Systematic Review

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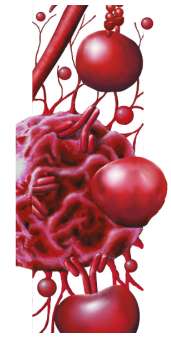
Immunotherapy



Subcutaneous immunoglobulin use in immunoglobulin-naive patients with primary immunodeficiency: a systematic review

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Aim: Identify and describe published literature on the use of subcutaneous immunoglobulin (SCIG) as initial immunoglobulin (IG)-replacement therapy for patients with primary immunodeficiency diseases (PID). **Methods:** We systematically identified and summarized literature in MEDLINE, Embase, BioSciences Information Service and Cochrane Library assessing efficacy/effectiveness, safety/tolerability, health-related quality-of-life (HRQoL) and dosing regimens of SCIG for IG-naive patients with PID. **Results:** Sixteen studies were included. In IG-naive patients, SCIG managed/reduced infections and demonstrated similar pharmacokinetic parameters to IG-experienced patients; adverse events were mostly minor injection-site pain or discomfort. Three studies reported improvements in HRQoL. Quality of studies was difficult to assess due to limited reporting. **Conclusion:** Although studies were lacking, available data suggest IG-naive and IG-experienced patients initiating SCIG likely have similar outcomes.

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Keywords: immunoglobulin-naive patients • immunoglobulin treatment initiation • primary immunodeficiency • quality-of-life • subcutaneous immunoglobulin • treatment outcomes

Primary immunodeficiency diseases (PID) are a group of rare, heterogeneous disorders composed of approximately 430 genetic conditions that impair the production or function of proteins with critical roles in the immune system [1]. The prevalence of PID is estimated to be 1:10,000 persons overall, but may differ among varied ethnic groups and countries [2]. Patients can develop PID any time throughout life [2,3]. Misdiagnoses are common because the diseases generally present as routine, chronic or recurrent infections, and diagnoses can be delayed for decades [4].

Immunoglobulin (IG)-replacement therapy (IGRT) is a mainstay for patients with significantly impaired antibody production to establish protection against infection [2,5]. Intravenous IG (IVIG) is the standard of care for initiation and long-term treatment of patients with PID [6,7], whereas subcutaneous IG (SCIG) is becoming a well-recognized option that offers patients previously treated by IVIG (IG-experienced) multiple administration options to customize their IG treatment to fit their needs [7]. Patients with PID have reported improved health-related quality-of-life (HRQoL) with SCIG treatment, but these studies are limited by small sample sizes [8]. In routine practice, newly diagnosed patients with PID but with no previous experience with IGRT (IG-naive) are frequently initiated on IVIG or directly on SCIG [8,9]. Although it may be generally accepted and common practice in the European Union to initiate patients with PID on SCIG, outcomes among IG-naive patients who are initiated on SCIG have not been well researched. While there have been systematic reviews of the use of SCIG in patients who are IG-experienced [10,11], a recent, comprehensive review of scientific literature that evaluates the safety, efficacy and HRQoL associated with SCIG treatment in IG-naive patients with PID is lacking.

This systematic literature review aimed to evaluate data on the use of SCIG in patients with PID who are IG-naive to advance the current understanding of this patient population. Data on clinical outcomes (efficacy/effectiveness and safety/tolerability), HRQoL, SCIG-dosing regimens and patient health and treatment pathways were examined.

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Table 1. PICOS framework for systematic literature review inclusion criteria.

Criteria	Included
Population	• Patients with PID who are IG-naive • Mixed populations of IG-naive and IG-experienced patients, provided results were reported separately for each subset of patients
Intervention/comparisons	• Studies that investigated any SCIG for PID treatment • Studies that compared different SCIGs or compared a SCIG with IVIG or placebo • Single-arm studies without comparators
Study design	• Observational and interventional studies • Systematic reviews and meta-analyses† • Pharmacokinetic studies • Economic evaluations and cost studies
Outcomes	• Any efficacy/clinical outcome (ie, infection rates, serum and trough IG levels, pharmacokinetics) • Any safety/tolerability outcome (ie, adverse events, discontinuations, mortality, tolerability) • Any HRQoL outcome • Information on SCIG-dosing regimens • Summaries of patient health and treatment pathways
Language	• All languages
Date	• Conference abstracts: 2014 to 2021 • No limit on database searches except for conference abstracts

†Hand searched to identify relevant studies but not included at level 2 screening.
HRQoL: Health-related quality-of-life; IG: Immunoglobulin; IVIG: Intravenous immunoglobulin; PID: Primary immunodeficiency diseases; PICOS: Participant, intervention, comparison, outcome and study design; SCIG: Subcutaneous immunoglobulin.

Methods

Literature searches with no language limitations were performed on MEDLINE, Embase, BioSciences Information Service and the Cochrane Library. Searches were first conducted on 28 April 2019 and updated on 11 August 2019 and 30 March 2021 to identify the most recent literature to supplement the initial search. Date limitations were not applied in the electronic database searches, except for conference abstracts, which were limited to abstracts published from 2014 to 2021. Searches with no language limitation were also conducted on trial registries, reference lists of any identified systematic literature reviews and meta-analyses published between 2014 and 2021, and websites of professional organizations to identify any articles that may not have been indexed in the electronic databases. Key health technology assessment and regulatory websites were also searched for information published between 2014 and 2019. The inclusion criteria, specified in terms of the participants, interventions, comparisons, outcomes and study design (PICOS) framework, are shown in Table 1. The full electronic search strategies for all databases used in this review are shown in Supplementary Table 1.

English-language articles or conference abstracts were screened and selected for inclusion in two levels against the predefined inclusion criteria (Figure 1). In the first level of screening, two researchers independently reviewed titles and abstracts of studies that were identified. In the second level of screening, full texts of studies included during level 1 were obtained and screened by two independent researchers to determine eligibility. Any discrepancies found were resolved by consensus between the two independent researchers. Data regarding study inclusion criteria and characteristics, patient demographics, treatment history, interventions and study end points were extracted using *a priori* standardized templates by one researcher from full-text publications, where available. All extracted data were verified against the source by a second researcher who was not involved in the extraction. Synthesis of data was not conducted for this review due to the lack of standardized definitions and inconsistent reporting of outcomes.

