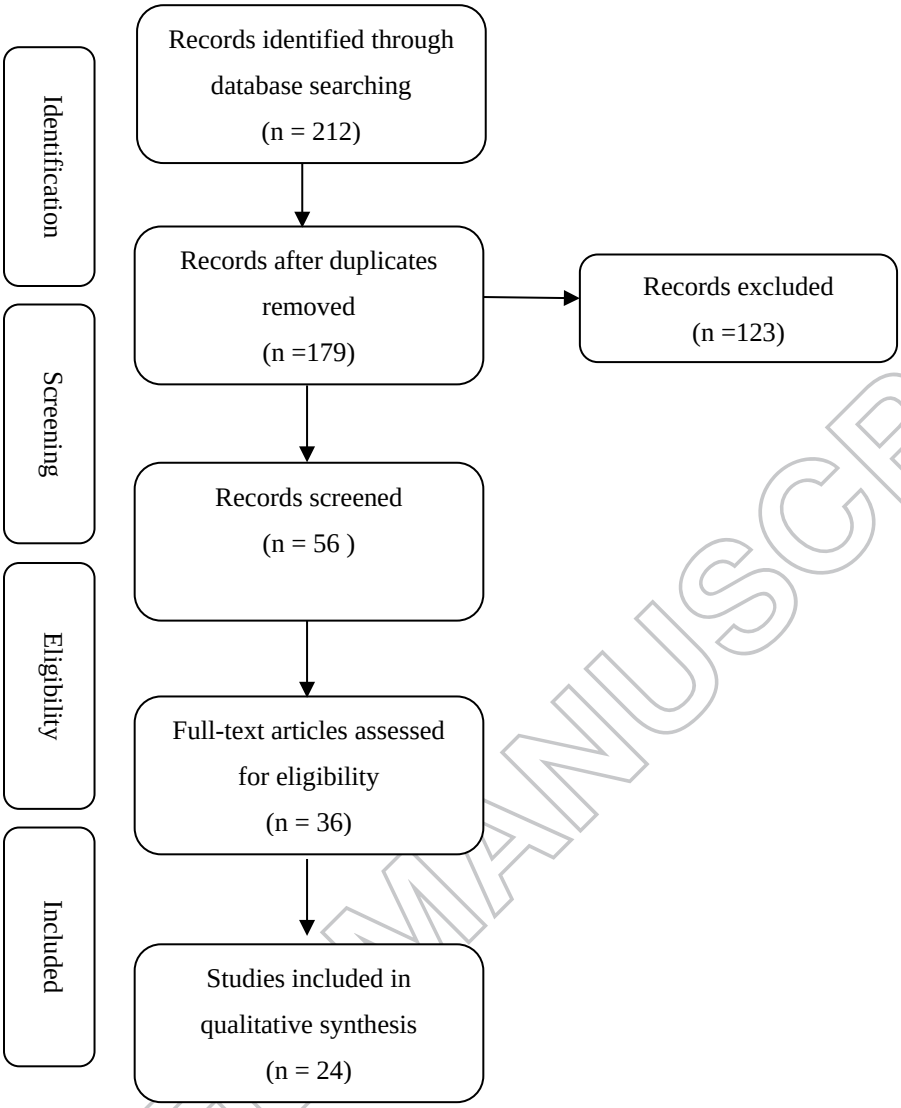

Fig. 1 Flow diagram of study selection process

Table 1. Characteristics of 24 eligible articles selected for systematic review

Ref	Authors	Year	Type of Study	Results	Compared patients (Adult/All)	Number of patients IVIG/SCIG	Age-year	Diseases	Value
[23]	Vultaggio	2015	Pr	AE,SBI	43/50	50/39	no age limit	CVID,XLA	H
[22]	Soler-Palacin	2014	Re	E,SA	23/48	23/23	0.7–25.7	CVID,XLA	L
[21]	Kanegane	2014	Pr	AE,SIgGL,SBI	17/24	24/24	<75	PID	M
[20]	Shapiro	2013	Re	E,S	17/40	17/17	0–67	PIDD	H
[19]	Bezrodnik	2013	Pr	SIgGL,SBIs	15/15	13/13	4–18	XLA, CVID, SAD	M
[26]	Empson	2012	Ra	AE,SBIs,SIgL	30/35	32/31	>3	XLA,CVID,SH	L
[37]	Wasserman	2011	Pr	AE,SBI	18/19	18/18	3–77	CVID,XLA,HY,IgGD,CVID,N,HY	M
[41]	Jolles	2011	Pr	AE,SIgGL,SBI	33/43	27/27	2 - 65	CVID,XLA	L
[27]	Borte	2011	Pr	AE,SIgGL	12/18	17/17	1–70	XLA,CVID	H
[42]	Wasserman	2011	Pr	SIgGL	18/21	19/18	6–75	CVID,XLA	L
[38]	Wasserman	2010	Ra	SBI,AE	35/35	32/26	13–75	PIDD	L
[43]	Hoffmann	2010	Pr	AE,SIgGL	65/82	48/43	no age limit	AD	M
[44]	Shapiro	2010	Re	AE,SIgGL	70/104	104/74	0.5–67.6	PIDD	M
[36]	Hagan	2010	Pr	SBIs	35/38	38/28	5 -72	CVID,XLA	H
[45]	Quinti	2008	Pr	AE, SIgGL	13/13	13/13	13-67	CVID	L
[16]	Fasth	2007	Pr	AE,SBI,SIgGL	12/12	12/12	1-18	PI	M
[46]	Gelfand	2006	Ra	AE	99/100	46/60	18 -75	A,CVID	H
[25]	Ochs	2006	Ra	AE,SBI,SIgGL	55/65	65/51	>2	CVID,XLA	L
[47]	Gardulf	2006	Pr	AE,SBI,SIgGL	44/60	49/52	2–75	CVID,XLA,SCID,N,W,ISIgGD,A	H
[48]	Eijkhout	2003	Re	AE	15/15	9/5	26-75	CVID,IgAD	L
