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20% subcutaneous immunoglobulin for patients with primary immunodeficiency diseases: A systematic review

Jie Song [a,b,c,d,e], Lingli Zhang [a,b,c,d,*], Youping Li [f,*], Shuyan Quan [a,b,c,d,e], Yi Liang [a,b,c,d], Linan Zeng [a,b,c,d], Yi Liu [a,b,c,d,e]

[a] Department of Pharmacy, West China Second University Hospital, Sichuan University, Chengdu 610041, China
[b] Evidence-Based Pharmacy Center, West China Second University Hospital, Sichuan University, Chengdu 610041, China
[c] Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu 610041, China
[d] Department of Pediatric, West China Second University Hospital, Sichuan University, Chengdu 610041, China
[e] West China School of Pharmacy, Sichuan University, Chengdu 610041, China
[f] Chinese Evidence-Based Medicine Centre, West China Hospital, Sichuan University, Chengdu 610041, China

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ABSTRACT

Background: Primary immunodeficiency diseases (PID) are a group of rare disorders that patients do not have normal function of the immune system. Subcutaneous immunoglobulin 20% (SCIG-20%) was a candidate when considering replacement therapy with immunoglobulin in PID, but the evidence was not clear. To understand and interpret the available evidence, we conducted a systematic review to assess the efficacy and safety of SCIG-20% for patients with PID.

Method: Literature searches were conducted in PUBMED, EMBASE, Cochrane Library, CBM, VIP, CNKI, WanFang, LILACS and U.S. ClinicalTrials.gov. Clinical studies published in full text that met predefined inclusion criteria were eligible irrespective of language. Reviewers independently assessed all potential studies and extracted data. The fixed-effect model was used in meta-analysis.

Results: 4 studies involving 100 patients were included. The pooled rate of infection was 0.80 with the annual rate of 3.74. 38% patients missed days from work/school and annual rate was 4.54 days in one year per patient. Only 4% patients were hospitalized due to infection and it costs 1.57 days in one year per patient. 70% patients used antibiotics during 58.4 days in one year per patient. 80 patients (80.0%) who experienced 1630 AEs were considered related to SCIG-20%. Only 7 related AEs were severe, of which, 4 were local reactions and 3 were headaches. Studies on health related quality of life and satisfaction suggested that patients with SCIG-20% had a good life quality and satisfied with SCIG treatment.

Conclusions: SCIG-20% treatment was not recommended for patients with primary immunodeficiency. Low quality of each outcome suggested that the evidence on effect of SCIG-20% for patients with PID is inadequate. Further comparative studies are urgently needed, especially in comparison with IVIG or SCIG of other concentrations.

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1. Introduction

Primary immunodeficiency diseases (PID) are a group of rare disorders wherein patients do not have normal development or function of the immune system. More than 200 types of PIDs were defined [1,2]. Incidence of PIDs is higher in children than in adults, and characterized by repeated infection, numerous complications and severe condition [3]. There is no accurate incidence of PID for the whole world. According to several studies, incidence of PIDs is 1/1200 in US, 0.282/10,000 in Australia, 1/8000 in Hong Kong, 1/5000 in Japan and 1/250–1/500 in Europe [4–8].

The goal of PID treatment is to achieve normal immunoglobulin level, reduce the risk of infection and keep patients' normal activities. Replacement therapy with immunoglobulin is recommended and widely used in patients with PID from 1980s [9,10]. Immunoglobulin can be given intravenously (IVIG), intramuscularly (IMIG) or by subcutaneous infusions (SCIG). Comparing with IVIG, there are less systemic reactions but more local reactions with SCIG infusions [11]. Meanwhile, home-based SCIG treatment has equal or even more benefits in some outcomes of efficacy, life quality and satisfaction comparing with hospital-based IVIG [12,13]. Therefore, SCIG treatment has been a standard regimen in US and EU [14].

Because patients have better tolerability in local reaction than systemic reactions, 10% and 16% SCIG are widely used in patients with PID for their life-long treatment. Several clinical data suggested that higher SCIG doses and serum IgG level improve clinical outcomes in individual patients [15]. According to several individual studies on SCIG-10% or SCIG-16%, incidence of adverse event had a slight reduction with higher concentration of SCIG (0.276–0.820 vs. 0.130–0.707 events

* Corresponding authors.

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per infusion between SCIG-10% and SCIG-16%) [37–41]. In 2010, US Food and Drug Administration (FDA) licensed a new human immunoglobulin preparation for subcutaneous administration (20% Liquid, Hizentra, CSL Behring) which has the highest concentration at present. Obviously, higher concentration results in lower infusion volumes to achieve target serum IgG levels. In 2013, SCIG-20% was considered by The WHO Expert Committee to be listed at Essential Medicines list, but the application was not approved due to insufficient evidence [16]. To understand and interpret the available evidence, we conducted a systematic review to assess the efficacy and safety of SCIG-20% for patients with PID.

2. Method

2.1. Data source

PUBMED, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Four Chinese database including CBM (Chinese BioMedical Literature Database), VIP (VIP Database for Chinese Technical Periodicals), CNKI (China National Knowledge Infrastructure) and WanFang (Knowledge service platform of WanFang Data) were searched in Chinese. LILACS (Latin American and Caribbean Health Sciences Literature) and the U.S. ClinicalTrials.gov website were also searched with the terms as primary immunodeficiency*, immunoglobulin* and subcutaneous*. The references of all retrieved articles were scanned for additional relevant citations. The deadline of all searching is the 4th week of November, 2013.

2.2. Eligibility criteria

Inclusion: All types of clinical studies on SCIG-20% for PIDs published only in full text were included, and no restriction on publication language. We included patients of all ages diagnosed with any type of PIDs. The intervention of SCIG20% was regardless of the dose and duration.