Quality assessments were performed for nonrandomized controlled trials evidence using Critical Appraisal Skills Programme (CASP) checklists (no randomized controlled trials were identified for inclusion in the review). The search protocol was designed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12]. A completed PRISMA checklist is provided in Supplementary Table 2. This review was not registered; the full protocol for the review is available on request.

Results

Screening results

Overall, 4010 articles were retrieved from the systematic database searches, internet searches and hand searches. After deduplication, 2533 articles remained for manual screening, of which 364 underwent full-text review. Of these, 16 studies met the inclusion criteria for this systematic review [13–28]. Figure 1 shows the PRISMA diagram

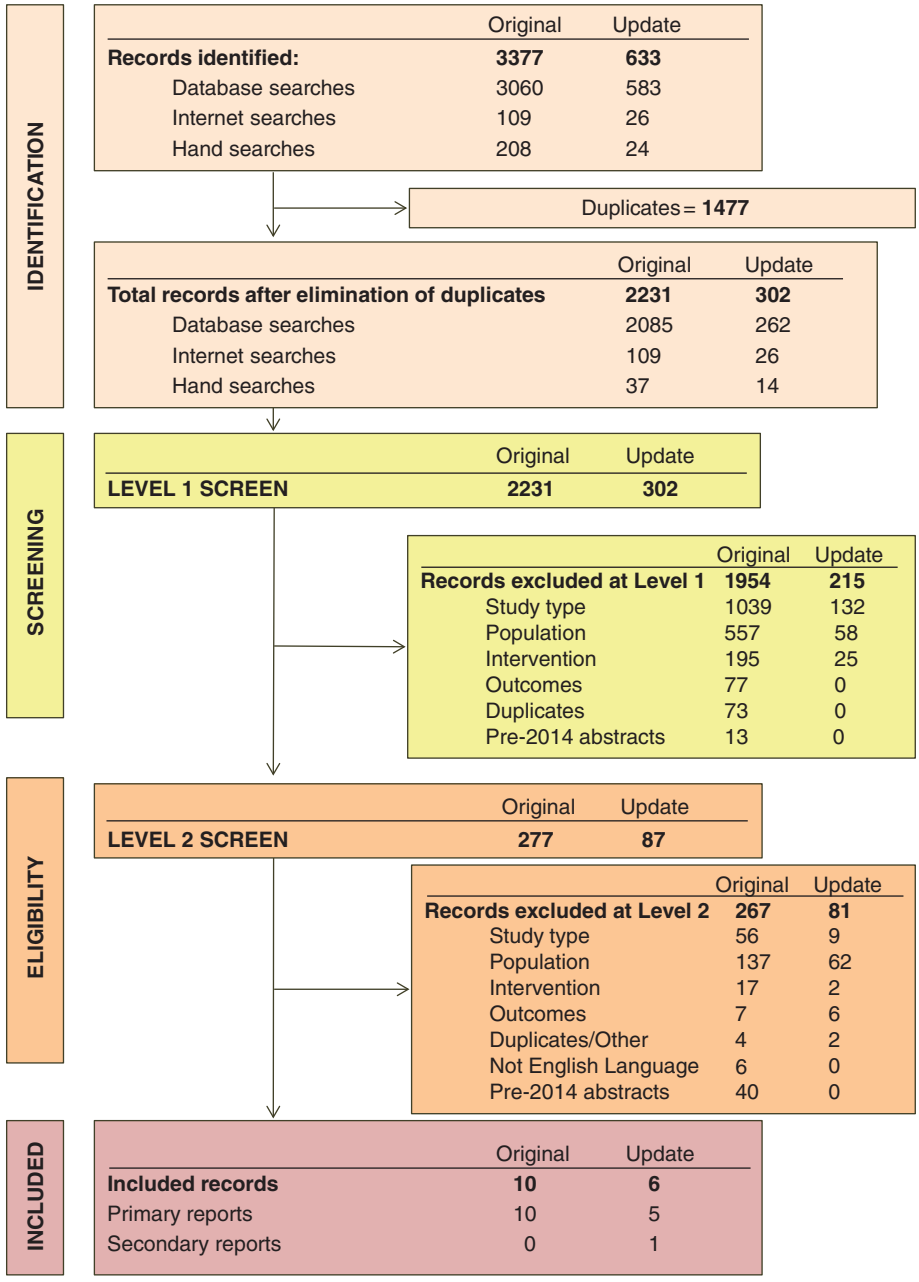

Figure 1. PRISMA diagram.

describing the screening process of this review, showing the records excluded at each level of screening, and reason for exclusion.

Study characteristics

No randomized controlled trials were identified for inclusion. Of the 16 studies included (Table 2), 14 were retrospective cohort studies [13,14,16–27], and one was a cross-sectional study [28]. Five studies included only patients who were IG-naive [15,17,22,23,25] and 11 studies included a mixed population of patients but reported results separately for those who were IG-naive [13,14,16,18–21,24,26–28]. Seven of these studies reported data for both IG-naive and IG-experienced patients [13,18–20,24,26,27].

Table 2. Summary of included studies and outcomes reported.