[15]	Chapel.	2000	Ra	I	22/30	16/14	> 13	CVID,IgGD,SAD	M
[24]	Gaspar	1998	Re	AE,I,SIgGL	26/26	15/15	1.5- 15	CVID,XLA,ISIgGD,HY	L
[49]	Schiff	1997	Ra	AE	20/27	26/17	1 - 74	XLA,CVID,HIgM,HIgE	M
[11]	Hammarstrom	1991	Re	AE,S	25/25	25/15	18 - 73	HI	L

AE Adverse effect;S Safety;SBI Severe bacterial infection;I Infection; SIgGL Serum Ig Levels; CVID Common variable immunodeficiency; HIGM Hyper-IgM syndromes; I Infection; IgGD IgG deficiency;NI Not indicated;Pr Prospective cohort study, Ra Randomized clinical trial; Re Retrospective cohort study;SAD Specific antibody deficiency; SCID Severe combined immunodeficiency; SIgGD IgG subclass deficiency;HI hypogammaglobulinemia of infancy; XLA X-linked agammaglobulinemia

Study	SMD	[95% Conf.	Interval]	% Weight
Vultaggio(2015)	0.156	-0.264	0.575	9.79
Kanegane(2014)	0.426	-0.141	0.993	5.36
Bezrodnik(2013)	0.488	-0.293	1.269	2.82
Shapiro(2013)	0.954	0.650	1.259	18.56
Borte(2011)	0.351	-0.219	0.921	5.29
Hagan(2010)	0.850	0.340	1.360	6.62
Quinti(2008)	-0.117	-0.886	0.653	2.91
Gardulf(2006)	-0.139	-0.536	0.257	10.95
Gaspar(1998)	-0.175	-0.892	0.542	3.35
Jolles(2011)	0.856	0.298	1.414	5.52
Wasserman(2011)	0.910	0.222	1.598	3.63
Hoffmann(2010)	-1.114	-1.499	-0.729	11.61
Shapiro(2010)	0.259	-0.535	1.052	2.73
Schiff(1997)	1.511	0.852	2.169	3.97
Wasserman(2011)	0.560	0.061	1.060	6.89
I-V pooled SMD	0.336	0.205	0.467	100.00

Heterogeneity chi-squared = **103.05** (d.f. = **14**) p = **0.000**
I-squared (variation in SMD attributable to heterogeneity) = **86.4%**