Exclusion: Other immunoglobulin treatments were given to PID patients during the SCIG-20% treatment. We excluded studies that included SCIG20% and other immunoglobulin preparation if data on SCIG20% could not be extracted separately.

2.3. Study selection and management

Two reviewers independently screened titles and abstracts of all studies identified by the search strategy according to predetermined inclusion criteria. The full texts of all potentially relevant articles were obtained for detailed review. Disagreements were resolved after discussing with the third reviewer.

Two reviewers independently extract data from each included study using a pre-designed data collection form. The number of patients experiencing the event and the total number of patients evaluated for that outcome were obtained for dichotomous outcomes. The mean values and standard deviation (SD) were obtained for continuous outcomes.

2.4. Quality assessment

The quality of including study was assessed according to the checklist developed by the UK National Institute for Clinical Excellence (NICE)

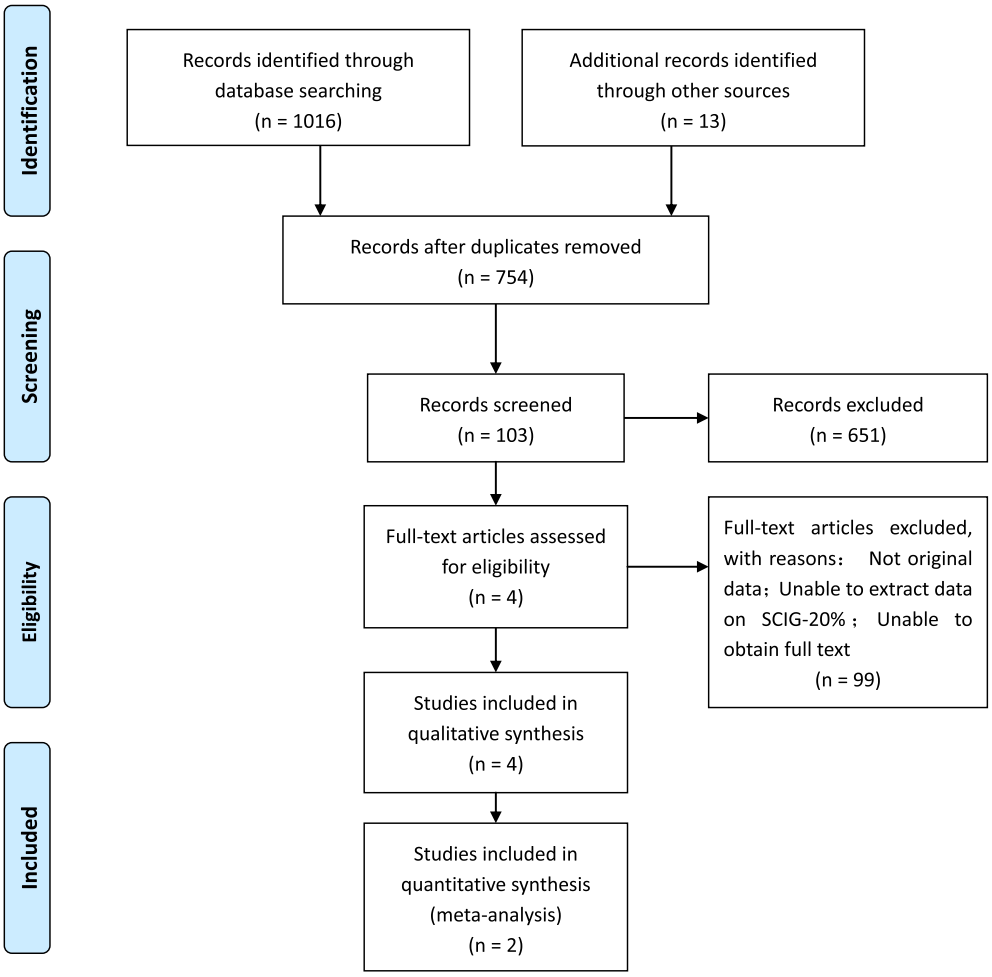


Fig. 1. Flow diagram of study selection process.

Table 1
Characteristics of included study.

Study	Type of study	Patients, *n* (Ch/Ado/Ad)	Age, years Median (range)	Diseases	Previous treatment	Study duration	Results
Jones 2012	Pr	16 (NR)	47.5 (22–69)	CVID = 16	IVIG or other SCIG	120 weeks	HRQoL, S
Jolles 2011	Pr	46 (17/5/24)	16.5 (3–60)	CVID = 28 XLA = 17 ARAG = 1	IVIG or other SCIG	40 weeks	I, SIgGL, H, MD, SE, AU
Borte 2011	Pr	51 (18/5/28)	Ch: 7.5 (3–11) Ado: 14.0 (13–15) Ad: 32.5 (16–60)	CVID(Ch = 7/Ados = 0/Adt = 23) XLA(Ch = 10/Ado = 5/Ad = 5) ARAG(Ch = 1/Ado = 0/Ad = 0)	IVIG or other SCIG	40 weeks	I, SIgGL, H, MD, SE, AU
Hagan 2010	Pr	38 (3/3/32)	36.5 (5–72)	CVID = 36 XLA = 2	IVIG or other SCIG	64 weeks	I, SIgGL, H, MD, SE, AU

Note: *Ch* children (2–11 years); *Ado* adolescent (12–15 years); *Ad* adult (>16 years); *Pr* prospective study; *NR* Not report; *CVID* common variable immunodeficiency; *S* satisfaction; *XLA* X-linked agammaglobulinemia; *ARAG* autosomal recessive agammaglobulinaemia; *HRQoL* health-related quality of life; *I* infection; *SIgGL* serum IgG levels; *H* hospitalization; *MD* missed days; *SE* side events; *AU* antibiotic usage.