Study (year), country	Study design and duration or follow-up period	Brief description of population and number of patients†	Interventions included in study	Outcomes reported	Ref.
Altook *et al.* (2019),‡ Canada [abstract only]	Retrospective cohort study; 12-months	Adult patients (≥18 years old) with PID; 24 were IG naive and 42 had previously received IVIG	Patients had received SCIG push for ≥12 months (SCIG brand not reported)	Efficacy: yes (PK, antibiotic use) Safety: yes HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: no	[13]
Anterasian *et al.* (2019), USA	Retrospective analysis of SF-36 surveys conducted every 3 months as part of standard care at a single center from 2014 to 2016	630 patients with PID receiving home SCIG or IVIG. 93 patients reported results before and after initiation of SCIG and 11 patients before and after initiation of IVIG. 85 patients receiving SCIG were naive to treatment	SCIG or IVIG at home (brand not reported)	Efficacy: no Safety: no HRQoL: yes SCIG-dosing regimens and/or patient health and treatment pathways: no	[14]
Borte *et al.* (2011), Canada, Germany, Italy and Spain	Prospective, single-arm, cohort study; 6-months	18 previously untreated patients with PID age range 1–70 years	Treatment with SCIG (Vivaglobin®), without receiving IVIG initially	Efficacy: yes (PK, antibiotic use) Safety: yes HRQoL: yes SCIG-dosing regimens and/or patient health and treatment pathways: yes	[15]
Cinetto *et al.* (2021), Italy	Retrospective single-center cohort study between September 2011 and February 2018	102 patients with primary antibody deficiency syndromes (CVID = 75) and 131 secondary antibody deficiencies at a single hematology and clinical immunology unit. Mean age was 51.58 ± 14.81 years. 53 patients with PAD were naive to IG treatment	≥12 weeks of SCIG treatment according to current guidelines Of the patients with PAD: 45 (44.1%) were on 20% SCIG, 43 (42.1%) were on 16% or 16.5% SCIG, and 14 (13.7%) were on 10% facilitated SCIG. Brand not reported	Efficacy: yes (PK, infections, antibiotic use) Safety: not for IG-naive subset HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: not for IG-naive subset	[16]
Duff and Leiding (2017), US [Abstract only]	Retrospective cohort study, 3–4 months	14 IG-naive patients with PID, age range 7–76 years	Received 20% SCIG therapy without first receiving a loading dose of IVIG (SCIG brand not reported)	Efficacy: no Safety: yes HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: yes	[17]
Gardulf *et al.* (1995), Sweden, Denmark, and Norway	Retrospective cohort study (used medical record and questionnaires); 36 months	165 patients with primary hypogammaglobulinemia or IgG-subclass deficiencies with ongoing or previous SC replacement therapy (age range 13–76 years); 24 patients were previously IG-naive	SCIG replacement therapy for 5 months to 9 years 8 months with Gammaglobulin Kabi, Gammabulin or Nordimmun	Efficacy: yes (PK) Safety: not for IG-naive subset HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: yes	[19]
Gardulf *et al.* (1993), Sweden	Cohort study (used medical records, data registries and questionnaires); duration not reported	25 patients aged ≥18 years with a diagnosis of hypogammaglobulinemia; 10 were IG naive	SCIG self-infusions (brand not reported)	Efficacy: no Safety: no HRQoL: yes SCIG-dosing regimens and/or patient health and treatment pathways: yes Other: perception of infections	[18]
Gaspar *et al.* (1998), UK	Retrospective cohort study and patient satisfaction question-naive; up to 3.5 years	26 children with PID who received replacement IG treatment by the rapid SC infusion; 11 were treated with SCIG from outset while 15 previously received IVIG	SCIG (Gammabulin)	Efficacy: yes (PK, infections, antibiotic use) Safety: yes HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: yes Other: parental satisfaction	[20]

†Due to insufficient information from the included studies, description of age may be from inclusion criteria or resulting patient demographics, depending on available information.
‡It could not be confirmed whether these publications are from the same study.
CVID: Common variable immune disorder; HRQoL: Health-related quality-of-life; IG: Immunoglobulin; IgG: Immunoglobulin G; IV: Intravenous; IVIG: Intravenous immunoglobulin; PAD: Primary antibody deficiency; PID: Primary immune deficiency; PK: Pharmacokinetic; SC: Subcutaneous; SCIG: Subcutaneous immunoglobulin; SF-36: Short-Form, 36 questions questionnaire; UK: United Kingdom; US: United States.

Table 2. Summary of included studies and outcomes reported (cont.).

Study (year), country	Study design and duration or follow-up period	Brief description of population and number of patients†	Interventions included in study	Outcomes reported	Ref.
Kearns *et al.* (2017), US	Retrospective analysis of patient registry; duration not reported	383 patients receiving IG therapy; 367 were diagnosed with PID and 33 made up a pediatric population	SCIGs or IVIGs (brand not reported); treatment information was not provided for IG-naive patients	Efficacy: not for IG-naive subset Safety: not for IG-naive subset HRQoL: not for IG-naive subset SCIG-dosing regimens and/or patient health and treatment pathways: not for IG-naive subset The only information reported for IG-naive patients was average age at admission	[21]
Noone *et al.* (2017), USA [abstract only]	Insurance databases analysis; duration not reported	1094 patients with PID who were treatment-naive and had ≥2 PID claims >90 days apart	853 patients were IV infused; 241 patients were SC treated (brand not reported)	Efficacy: no Safety: no HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: no Other: cost	[22]
Ritchey *et al.* (2020), USA [abstract only]	Retrospective cohort study using IBM MarketScan Research Databases from 2012 to 2018	Patients with PID who were new users of IG replacement therapy from 2012 to 2018. 2604 patients initiated SCIG and 15,327 initiated IVIG. Age was not reported	SCIG or IVIG (brand not reported). Of 17,961 patients on IG, 15,297 were on IVIG, 2269 were on 20% SCIG and 395 were on facilitated SCIG	Efficacy: no Safety: no HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: no Other: markers for severity	[23]
Samaan *et al.* (2014), Canada	Retrospective cohort study; range of follow-up 7.9 to 66.3 months	Pediatric cohort of 143 patients with PID on IG replacement: 'switch' cohort (n = 51) included patients already on IVIG when SCIG became available in Quebec in 2007; 'new' cohort (n = 92) consisted of patients diagnosed after 2007 and therefore given the choice at the beginning of IG replacement	Patients could choose between IVIG or SCIG (brand not reported)	Efficacy: no Safety: yes HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: yes Other: stress, compliance	[24]
Sharma *et al.* (2019), US	Retrospective review of medical records at a single center between 2011 and 2018	71 patients diagnosed with primary hypogammaglobulinemia followed up at the University of California at Irvine Immunology Clinic, mean age was 58 years (range 13–92) and 80% were females	11 patients (16%) were on SCIG, 55 (77%) were on IVIG and 5 (7%) were on facilitated SCIG (brand not reported)	Efficacy: yes (PK, infections) Safety: no HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: yes	[25]
Walter *et al.* (2020a),‡ Canada	Retrospective chart review of the SCIG push program in Manitoba, Canada from November 2007 to September 2018	62 patients aged ≥18 years and with PID, enrolled in the SCIG push program. 27 were IG naive and 35 had prior IVIG. Overall, 38.7% had CVID and 33.8% had IgG subclass deficiency	Patients had received SCIG push for ≥12 months (SCIG brand not reported)	Efficacy: yes Safety: yes HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: yes	[26]
Walter *et al.* (2020b) [abstract only],‡ Canada	Retrospective chart review of the SCIG push program in Manitoba, Canada, at least 12 months – dates not provided	65 patients with PID aged ≥18 years, enrolled in the SCIG push program. 28 were IG naive and 37 had prior IVIG	Patients had received SCIG push for ≥12 months (SCIG brand not reported)	Efficacy: yes Safety: yes HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: no	[27]
Westh *et al.* (2017), Denmark	Nationwide retrospective, cross-sectional study; conducted from December 2013 to November 2014	179 adult patients with CVID; 144 (80.5%) categorized as 'probable CVID'; 35 (19.5%) categorized as 'possible CVID'	170 (95.0%) patients were on IG replacement therapy; initially, the chosen route was SC for 97 (57.1%) and IV for 62 (36.5%) patients (brand of SCIG not reported)	Efficacy: no Safety: no HRQoL: no SCIG-dosing regimens and/or patient health and treatment pathways: yes	[28]