Test of SMD=0 : z= **5.02** p = **0.000**

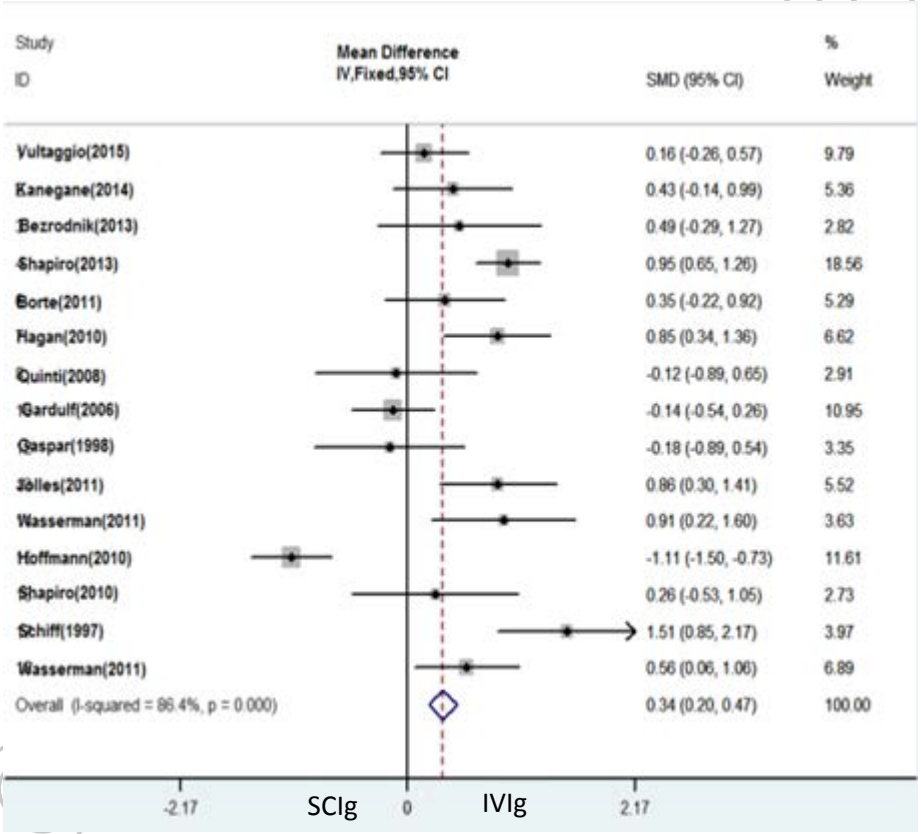

Fig. 2 Forest plot and meta-analysis of 18 studies evaluating the IgG trough levels achieved in PAD patients on SCIg or IVIg

Study	OR	[95% Conf.	Interval]	% Weight
1 Vultaggio(2015)	0.164	0.044	0.615	8.02
2 Kanegane(2014)	3.273	0.317	33.837	6.22
3 Bezrodnik(2013)	66.000	5.226	833.557	5.88
4 Empson(2012)	0.040	0.008	0.196	7.58
5 Borte(2011)	0.013	0.001	0.110	6.56
6 Hagan(2010)	0.202	0.057	0.718	8.11
7 Ochs(2006)	0.070	0.026	0.190	8.51
8 Gardulf(2006)	0.226	0.102	0.502	8.78
9 Chapel(2000)	13.500	4.020	45.330	8.20
10 Jolles(2011)	1.490	0.433	5.121	8.16
11 Shapiro(2010)	0.568	0.146	2.216	7.95
12 Schiff(1997)	0.444	0.078	2.519	7.30
13 Wasserman(2010)	0.980	0.423	2.269	8.73
D+L pooled OR	0.497	0.180	1.371	100.00

Heterogeneity chi-squared = 94.55 (d.f. = 12) p = 0.000
I-squared (variation in OR attributable to heterogeneity) = 87.3%
Estimate of between-study variance Tau-squared = 2.8947

Test of OR=1 : z= 1.35 p = 0.177

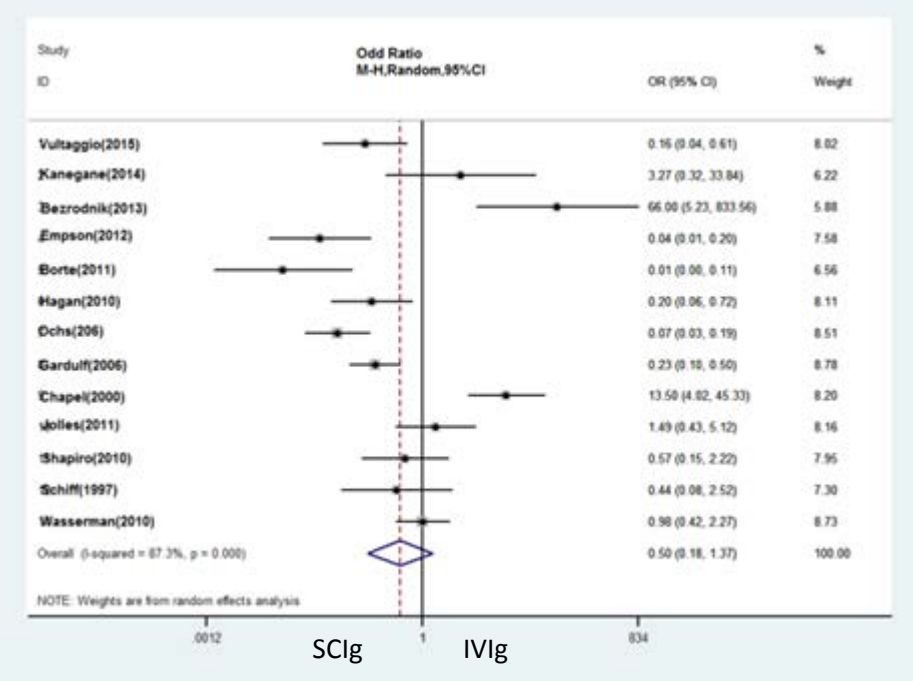

Fig. 3 Forest plot and meta-analysis of systemic adverse events (SCIg/IVIg) reported by 13 eligible articles