[17]. 8 questions included in the checklist were answered with yes, no, or unclear. The GRADE approach was used for assessing evidence quality for each outcome based on the GRADE handbook [18]. A GRADE evidence profile was used to show the details of evidence quality and the main result for each important outcome.

2.5. Outcome measures

Efficacy outcomes: number of infections, days missed from work/school, hospitalized due to infection, and days with antibiotics. All above outcomes were reported in incidence and annual rate.

Safety outcomes: all types of adverse events (AEs). The results were reported in number of AEs and numbers per infusion.

Life quality and satisfaction outcome: In including studies, 5 tools were used to access the health related quality of life (HRQoL) and satisfaction. They are Medical Outcomes Study 36-Item Short Form (SF-36), EuroQol 5D (EQ-5D), Life Quality Index (LQI), Treatment Satisfaction Questionnaire for Medication (TSQM) and IgG Therapy-Specific Questionnaire (IgG-TSQ). The scores of above measures were reported.

2.6. Statistical synthesis

The incidences in each efficacy outcome were calculated for the meta-analysis with 95% confidence interval (CI) by using the software STATA 12.0. Heterogeneity test was done by using I^2 statistic. The fixed-effect model was used to combine effect size (ES) in the absence of significant heterogeneity ($I^2 < 50\%$), and random-effect model was used if heterogeneity was significant ($I^2 \geq 50\%$). Other outcomes were analyzed in description.

3. Results

3.1. Result of study selection

754 citations without duplicates were identified from database, and 103 citations were included in full-text screening. Finally, 4 studies [19–22] were included this systematic review. Data of the 4 studies were from 2 clinical trials. 2 [19,22] are from an US trial, and the other 2 [20,21] are from an EU trial. Because those papers report hierarchical data from the 2 clinical trials, all 4 papers were included in current study. Fig. 1 shows the literature selection process.

3.2. Characteristics of included studies

The trials were single-arm study with a 12-week wash-in/wash-out period followed by an efficacy period (range 28–52 weeks). 100 patients (all-treat population) were included in this review, and 84 patients (intention-to-treat population) were included in efficacy analysis. Mean age was 28.9 (range 3–72). Patients were diagnosed with common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), or autosomal recessive agammaglobulinaemia (ARAG). The dose of SCIG20% was 1 time (EU trial) or 1.53 times (US trial) of that in previous non-SCIG20% treatment (range 117.0–224.3 mg/kg bw per week). Table 1 shows the characteristics of each study.

3.3. Quality of included studies

All studies were involved in the quality assessment (Table 2). All studies were multicenter report, and their objectives were described clearly. Only 1 study [22] did not describe inclusion/exclusion criteria for patients. Consecutive recruiting of patients was not reported in all studies. All studies clearly defined outcomes, prospectively collected data, and described main findings. 2/4 studies [19,22] reported results hierarchically. All study got score above 5, and had moderate to high quality. Therefore, low risk of bias was suggested when included studies considered as observational, single-arm study.

3.4. Patients with infections

67 of 84 patients experienced 220 infection episodes (annual rate was 3.74, Table 3). The rate of patients experienced infection in primary studies was 0.78 and 0.82, and the pooled rate was 0.80 (95% CI, 0.71–0.88) (Fig. 2). The heterogeneity between studies was not statistically significant ($p = 0.704$). No serious bacterial infection was reported in including studies. 1 study [21] reported the stratified outcomes in children (2–11 years), adolescent (12–15 years) and adult (16–64 years). The rate of infection was 0.88, 0.60 and 0.75 respectively (annual rate was 4.77 vs. 5.18 vs. 5.47).

Table 2
Quality assessment of including studies.

Study	Multi-center study	Objective clearly described	Inclusion/exclusion criteria clearly described	Clear definition of outcomes	Data collected prospectively	Patients recruited consecutively	Main finding clearly described	Outcomes stratified	Scores
Hagan 2010	Y	Y	Y	Y	Y	NR	Y	N	6
Borte 2011	Y	Y	Y	Y	Y	NR	Y	Y	7
Jolles 2011	Y	Y	Y	Y	Y	NR	Y	Y	7
Jones 2012	Y	Y	N	Y	Y	NR	Y	N	5

Note: *Y* yes, *N* no, *NR* not report.

Table 3
Number and annual rate for each outcome.

Efficacy end point	Number of patients	Number of events/days	Total number of days in studies	Annual rate of events/days
Infection episodes	67	220	21,442	3.74
Days missed from work/school	32	269	21,638	4.54
Days hospitalized due to infection	5	93	21,638	1.57
Days with antibiotics	59	3431	21,442	58.40

3.5. Days missed from work/school

32 of 84 patients missed 269 days from work/school (annual rate was 4.54, Table 3). The rate of patients who missed days was 0.43 and 0.32 in primary study, and the pooled rate was 0.38 (95% CI, 0.27–0.48) (Fig. 3). Heterogeneity was not statistically significant ($p = 0.257$). The percentage was 0.47, 0.80 and 0.33 in children, adolescent and adult (annual rate was 14.9 vs. 1.79 vs. 4.28) [21].

3.6. Hospitalized due to infection

5 of 84 patients were hospitalized due to infection. A total of 93 days were recorded (annual rate was 1.57, Table 3). The hospitalized rate was 0.09 and 0.03 in primary study, and the pooled rate was 0.04 (95% CI, 0.00–0.09) (Fig. 4). No significant heterogeneity was detected ($p = 0.216$). The percentage was 0.18, 0.00 and 0.04 in children, adolescent and adult (annual rate was 8.36 vs. 0.00 vs. 0.63) [21].