†Due to insufficient information from the included studies, description of age may be from inclusion criteria or resulting patient demographics, depending on available information.
‡It could not be confirmed whether these publications are from the same study.
CVID: Common variable immune disorder; HRQoL: Health-related quality-of-life; IG: Immunoglobulin; IgG: Immunoglobulin G; IV: Intravenous; IVIG: Intravenous immunoglobulin; PAD: Primary antibody deficiency; PID: Primary immune deficiency; PK: Pharmacokinetic; SC: Subcutaneous; SCIG: Subcutaneous immunoglobulin; SF-36: Short-Form, 36 questions questionnaire; UK: United Kingdom; US: United States.

Sample sizes of included studies ranged from 14 patients [17] to 15,327 patients [23]. Two studies were multinational: that by Borte *et al.* (2011) was undertaken in Canada, Germany, Italy and Spain [15], and the study by Gardulf *et al.* (1995) was performed in Sweden, Denmark and Norway [19]. The remaining 14 studies were conducted in a single country, including six in USA [14,17,21–23,25], four in Canada [13,24,26,27] and one each in UK [20], Denmark [28], Italy [16] and Sweden [18]. Five of the studies included adults only [13,18,26–28], two included children only [20,24] and five included both adults and children [15,17,19,21,25]. Four studies did not specify an age range [14,16,22,23].

Outcomes of interest

Outcomes reported in each of the included studies are summarized in Table 2.

Efficacy & effectiveness

Efficacy and effectiveness outcomes reported in the studies included immunoglobulin G (IgG) levels, infections and antibiotic use in response to infections.

Eight studies included data on IgG levels (Table 3) [13,15,16,19,20,25–27]. The time points at which IgG levels were measured varied between studies, as did the follow-up period for IgG levels (ranging from 25 weeks [15] to 36 months (Table 3) [19]. Overall, SCIG treatment was shown to be effective in increasing mean IgG levels in both IG-naive and IG-experienced patients. At baseline, mean IgG levels ranged from 1.7 g/l [19] to 6.6 g/l [13] for IG-naive patients (Table 3), and up to 8.5 g/l for IG-experienced patients [13]. At 12 months after SCIG treatment initiation, mean IgG levels were reported by Altook *et al.* (2019) to have increased to 11.3 g/dL in IG-naive (n = 24) patients, similar to that achieved in IG-experienced (n = 42) patients (11.8 g/l) [13]. Gardulf *et al.* (1995) reported mean IgG levels at 12 months after SCIG treatment initiation to be 7.5 g/l in IG-naive patients older than 12 years (n = 18) [19].

Four studies included data on infections (Table 4) [15,16,20,25]. Gaspar *et al.* reported that in children with PID who received IGRT by rapid subcutaneous infusion (n = 26), no serious life-threatening infections and no infections requiring admission to hospital were observed [20]. In a prospective cohort study, Borte *et al.* found that annualized rates of infections per patient decreased from 4.73 infections per patient to 3.95 infections per patient in 18 previously untreated patients with PID who received SCIG treatment without receiving initial IVIG [15]. In a cohort of 102 patients, Cinetto *et al.* reported a significant (Wilcoxon matched-pairs signed rank test; $p < 0.0001$) decrease in the infection rate in patients with PID who were IG-naive from 3.69 ± 2.81/year per patient to 0.52 ± 1.18/year per patient after SCIG [16]. In a retrospective review of 71 patients with PID, Sharma *et al.* reported average annual infection rate of 0.88 in patients treated with conventional SCIG, and 0.6 for patients treated with facilitated SCIG [25].

Six studies reported antibiotic use to treat infections [13,15,16,20,26,27]. Based on patient records, Gaspar *et al.* found antibiotic requirement was reduced after starting SCIG in the IG-naive group (n = 11) and showed no noticeable difference in the IG-experienced group (n = 15) [20]. Two further studies [15,17] reported information on infections as safety data rather than as an efficacy outcome and are summarized in Table 5; no serious infections related to SCIG treatment were reported.

Safety & tolerability

Safety and tolerability data were reported for five studies (Table 5) [13,15,17,20,24], with results suggesting that adverse events (AEs) were generally mild to moderate and primarily occurred locally at the injection site among IG-naive patients receiving SCIG. Of the 18 IG-naive patients included in the Borte *et al.* study, 14 (78%) experienced AEs from SCIG treatment, most of which were mild or moderate in intensity [15]. Severe systemic infections were reported as AEs by two patients but were considered unrelated to study treatment [15]. Overall, the most commonly reported AEs were erythema, and swelling or pain or discomfort at the infusion site. Statistical analyses or specific comparisons of safety data between IG-naive and IG-experienced patients were not conducted in any of the studies reviewed.

HRQoL

Three studies reported HRQoL outcomes [14,15,18]. Borte *et al.* found IG-naive patients (n = 18) experienced improved HRQoL following initiation of SCIG, with improvements observed at 6 months in selected domains of the 36-Item Short-Form Survey (SF-36) and all domains of the Child Health Questionnaire-Parent Form 50

Table 3. IgG levels in immunoglobulin-naive patients treated with subcutaneous immunoglobulin.

Study (year)	Study design	Brief description of population age†	Study arm/intervention/subgroup	IgG levels	Ref.
Altook *et al.* (2019) [abstract only]	Retrospective cohort study	≥18 years old	IG-naive patients (n = 24)	Mean IgG levels, g/l (range): ■ 6 months prior to SCIG = 6.6 (<0.33–15.8) ■ 12 months after SCIG = 11.3 (6.52–16.1)	[13]
			Patients who previously received IVIG (n = 42)	Mean IgG levels, g/l (range): ■ 6 months prior to SCIG = 8.5 (0.38–15.5) ■ 12 months after SCIG = 11.8 (4.9–39)	
Borte *et al.* (2011)	Prospective, single-arm, cohort study	1–70 years old	SCIG (Vivaglobin) treatment without receiving initial IVIG	Proportion of patients with response (IgG trough levels ≥5 g/l), n/N (%) [95% CI]: ■ Day 12 = 17/18 (94) [0.727–0.999] ■ Day 19 = 17/18 (94) [0.727–0.999] ■ Day 26 = 18/18 (100) [0.815–1.000] IgG trough level response: ■ Trough IgG levels at days 19 and 26 were maintained at >5 g/l in the 17 patients who completed the study ■ Mean (SD) increase in serum IgG level on day 12 was 3.941 g/l (0.7466 g/l), with individual increases ranging from 2.44 to 5.50 g/l ■ Mean serum IgG levels (g/l) (of individual median values) over course of study: – Screening = 3.6; Day 1 = 3.6; Day 5 = 6.7; Day 12 = 7.5; Day 19 = 7.6; Day 26 = 7.4; Week 6 = 7.5; Week 8 = 7.8; Week 12 = 8.0; Week 25 = 8.0	[15]
Cinetto *et al.* (2021)	Retrospective single-center cohort study	Mean age was 51.58 ± 14.81 years	SCIG in IG-naive PAD patients (n = 53)	■ Mean serum IgG before SCIG was 3.46 ± 1.90 g/l ■ Mean IgG through levels during SCIG treatment was 7.67 ± 1.45 g/l There was no statistical correlation between SCIG dose and IgG through levels at steady state (r = 0.1234, p = 0.2414)	[16]
Gardulf *et al.* (1995)	Retrospective cohort study (used medical record and questionnaires)	13–76 years old	SCIG replacement therapy for 5 months to 9 years 8 months	**Mean subclass concentrations during first 6 months (for patients not previously treated):** ■ In patients with IgG1 deficiency, the mean IgGI1 concentration increased from 3.1 to 5.5 g/l ■ In patients with IgG2 deficiency, the mean IgG2 concentration increased from 0.6 to 4.1 g/l ■ In patients with IgG3 deficiency, the mean IgG3 concentration increased from 0.13 to 0.22 g/l **Mean (range) serum IgG levels (g/l) before and during 36 months SCIG in previously unsubstituted CVID/XLA patients:** ■ Stockholm: baseline (n = 8) = 2.1 (0.4–4.2); month 6 (n = 8) = 8.2 (6.0–11.0); month 12 (n = 8) = 10.1 (7.9–14.7); month 24 (n = 8) = 10.9 (7.5–14.0); month 36 (n = 7) = 9.9 (6.9–12.7) ■ Copenhagen: baseline (n = 8) = 0.5 (0–1.6); month 6 (n = 6) = 5.9 (2.3–9.2); month 12 (n = 5) = 4.9 (2.3–8.7); month 24 (n = 5) = 5.6 (3.8–7.1); month 36 (n = 6) = 6.7 (5.3–8.9) ■ Oslo: baseline (n = 8) = 2.5 (0.1–4.7); month 6 (n = 8) = 5.0 (2.5–7.8); month 12 (n = 5) = 5.9 (4.2–7.1); month 24 (n = 4) = 6.4 (4.5–8.3); month 36 = not reported ■ Total: baseline (n = 24) = 1.7 (0–4.7); month 6 (n = 22) = 6.4 (2.3–11.0); month 12 (n = 18) = 7.5 (2.3–14.7); month 24 (n = 17) = 8.3 (3.8–14.0); month 36 (n = 13) = 8.4 (5.3–12.7)	[19]
Gaspar *et al.* (1998)	Retrospective cohort study and patient satisfaction questionnaire	Pediatrics (1.5 months–15 years)	SCIG (Gammabulin) in IG-naive patients (n = 11)	■ Eight patients had a pretreatment GMT for IgG below the normal range of age-matched reference values, but all achieved normal IgG concentrations by 3 months, except for two children with pretreatment IgG concentrations of <20% of the GMT ■ All patients achieved normal concentrations at 6 months (results were presented graphically)	[20]
			SCIG (Gammabulin) in IG-experienced patients (n = 15)	■ Eight patients had a GMT for IgG below the normal range at the initiation of IVIG, and all patients had a normal IgG GMT at the time of starting SCIG; these were maintained (results were presented graphically)	

†Due to insufficient information from the included studies, description of age is found in inclusion criteria or resulting patient demographics.

CI: Confidence interval; CVID: Common variable immune disorder; GMT: Geometric mean titer; IG: Immunoglobulin; IgG: Immunoglobulin G; IVIG: Intravenous immunoglobulin; PAD: Primary antibody deficiency; SCIG: Subcutaneous immunoglobulin; SD: Standard deviation; XLA: X-linked agammaglobulinemia.

Table 3. IgG levels in immunoglobulin-naive patients treated with subcutaneous immunoglobulin (cont.).