3.7. Days with antibiotics

59 of 84 patients were treated with antibiotics on 3431 days (annual rate was 58.40, Table 3). 54 patients (64.3%) used antibiotics for treating adverse events, 6 patients (7.1%) for prophylaxis, and 16 patients (19.0%) for the treatment of medical/surgical/current conditions. The rate of patients who used antibiotics was 0.70 and 0.71 in primary study, and the pooled rate was 0.70 (95% CI, 0.60–0.80) (Fig. 5). Heterogeneity was not statistically significant ($p = 0.882$). The percentage was 0.65, 0.20 and 0.71 in children, adolescent and adult (annual rate was 49.04 vs. 0.37 vs. 59.38) [21].

3.8. Adverse events

The safety analysis was conducted in all-treatment population ($n = 100$). Overall, 2276 AEs occurred during a total of 4095 infusions (0.56 AEs per infusion). 99 patients (99.0%) experienced at least 1 AE. Of those, 1890 temporally associated AEs (72 h) occurred in 78 patients (0.38 AEs per infusion) and 80 patients (80.0%) experienced 1630 AEs considered possibly related to medication (0.40 AEs per infusion). Only 26 severe AEs were reported and 7 severe AEs were considered related to study medication.

74 patients (74.0%) had 1450 local reaction (0.35 per infusion, but there was a significant difference between primary studies which was 0.59 vs. 0.06). Of those, 1427 events in 73 patients were temporally associated (72 h) and 74 patients experienced 1445 local reactions considered related to study medication. Most (92.9%) local reactions were mild, 6.8% local reactions were moderate, and only 5 (0.3%) local reactions were severe in intensity. 4 severe local reactions, all of which were infusion site reactions, were related to medication. Both including studies [19,20] suggested that incidence of local reaction showed a slight tendency to decrease over time, but the trend was not clearly. Meanwhile, patients' assessment of tolerating local reaction appeared to improve overtime.

Without local reactions, 826 adverse events were reported (0.21 AEs per infusion). Of those, 463 were temporally associated AEs, and 185 AEs were considered related to study medication. The top-five related systemic AEs were headache (49 events in 18 patients), fatigue (8 events in 6 patients), pruritus (14 events in 4 patients), abdominal discomfort (5 events in 4 patients) and rash (4 events in 4 patients) (Table 4). Only 3 systemic AEs were severe, all of which were headaches.

There were no deaths reported in the included studies. 8 patients discontinued the study because of AEs, of which 5 were considered related to medication. In 5 patients, 9 related AEs that led to discontinuation were reported: injection site pain, injection site pruritus, injection site reaction (3 events), fatigue, feeling cold, myositis and hypersensitivity. All the related AEs that led to discontinuation were resolved finally.

3.9. HRQoL and treatment satisfaction

One study [22] enrolling 16 patients reported the data on HRQoL and treatment satisfaction. With the fact that high scores represent the

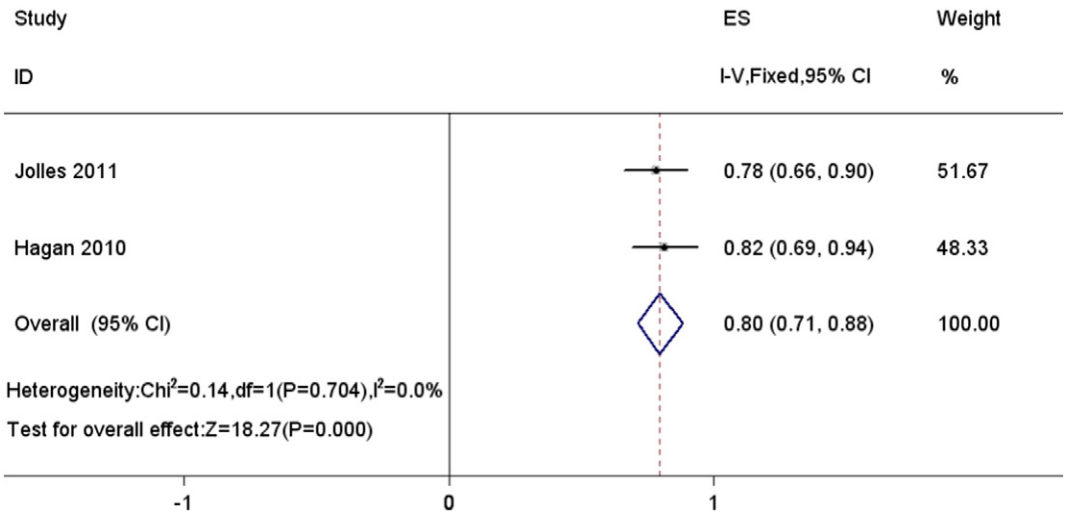


Fig. 2. Rate of patients with infections.

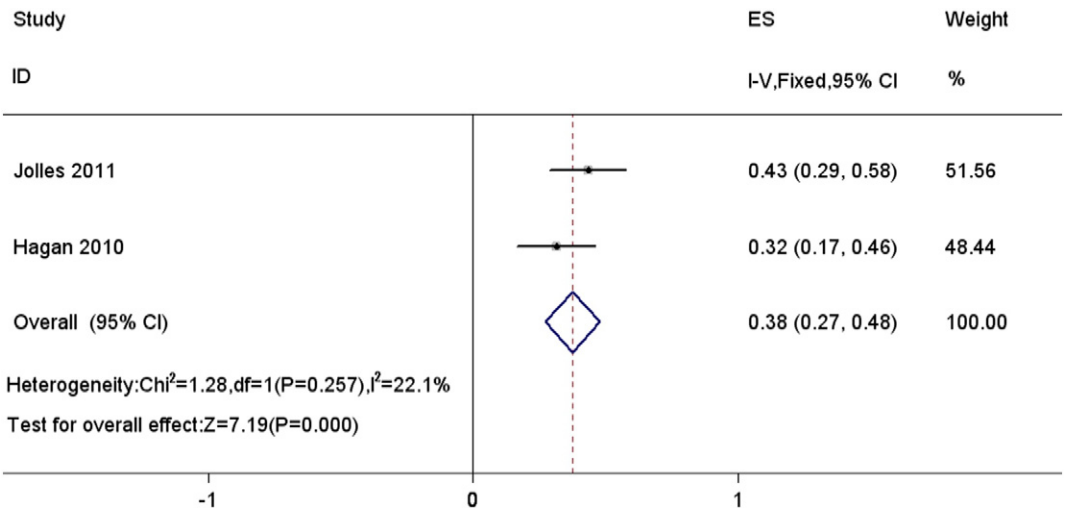


Fig. 3. Rate of patients missed days from work/school.

better result, the score of EQ-5D ranges from −1 to 1 and other measures range from 0 to 100. In SF-36v2, most domain scores were close to the US norms but only general health domain (56.1 ± 23.14) was below the US norms (70.85) with the 95% CI. 4 domain scores (physical functioning, mental health, vitality, general health) improved and 6 domain scores (role physical, role emotional, social functioning, bodily pain, PCS, MCS) worsened at the end when comparing with the start of the study. In EQ-5D, the scores (0.807 ± 0.1331) was close to the US norms (0.87), and it implied worsening at the end of study. The result of LQI (scores range 77.3 ± 17.01 to 92.3 ± 11.52) did not indicate low levels of life quality, and all domain scores in LQI showed a slight improvement over time. In TSQM, it suggested high levels of satisfaction (scores range 74.7 ± 29.81 to 88.3 ± 21.08), and domain scores also showed improvement over time. The result of IgG-TSQ (scores range 82.2 ± 29.19 to 86.9 ± 21.86) suggested that patients had a good feeling about the IgG treatment.

3.10. GRADE profile of important outcomes

The evidence quality for each outcome was evaluated by using GRADE approach. Level of evidence was graded into four classifications (high, moderate, low and very low) according to the GRADE handbook. Because of the observational design of included studies, low quality was given to each outcome as primary grade. Only 1 downgrading was given to "Hospitalized due to infection" because imprecision was identified in this term. No upgrading factor was identified. Finally, 3 outcomes had low quality and 1 had very low quality. For importance of outcomes, infections were critically important, and others were important. All important results and the evidence quality were shown in GRADE evidence profile (Table 5).

4. Discussion

In our study, we summarized the efficacy and safety of SCIG20% in patients with PIDs, and this is the first systematic review including meta-analysis and specific levels of evidence for this drug. In this review, infection rate was 0.80. It seems that the rate was still high. However, as the primary outcome of IgG studies, no serious bacterial infections were reported. All infections were mild to moderate; the most common type of infection were cough, sinusitis, nasopharyngitis and bronchitis. Frequent usage of antibiotics was suggested under the high infection rate, although some of antibiotics were used for prophylaxis. The usage rate of antibiotics was 0.7, and antibiotics were used in mean 58.40 days in one year per patients in this review. Only 4% patients were hospitalized due to infection, but there were also 38% patients who missed days from work/school in this review. It is suggested that few patients with serious condition had to be hospitalized, but a number of patients could not have normal activities. In a different age

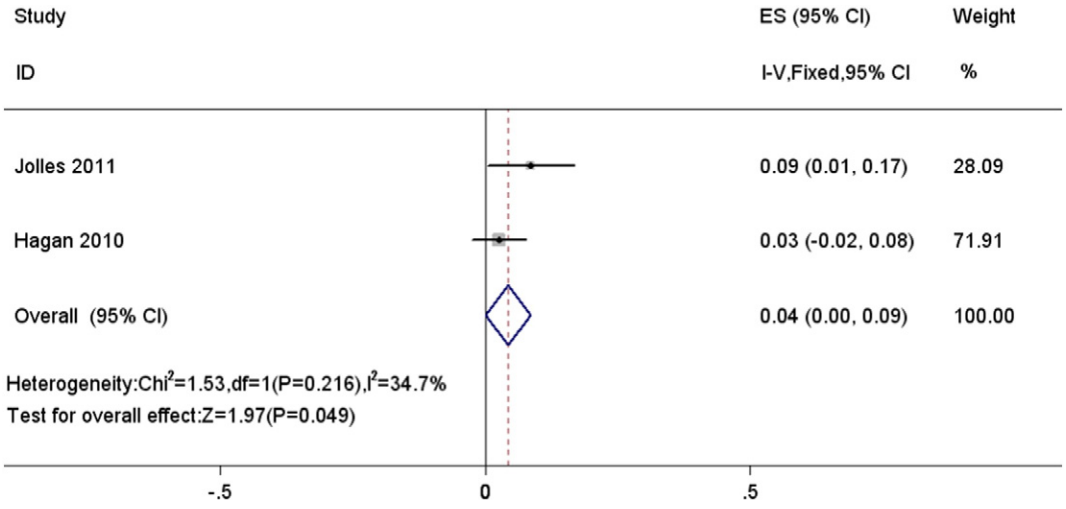


Fig. 4. Rate of patients hospitalized due to infection.