Study (year)	Study design	Brief description of population age†	Study arm/intervention/subgroup	IgG levels	Ref.
Sharma *et al.* (2019)	Retrospective review of medical records at a single center	Mean age 58 years (range 13–92)	Primary hypogammaglobulinemia starting SCIG (n = 11)	▪ Mean IgG at diagnosis for all patients (including those who received IVIG) was 554 mg/dl ▪ Mean IgG trough level was 1005 mg/dl (range 800–1320) ▪ 8/11 (72%) patients had completed subclass reconstitution ▪ Mean IgG trough level for those with reconstituted subclasses was 1058 mg/dl (range 847–1320) ▪ Mean IgG trough level without reconstituted subclasses was 864 mg/dl (range 800–980) ▪ At baseline two patients had IgG3 deficiency, after 12 months SICG, one patient still had IgG3 defiance ▪ Study reports IgG levels before and after treatment for individual patients	[25]
			Primary hypogammaglobulinemia starting facilitated SCIG (n = 5)	▪ Mean IgG trough level was 917 mg/dl (range 679–1171) ▪ At baseline three patients had IgG3 deficiency, after 12 months of treatment no patients were still deficient ▪ All five patients had complete subclass reconstitution ▪ Study reports IgG levels before and after treatment for individual patients	
Walter *et al.* (2020a)	Retrospective chart review of the SCIG push program in Manitoba, Canada	≥18 years old	IVIG-naive (n = 27)	Mean IgG levels, g/l (range): ▪ 6 months prior to SCIG = 4.87 (<0.33–12.30) ▪ 12 months after SCIG = 10.83 (5.85–16.1) ▪ Mean (SD) difference in IgG level before and after 12 months SCIG was 5.96 (2.82) g/l, $p < 0.0001$	[26]
			Patients who previously received IVIG (n = 35)	Mean IgG levels, g/l (range): ▪ 6 months prior to SCIG = 10.72 (6.76–16.80) ▪ 12 months after SCIG = 12.22 (4.99–16.20) ▪ Mean (SD) difference in IgG level before and after 12 months SCIG was 1.50 (3.54) g/l, $p < 0.0017$	
Walter *et al.* (2020b) [abstract only]	Retrospective chart review of the SCIG push program in Manitoba, Canada	≥18 years old	IVIG-naive (n = 28)	Mean IgG levels, g/l (range): ▪ 6 months prior to SCIG = 5.22 (<0.33–12.3) ▪ 12 months after SCIG = 10.75 (5.85–16.1)	[27]
			Patients who previously received IVIG (n = 37)	Mean IgG levels, g/l (range): ▪ 6 months prior to SCIG = 11.67 (6.76–45.9) ▪ 12 months after SCIG = 13.07 (4.99–44.0 g/l)	

†Due to insufficient information from the included studies, description of age is found in inclusion criteria or resulting patient demographics.
CI: Confidence interval; CVID: Common variable immune disorder; GMT: Geometric mean titer; IG: Immunoglobulin; IgG: Immunoglobulin G; IVIG: Intravenous immunoglobulin; PAD: Primary antibody deficiency; SCIG: Subcutaneous immunoglobulin; SD: Standard deviation; XLA: X-linked agammaglobulinemia.

Table 4. Infections in IG-naive patients treated with subcutaneous immunoglobulins.

Study (year)	Details on prophylactic antibiotics	Infections at baseline	Interventions included in study	Infection outcomes	Ref.
Borte *et al.* (2011)	1 patient (6%) was treated with antibiotics for infection prophylaxis for 166 days	In 6 months prior to study: 15 patients experienced 42 infection episodes (annualized rate = 4.73 infections per patient); 11 were ongoing at start of study	SCIG (Vivaglobin) treatment without receiving initial IVIG	■ During the study: 34 infection episodes in 10 of 18 patients; annualized rate of 3.95 infections per patient (four episodes started early in the loading phase, an episode of nasopharyngitis started on day 1, and three other infections developed on day 3) **Infections occurring in ITT population (n = 18), number of patients:** ■ Total infections = 10, pyrexia = 3, nasopharyngitis = 2, upper respiratory tract infection = 3, gastroenteritis = 1, ear infection = 1, respiratory tract infection = 1, enteritis = 1, toothache = 1, vomiting = 1, *Haemophilus* infection = 1, meningitis = 1, otitis media = 1, *Pseudomonas* bacteremia = 1, *Pseudomonas* bronchitis = 1, sinusitis = 1, pharyngolaryngeal pain = 1, rosacea = 1. Eight patients (44%) used antibiotics for treatment of infection for a total of 267 days of the 3145 study days (rate 19.3 days per patient per year) These infections might have been present in an asymptomatic form before commencement of SCIG therapy (note this doesn't cover all infections related to specific infections).	[15]
Cinetto *et al.* (2021)	Not reported	IgG-naive PAD patients had a total of 487 infections (40 SBI) before SCIG with an infection rate of 3.69 ± 2.81/year per patient	At least 12 weeks of SCIG treatment according to current guidelines. Of the patients with PAD: 45 (44.1%) were on 20% SCIG; 43 (42.1%) were on 16% or 16.5% SCIG; and 14 (13.7%) were on 10% facilitated SCIG. Brand not reported	■ During SCIG steady state, there were 138 infections (1 SBI), infection rate of 0.52 ± 1.18/year per patient. This was a significant decrease ($p < 0.0001$)	[16]
Gaspar *et al.* (1998)	Not reported	Not reported	SCIG (Gammabulin) in IG-naive patients (n = 11)	■ During the observation period, no serious life-threatening infections and no infections requiring admission to hospital were reported ■ Patient records for infection frequency showed it was reduced after starting SCIG in the IG-naive treatment group and showed no noticeable difference in the IG-experienced group; this statement was subjective, and data were not shown	[20]
Sharma *et al.* (2019)	Not reported	Study reports pre-treatment annual infection rate for individual patients	11 patients (16%) were on SCIG; 55 (77%) were on IVIG; and 5 (7%) were on facilitated SCIG. Brand not reported	■ For the 11 patients treated with SCIG, average infection rate was 0.88 per year. Types of infections included laryngitis, sinus infection, urinary tract infection, upper respiratory tract infection and sinusitis ■ For the five patients treated with facilitated SCIG, average infection rate was 0.6 per year. Types of infections included bronchitis and inguinal abscess ■ Study reports annual pre and post treatment infection rates for individual patients	[25]

IG: Immunoglobulin; ITT: Intention-to-treat; PAD: Primary antibody deficiency; SBI: Serious bacterial infection; SCIG: Subcutaneous immunoglobulin; SD: Standard deviation.

Table 5. Safety outcomes reported for IG-naive patients.