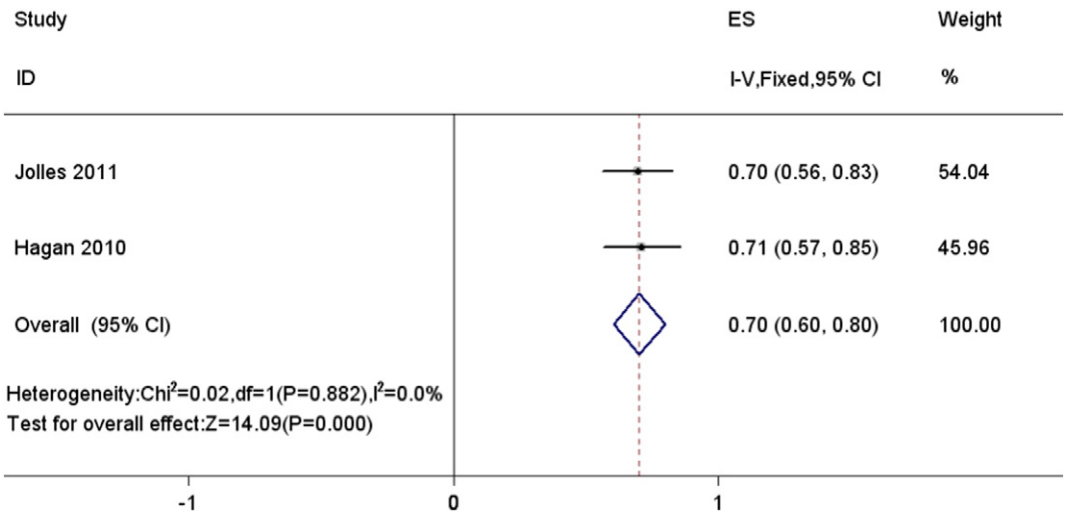


Fig. 5. Rate of patients with antibiotics.

group, some difference was identified. In general, children had better outcome on "Infections" and "Days with antibiotics", but were worse in "Days missed from work/school" and "Hospitalized due to infection" than adult. Except "Infections", adolescent had the best outcome compared with children and adult.

As a subcutaneous preparation, local reactions were the main adverse events. In the current study, 63.7% AEs were local reactions and 99.7% of which were considered possibly related to SCIG-20%. Fortunately, 98.4% local reactions were temporally associated, and 99.7% local reactions were mild to moderate in intensity. Meanwhile, a slight tendency that incidence of local reaction decreases over time was reported. In a case report, SCIG-20% was given to 2 infants aged 4 and 14 mouths for 47 and 35 weeks, and it was well tolerated [23]. Systemic AEs were much more significant and meaningful to the patients, and there were also systemic AEs for SCIG-20%. In the current study, 22.4% systemic AEs were considered related to study medication. Most (98.4%) related systemic AEs were mild to moderate, and only 3(1.6%) were severe in intensity. Overall, 99.0% patients experienced AEs. Incidences of AEs were still high for SCIG-20%, but most AEs were local AEs and few (0.4%) related AEs were severe in intensity.

No comparative studies on SCIG-20% were found, but some data from studies of other immunoglobulin drugs may give a compared profile. For efficacy, no. of annual infections per patient was 4.1–4.7, 2.0–3.8 and 2.0–4.1 in SCIG-10%, SCIG-16% and IVIG respectively [37,40,42,43]. In our review, annual rate of infection was 3.74. It was only obviously better than SCIG-10%, and had a similar rate to SCIG-16% and IVIG. For safety, no. of adverse event per infusion was 0.276–0.820, 0.130–0.707 and 0.250–1.087 in SCIG-10%, SCIG-16% and IVIG respectively [37–41]. The data on SCIG-20% was 0.56, and it suggested that SCIG-20% had a similar incidence of AEs compared with other immunoglobulin drugs. But we have to declare that there were no direct comparative studies between SCIG-20% and other immunoglobulin drugs; this result will be very likely to be impacted by further research.

We only included 1 study on HRQoL and treatment satisfaction. 5 measures (SF-36, EQ-5D, LQI, TSQM and IgG-TSQ) were used to assess health quality and satisfaction. Only 1 domain in SF-36 was below the US norms, and all other domains were close to the US norms or had high scores. In general, the results of HRQoL and treatment satisfaction suggested that patients had positive responses on their SCIG-20% therapy, and indicated satisfaction with their treatment [22].

Serum IgG levels as an outcome were reported in primary studies, but we did not include this outcome measures in current systematic review. In including studies, the dose of SCIG-20% (117.0–120.7 vs. 179.6-224.3 mg/kg bw) was 1 time [20] or 1.53 times [19] of that in previous non-SCIG20% treatment. The difference in dosage led to different serum IgG levels. As a result, serum IgG levels reported in primary studies were 8.10 (±1.340) g/L and 12.53 (±3.21) g/L respectively. Both including studies were single-arm study, and we were unable to combine

Table 4
Most common related adverse events (experienced by ≥2 patients).

Adverse event	Infusion-related		Infusion-related and temporally associated (72 h)	
	No. of patients (%, $N = 100$)	No. of events (per infusion, $N = 4095$)	No. of patients (%, $N = 100$)	No. of events (per infusion, $N = 4095$)
Headache	18 (18.0)	49 (0.012)	17 (17.0)	40 (0.009)
Fatigue	6 (6.0)	8 (0.002)	5 (5.0)	6 (0.001)
Pruritus	4 (4.0)	14 (0.003)	4 (4.0)	13 (0.003)
Respiratory tract infection	4 (2.0)	6 (0.001)	2 (1.0)	2 (<0.001)
Abdominal discomfort	4 (4.0)	5 (0.001)	4 (4.0)	5 (0.001)
Rash	4 (4.0)	4 (<0.001)	3 (3.0)	3 (<0.001)
Pain	3 (3.0)	4 (<0.001)	2 (2.0)	3 (<0.001)
Pyrexia	3 (3.0)	3 (<0.001)	2 (2.0)	2 (<0.001)
Vomiting	3 (3.0)	3 (<0.001)	3 (3.0)	3 (<0.001)
Erythema	2 (2.0)	4 (<0.001)	2 (2.0)	4 (<0.001)
Contusion	2 (2.0)	3 (<0.001)	2 (2.0)	3 (<0.001)
Back pain	2 (2.0)	3 (<0.001)	2 (2.0)	2 (<0.001)
Migraine	2 (2.0)	3 (<0.001)	1 (1.0)	2 (<0.001)
Hypothermia	2 (2.0)	2 (<0.001)	1 (1.0)	1 (<0.001)
Diarrhea	2 (2.0)	2 (<0.001)	2 (2.0)	2 (<0.001)
Nausea	2 (2.0)	2 (<0.001)	2 (2.0)	2 (<0.001)
Arthralgia	2 (2.0)	2 (<0.001)	1 (1.0)	1 (<0.001)

Table 5
GRADE evidence profile for each outcome.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Events	Total	Pooled ES	95% CI		
Infections												
2	Observational studies[a]	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	67	84	0.80	(0.71,0.88)	⊕⊕OO low	Critical
Missed from work/school												
2	Observational studies[a]	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	32	84	0.38	(0.27,0.48)	⊕⊕OO low	Important
Hospitalized due to infection												
2	Observational studies[a]	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious	None	5	84	0.04	(0.00,0.09)	⊕OOO very low	Important
Patients with antibiotics												
2	Observational studies[a]	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	59	84	0.70	(0.60,0.80)	⊕⊕OO low	Important

[a] Prospective, open-label, single-arm study.

continuous variables without control group. Pharmacokinetic parameters on SCIG-20% were reported in primary studies [20,24], but we also did not select this outcome because of above reasons.

We did not find any studies on the economic benefits of SCIG-20%. Because SCIG could be used by patients themselves at home, home-based SCIG was more cost-effective when compared with hospital-based IVIG in PIDs patients. Some studies had demonstrated that SCIG was equal to or less costly than IVIG [25–28].

Studies we included were prospective, observational, single-arm study, and each individual study had a low risk of bias in the current review for this type of studies. But in GRADE evidence profile, it showed low quality for outcomes. In the GRADE approach, observational studies were assessed with low quality as primary grade. Upgrading factors ("large effect", "plausible confounding would change the effect" or "dose response gradient") were not found in included studies. Instead, a downgrading factor was observed in "hospitalized due to infection". Therefore, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. But during the process of literature selecting, we found that about 8 studies [29–36] on SCIG-20% were in process. After those studies were published in full text, a new systematic review that included all of them will have a better result and higher quality in some terms.

We only included 4 studies based on 2 trials involving 100 patients; small sample size may be a limitation in our review. All included studies did not have control group, even historical controls. Judgments of any IgG therapy should be made based on a comparison to no IgG therapy, but such a study would be considered unethical currently. In the future, comparative studies of SCIG-20% versus IVIG or SCIG 10% may have more power to show efficacy and safety of SCIG-20%.

5. Conclusions

Although there were some limitations, we can also conclude that the uncontrolled studies with good quality for individual study but low quality for each outcome showed inadequate evidence on efficacy and safety of SCIG-20%. No evidence could prove that SCIG-20% was better than other immunoglobulin drugs. We do not recommend this drug for patients with PIDs based on our results. Further comparative studies are urgently needed, especially in comparison with IVIG or SCIG of other concentrations.

Author contributions

Conceived and designed the experiments: Jie Song, Lingli Zhang, Youping Li.

Performed the experiments: Jie Song, Shuyan Quan, Yi Liu.

Analyzed the data: Jie Song, Yi Liang.

Contributed reagents/materials/analysis tools: Lingli Zhang, Linan Zeng.

Wrote the paper: Jie Song, Lingli Zhang, Linan Zeng.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.intimp.2015.01.016.

References

[1] Notarangelo LD, Fischer A, Geha RS. Primary immunodeficiencies: 2009 update. International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies. J Allergy Clin Immunol 2009;124(6):1161–78.
[2] Geha RS, Notarangelo LD, Casanova JL. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007;120(4):776–94.
[3] Conley ME. Genetics of primary immunodeficiency diseases. Rev Immunogenet 2000;2(2):231–42.
[4] Boy le JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol 2007;27:497–502.
[5] Baumgart KW, Britton WJ, Kemp A, French M, Roberton D. The spectrum of primary immunodeficiency disorders in Australia. J Allergy Clin Immunol 1997;100(3):415–23.
[6] Lau YL. Primary immunodeficiencies in Hong Kong. Hon Kong J Paediatr 1992;1(2):15–29.
[7] Hayakawa H, Iwata T, Yata J, Kobayashi N. Primary immunodeficiency syndrome in Japan. I. Overview of a nationwide survey on primary immunodeficiency syndrome. J Clin Immunol 1981;1(1):31–9.
[8] European Primary Immunodeficiencies Consensus Conference. Consensus report and recommendations; 2006 [Budapest].
[9] Blaese R, et al, editors. Patient and family handbook for primary immunodeficiency diseases. 4th ed. Towson, MD: Immune Deficiency Foundation; 2007.
[10] Berger M. Principles of and advances in immunoglobulin replacement therapy for primary immunodeficiency. Immunol Allergy Clin N Am 2008;28:413–37.
[11] Stiehm ER. Adverse effects of human immunoglobulin therapy. Transfus Med Rev 2013;27(3):171–8.
[12] Abolhassani H, Sadaghiani MS, Aghamohammadi A, Ochs HD, Rezaei N. Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta analysis. J Clin Immunol 2012;32(6):1180–92.
[13] Lingman-Framme J, Fasth A. Subcutaneous immunoglobulin for primary and secondary immunodeficiencies: an evidence-based review. Drugs 2013;73(12):1307–19.
[14] Weiler CR. Immunoglobulin therapy: history, indications, and routes of administration. Int J Dermatol 2004;43:163–6.
[15] Orange JS, Belohradsky BH, et al. Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clin Exp Immunol 2012;169(2):172–81.
[16] WHO. The selection and use of essential medicines. Report of the WHO Expert Committee; 2013 [Available: http://www.who.int/medicines/EC19uneditedReport.pdf?ua=1].
[17] National Institute for Health and Clinical Excellence (NICE) website. Quality assessment for case series. [Available: http://www.nice.org.uk/nicemedia/live/10919/29075/29075.pdf].