Study (year), study duration or follow-up period	Interventions included in study	Safety outcomes	Ref.
Altook *et al.* (2019), 12 months	Patients had received SCIG push for at least 12 months	AEs were all localized and of mild severity; statistical analysis was pending at time of publication	[13]
Borte *et al.* (2011), 6 months	Treatment with SCIG (Vivaglobin), without receiving IVIG initially	■ 14 (78%) patients experienced 168 AEs (including local reactions) (rate = 0.305 AEs per infusion); most were of mild (145) or moderate (19) severity ■ Two patients (11%) had four severe AEs (considered not related to study medication); these were also classed as SAEs. These events included meningococcal infection, *Haemophilus* infection, *Pseudomonas* bacteremia and *Pseudomonas* bronchitis ■ Six patients (33%) reported 42 local reactions; rate = 0.076 episodes per infusion (most frequent were erythema and infusion-site swelling) ■ Nine (50%) patients had 58 AEs considered at least possibly related to Vivaglobin; rate = 0.105 AEs per infusion; all were mild ■ All local reactions were considered "*at least possibly related*" to the study medication; these comprised most of the related AEs ■ Only a few other of the most common AEs were considered 'probably related' or 'related': one episode each of headache, pyrexia and nasopharyngitis ■ There were no deaths during the study ■ Two patients (11%) experienced seven SAEs (none were considered related to study medication) ■ None of the AEs led to the discontinuation of patients from the study ■ Apart from the low lymphocyte count in one patient, there were no clinically relevant abnormalities in the laboratory parameters ■ AEs that occurred in ≥ two patients in order of frequency (high to low): headache, pyrexia, infusion-site erythema, infusion-site swelling, nausea, infusion-site pruritis, asthenia, vomiting, fatigue, nasopharyngitis, urticaria, arthralgia ■ Rate of AEs per infusion ranged from 0.004 to 0.025 for AEs that occurred in ≥ two patients	[15]
Duff and Leiding (2017) [Abstract only], 3–4 months	Received 20% SCIG therapy without first receiving a loading dose of IVIG	■ No serious bacterial infections or serious adverse reactions were noted for any patient	[17]
Gaspar *et al.* (1998), up to 3.5 years	SCIG (Gammabulin)	■ All children developed painless raised lumps over the infusion site; these lasted between 2 and 24 h ■ Ten patients had local erythema; no treatment was required ■ Two patients found the infusions uncomfortable at the faster rate and preferred to run the infusions at 10 ml/h	[20]
Samaan *et al.* (2014), range of follow-up 7.9 to 66.3 months	Patients could choose between IVIG or SCIG	■ Safety data were not reported separately for the new and switch cohorts ■ SCIG was well tolerated without any systemic reaction ■ No cases of anaphylaxis occurred in either cohort	[24]
Walter *et al.* (2020a), Canada, November 2007 to September 2018	Patients had received SCIG push for at least 12 months	■ Eight patients out of 62 discontinued SCIG. Reasons for discontinuation included infection perceived by the patient to be SCIG-related (n = 1), pregnancy (n = 1), infusion pain related to prior surgical scars at infusion site (n = 1), and fatigue perceived to be related to infusion (n = 2). It was not reported if these patients were IG-naive or experienced	[26]
Walter *et al.* (2020b) [abstract only], Canada, duration not reported	Patients had received SCIG push for at least 12 months	■ AEs were generally local and mild, with only two out of 65 patients discontinuing SCIG replacement secondary to side effects. It was not reported if these patients were IG-naive or experienced	[27]

AE: Adverse event; IG: Immunoglobulin; IVIG: Intravenous immunoglobulin; SAE: Serious adverse event; SCIG: Subcutaneous immunoglobulin.

(CHQ-PF50). Anterasian *et al.* (2019) collected SF-36 results every 3 months as available for patients with PID receiving IVIG or SCIG from 2014 to 2016 and showed statistically significant (two-sample t-test, $p < 0.05$) improvements over baseline in all eight domains of SF-36 among patients initiating SCIG (n = 93) and in five of eight SF-36 domains in patients who were started on IVIG (n = 11) [14]. Gardulf *et al.* reported that, prior to initiating SCIG treatment, patients (n = 25) diagnosed with PID perceived restrictions in several areas of their daily life and reported poorer functional status, as indicated by the Sickness Impact Profile (SIP) scores, than the randomly sampled general population reference group. Significantly higher scores ($p = 0.0001$; implying poorer functional status) were seen in the IG-naive group (n = 10) prior to SCIG treatment for 8 of the 12 SIP scales compared with the general population reference group [18]. After SCIG treatment initiation, significantly lower scores were recorded in treated patients for 3 of the 12 SIP scales, namely ambulation ($p < 0.05$), mobility ($p < 0.01$), and social interaction ($p < 0.05$) compared with the reference group [18].

SCIG-dosing regimens & patient health & treatment pathways

Detailed information on SCIG-dosing regimens and/or patient health and treatment pathways were included in seven of the studies (Supplementary Table 3) [15,17–20,24,28]. Only three studies reported the brand of SCIG used [15,19,20]. Although Gardulf *et al.* evaluated a mixed population of IG-naive (n = 24) and IG-experienced (n = 165) patients, no separate information on the infusion parameters for those who were IG-naive were reported [19]. Most studies did not report information on location and number of infusion sites and only five studies reported detailed dosing information [15,18–20,24].

Dosing regimens for SCIG were similar among the studies that reported detailed dosing information [15,18–20,24]. The planned treatment in Borte *et al.* consisted of a loading phase of 100 mg/kg SCIG administered in the hospital, followed by a maintenance phase of 100 mg/kg/week SCIG administered at home as a single weekly infusion or divided into two infusions per week [15]. Information on loading regimens from the available studies is presented in Supplementary Table 4. Similarly, patients (n = 10) in Gardulf *et al.* received SCIG self-infusions at home at a dose of 100 mg/kg/week, after an introductory period in which treatments were administered in the hospital [18]. Other dosing regimens were reported at a mean dosage of 160 mg/kg/week (range 70 to 260) [20] and 400 mg/kg/4 weeks [24] for IG-naive patients, which are also similar to the dosing regimens in Borte *et al.* (2011) [15] and Gardulf *et al.* [18].

Other outcomes

Other outcomes reported in the included studies covered patient perception of infections, parental satisfaction with SCIG treatment [20], compliance [24] and stress [24]. Gaspar *et al.* reported generally positive satisfaction levels among parents of children receiving rapid SCIG as initial IGRT (n = 9), as well as among those who were IG-experienced (n = 11) [20].

Quality assessments of included studies

Quality assessments were performed for the included studies using CASP checklists (https://casp-uk.b-cdn.net/wp-content/uploads/2018/03/CASP-Cohort-Study-Checklist-2018_fillable_form.pdf) for case-control and cohort studies. The results of the quality assessments are reported in Supplementary Table 5.

Discussion

This systematic literature review highlighted a lack of studies investigating the use of subcutaneous immunoglobulin (SCIG) specifically in patients with primary immune deficiency (PID) not previously treated with immunoglobulin (IG). Although three of the included studies were published in the 1990s, indicating a long history of studying IG-naive patients, many (n = 27) of the studies identified did not report results for IG-naive patients separately and were, thus, excluded from this review. The lack of studies reporting results separately for IG-naive and IG-experienced patients also suggests that initiating SCIG is commonplace in clinical practice and that researchers do not feel the need to differentiate patients by IG-experience status. IG-naive patients may not have appreciably different experiences from IG-experienced patients in terms of response to SCIG treatment, AEs, and dosing schedules.

Overall, SCIG treatment in IG-naive patients with PID was found to improve IgG levels and decrease the burden of infections due to PID. Similar pharmacokinetic parameters and responses were seen in IG-naive and IG-experienced patients after the loading dose period ended for IG-naive patients. These real-world findings are consistent with results from a recent population-level pharmacokinetic modeling study that simulated serum IgG profiles in IG-naive patients with PID, and which suggested that attainment of IgG levels above a protective target threshold can be achieved with SCIG using appropriate loading-dose regimens [29]. However, IG-naive patients required a short loading phase (1 week) with frequent administration to achieve therapeutic target IgG levels, and the loading dose needed varied considerably depending on endogenous baseline IgG levels, with steady-state serum IgG levels achieved by approximately 12 weeks [29]. New SCIG users who were previously IG-naive also demonstrated a substantial reduction in infections [15,20] and antibiotic use [26], further supporting the suggestion that IG-naive patients do not appear to differ from IG-experienced patients in terms of their ability to achieve therapeutic levels of IgG following initiation of SCIG. Collectively, these results highlight a need for future investigation of whether initiating SCIG without previous IVIG treatment can achieve similar therapeutic benefits in a comparable timeframe to initiating SCIG with prior IVIG treatment. Furthermore, future studies should investigate what

loading regimens may be needed in IG-naive patients to achieve therapeutic IgG levels in a reasonable time period while maintaining favorable safety and tolerability profiles.

Three studies reported substantial improvements in HRQoL outcomes following initiation of SCIG [14,15,18]. The study by Anterasian *et al.* [14] specifically showed that initiating on SCIG treatment led to more favorable outcomes in the SF-36 (significant improvements in all 8 domains) compared with patients who were started on IVIG (significant improvements in 5 domains). Studies that reported safety and tolerability data for SCIG treatment in IG-naive patients with PID showed that AEs were generally local and mild to moderate, and consistent with the overall safety and tolerability profile reported in studies of IG-experienced patients switching to SCIG [30]. Most studies did not report information on location and number of infusion sites, and dosing regimens of SCIG were similar across the seven studies with available detailed data.

Few studies compared SCIG treatment in IG-naive and IG-experienced patient populations. Additionally, the available literature had limited data on patients who withdrew from SCIG or switched to IVIG because of a preference for the latter. Available data for some clinical outcomes, such as IgG level achieved and antibiotic requirement, showed no notable differences between IG-naive and IG-experienced patients. Information on loading regimens was scarce or was not detailed, and it is possible that the studies not reporting a loading dose did not use any loading regimens.

Quality assessments of included studies were generally graded as low, with many studies not reporting enough information to determine whether the methods were appropriate (five of the studies were only available as abstracts). Inherent biases and incomplete information also often exist in observational studies, particularly retrospective studies.

One limitation of this systematic literature review is that, although substantial and rigorous search methods were employed, we limited our search terms to the focus of the research question and restricted the population and intervention terms because PID covers an extensive range of disorders in which studies can use broad index terms. This targeted approach allowed us to maintain a feasible quantity of literature to review but may have resulted in some potentially relevant studies not being captured. However, supplementary database searches were conducted to ensure the review was robust. Another limitation is that although language was not limited to English in the initial searches, only English-language articles were screened. There were limitations to the results of this review because only five studies provided detailed information on SCIG dosing in treatment-naive patients [15,18–20,24]; hence the reported dosing regimens may not be generalizable to all populations. Additionally, HRQoL data specifically evaluating the difference in clinical outcomes between IG-naive versus IG-experienced patients receiving SCIG are lacking, and quality of studies was difficult to assess because many studies had limited reporting and insufficient information. Finally, a meta-analysis could not be conducted due to the heterogeneity of the studies identified.

Conclusion

Although numerous studies have been published on the use of subcutaneous immunoglobulin (SCIG) in IG-experienced patients with PID, this review revealed that few studies specifically reported on use in the IG-naive population. Based on data from the available studies, patients initiating SCIG without previous IGRT experience appear to have treatment tolerability profiles, infection rates, attainment of target IG levels, and improvement in HRQoL benefits consistent with those previously reported for IG-experienced patients. Owing to the limited literature, however, there is a lack of conclusive data on safety/tolerability profiles and optimal dosing. Future studies that evaluate optimal loading regimens for IG-naive patients and that directly compare clinical or HRQoL outcomes by IG-experience status would help to corroborate the available findings.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/imt-2021-0265

Author contributions

C Anderson-Smits, M Park, S Mitchell and E Hawe contributed to the conception and design of the review. J Bell, L Hartley, S Mitchell and E Hawe contributed to the acquisition of data. All authors contributed to the interpretation of the data and drafting or critical revision of the manuscript for important intellectual content, approved the final version for submission, and agree to be accountable for all aspects of the work to ensure that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data

The datasets, including template data collection forms, data extracted from included studies, and any other materials used in the review, are available upon request.

Summary points

- In total 16 studies were included in this systematic literature review. The review excluded 116 studies because it was unclear whether patients were immunoglobulin (IG)-naive (89 studies) or because results were not reported separately for IG-naive and IG-experienced patients (27 studies).
- Efficacy and effectiveness outcomes (reported in 8 studies) included IgG levels (eight studies), infections (four studies) and antibiotic use in response to infections (six studies).
- Overall, subcutaneous immunoglobulin (SCIG) treatment was shown to be effective in increasing mean IgG levels in both IG-naive and IG-experienced patients.
- AEs were generally mild to moderate and primarily occurred locally at the injection site among IG-naive patients receiving SCIG.
- Improvements in HRQoL were seen after SCIG treatment initiation in IG-naive patients (three studies), in some cases more favorable to SCIG compared with IVIG.
- Dosing regimens for SCIG were similar among the studies that reported detailed dosing information.
- The quality of the studies was graded as low, with many studies not reporting enough information to determine whether the methods were appropriate.
- There is a lack of studies investigating SCIG use in IG-naive patients with PID. Data from available studies suggest that IG-naive patients initiating SCIG have similar clinical and HRQoL outcomes as reported for IG-experienced patients.

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