[18] GRADE handbook for grading quality of evidence and strength of recommendation. Version 3.2 (updated March 2009) The GRADE Working Group; 2009[Available: http://www.who.int/hiv/topics/mtct/grade_handbook.pdf].
[19] Hagan JB, Fasano MB, et al. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. J Clin Immunol 2010;30(5):734–45.
[20] Jolles S, Bernatowska E, et al. Efficacy and safety of Hizentra in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. Clin Immunol 2011;141(1):90–102.
[21] Borte M, Pac M, et al. Efficacy and safety of hizentra(R), a new 20% immunoglobulin preparation for subcutaneous administration, in pediatric patients with primary immunodeficiency. J Clin Immunol 2011;31(5):752–61.
[22] Jones CA, Rojavin M, Baggish JS. Patients with primary immunodeficiency receiving subcutaneous immune globulin Hizentra maintain health-related quality of life and treatment satisfaction in a multicentre extension study of efficacy, tolerability and safety. J Pharm Health Serv Res 2012;3(1):41–7.
[23] Gallagher JL, Patel NC. Subcutaneous immunoglobulin replacement therapy with Hizentra is safe and effective in two infants. J Clin Immunol 2012;32(3):474–6.
[24] Wasserman RL, Melamed I, et al. Pharmacokinetics of subcutaneous IgPro20 in patients with primary immunodeficiency. Clin Pharmacokinet 2011;50(6):405–14.
[25] Högy B, Keinecke HO, Borte M. Pharmacoeconomic evaluation of immunoglobulin treatment in patients with antibody deficiencies from the perspective of the German statutory health insurance. Eur J Health Econ 2005;6(1):24–9.
[26] Membe SK, Ho C, Cimon K, Morrison A, Kanani A, Roifman CM. Economic assessment of different modalities of immunoglobulin replacement therapy. Immunol Allergy Clin North Am 2008;28(4):861–74.
[27] Beaute J, Levy P, et al. Economic evaluation of immunoglobulin replacement in patients with primary antibody deficiencies. Clin Exp Immunol 2010;160(2):240–5.
[28] Martin A, Lavoie L, Goetghebeur M, Schellenberg R. Economic benefits of subcutaneous rapid push versus intravenous immunoglobulin infusion therapy in adult patients with primary immune deficiency. Transfus Med 2013;23(1):55–60.
[29] Quevedo TG, Mannhardt-Laakmann W, et al. Health-related quality of life of patients with primary immunodeficiency switching from intravenous IgG to a new 20% subcutaneous IgG. Clin Immunol 2010;135:S87.
[30] Kim JY, Kuryan J, Bonagura VR. Tolerability and efficacy of 20% subcutaneous immune globulin (ScIg) delivered by rapid push. J Allergy Clin Immunol 2012; 129(2):AB109.
[31] Koterba A, Farnan K, Sierra C, Eufrasio D, Stein MR. Experience with subcutaneous loading of vivaglobin or hizentra in primary immunodeficiency patients naive to immunoglobulin replacement therapy. Ann Allergy Asthma Immunol 2012;109:A101.
[32] Nguyen D, Dorsey M, Alberdi T, Duff C, Sleasman J. Subcutaneous hizentrareg; (20%) is better tolerated and shares similar efficacy compared to subcutaneous vivaglobin (registered trademark) (16%). J Allergy Clin Immunol 2012;129(2):AB15.
[33] Panahloo Z, Jolles S. Factors affecting infusion of high (20%) vs lower concentration (16%) SCIG in primary immunodeficiency disorders. J Allergy Clin Immunol 2012; 129(2):AB14.
[34] Borte M, Wasserman RL, Rojavin M, Bexon M, Jolles S. Long-term efficacy and tolerability of 20% SCIG in the treatment of patients with primary immunodeficiency disease. J Allergy Clin Immunol 2013;131(2):AB157.
[35] Gregory R, Malcolmson C, Patel C, Woolley T, Jones A. Experience with a 20% subcutaneous immunoglobulin (Hizentra) in children with primary immunodeficiency diseases: a single-center review. J Allergy Clin Immunol 2013;131(2):AB154.
[36] Malcolmson C, Gregory R, Patel C, Panahloo Z, Jones A. Patient satisfaction with 20% subcutaneous immunoglobulin (Hizentra) treatment: results from a single-center study in children with immunodeficiencies. J Allergy Clin Immunol 2013;131(2): AB155.
[37] Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 2000;20(2):94–100.
[38] Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol 2006;26(3):265–73.
[39] Berger M, Murphy E, Riley P, Bergman GE. Improved quality of life, immunoglobulin G levels, and infection rates in patients with primary immunodeficiency diseases during self-treatment with subcutaneous immunoglobulin G. South Med J 2010;103(9):856–63.
[40] Wasserman RL, Irani AM, et al. Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purified in patients with primary immunodeficiency disease. Clin Exp Immunol 2010;161(3): 518–26.
[41] Wasserman RL, Melamed I. Efficacy, safety, and pharmacokinetics of a 10% liquid immune globulin preparation (GAMMAGARD LIQUID, 10%) administered subcutaneously in subjects with primary immunodeficiency disease. J Clin Immunol 2011; 31(3):323–31.
[42] Fasth A, Nystrom J. Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. Acta Paediatr 2007;96(10):1474–8.
[43] Desai SH, Chouksey A, Poll J, Berger M. A pilot study of equal doses of 10% IGIV given intravenously or subcutaneously. J Allergy Clin Immunol 2009;124(4):854–6.