Patient Preference and Adherence

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REVIEW

Patient Preferences for Subcutaneous versus Intravenous Administration of Treatment for Chronic Immune System Disorders: A Systematic Review

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Background: For many chronic immune system disorders, the available treatments provide several options for route of administration. The objective of this systematic literature review is to inform discussions about therapy choices for individual patients by summarizing the available evidence regarding the preferences of patients with chronic immune system disorders for intravenous (IV) or subcutaneous (SC) administration.

Methods: Searches of the MEDLINE, Embase and Cochrane Library databases were conducted using terms designed to capture studies reporting patient preferences between IV and SC therapy published in English. Relevant studies were limited to those in which mode of administration, including treatment frequency and setting, was the main difference between comparators.

Results: In total, 49 studies were included in the review. Among 18 studies that compared IV and SC immunoglobulin therapy, 16 found patients to prefer the SC administration route. The results of the 31 studies comparing IV infusion and SC injection of non-immunoglobulin therapies were mixed, with patients favoring SC administration in 20, IV infusion in seven, and having no overall preference in four. Patient experience had a strong effect on preferences, with treatment-experienced patients preferring their current administration route in most studies. Patients preferring SC administration tended also to prefer treatment at home, mainly due to the convenience and comfort of home treatment and the avoidance of having to attend hospital. By contrast, patients preferring IV infusion tended to cite the lower treatment frequency and a dislike of self-injecting, and preferred hospital treatment, mainly due to the presence of healthcare professionals and resulting feelings of safety.

Conclusion: In general patients with chronic immune system disorders tend to be more likely to choose SC administration than IV infusion, but preferences may vary according among individuals. These findings may assist discussions around appropriate treatment choices for each patient.

Keywords: systematic literature review, decision making, preference, administration route, immunodeficiency, autoimmune disorders

Plain Language Summary

Patients' individual preferences are an important factor in deciding which treatment to use. Many chronic immune system disorders – immunodeficiencies and autoimmune conditions – have several available treatments which can be administered by infusion into a vein (intravenously) or under the skin (subcutaneously). The most suitable treatment may vary for each patient, depending on their individual preferences and circumstances.

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We conducted this systematic review of the published literature to provide an overview of studies describing patients' preferences for intravenous or subcutaneous treatment. In total, we included 49 references. Of these, the majority found that patients preferred subcutaneous treatment, a major advantage of which was the possibility of treatment at home, which was seen as more convenient and comfortable than hospital treatment. Among patients who preferred intravenous infusions, the main advantages were the lower treatment frequency, the presence of healthcare professionals and the resulting feelings of safety. Many patients had experience of either intravenous or subcutaneous treatment, and tended to prefer their current treatment option.

By describing what is known about patients' preferences for treatment administration route, and the reasons for those preferences, this review is intended to inform discussions about available treatments and help decide on the most appropriate choice of therapy for individual patients.

Introduction

For many chronic immune system disorders – immunodeficiencies and autoimmune conditions – treatments with multiple administration routes are available. For example, for patients with immunodeficiency and some autoimmune conditions, subcutaneous (SC) infusions of immunoglobulin (SCIg) may be used as an alternative to intravenous (IV) immunoglobulin (IVIg).[1] Similarly, the tumor necrosis factor inhibitor (TNFi) class of therapies, widely used in the treatment of autoimmune conditions, includes both infliximab, administered as an IV infusion, and multiple agents which are administered by SC injection (eg adalimumab and etanercept).[2]

In situations where different therapies are expected to have generally similar efficacy and safety, patients' individual preferences are an important factor in deciding which treatment to use. Matching treatment attributes to patients' individual preferences has been associated with increased treatment satisfaction and adherence, and with improved health-related quality of life (HRQoL).[3,4] Involvement of patients in treatment choices is also central to shared decision making approaches.[5,6]

In the case of SC formulations of therapies, one potential advantage is the possibility of patients administering their own treatment at home, without needing to depend on a healthcare provider for administration of the therapy. Home self-administration of treatment may be beneficial to patients, by improving convenience, and to healthcare systems, by reducing costs.[7] The desire for patients and providers to minimize hospital exposure or in-person contact is especially relevant within the context of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. It is possible that some preferences established during the pandemic will persist even when vaccination for the virus becomes widely available.

The objective of this systematic literature review (SLR) is to provide evidence to inform discussions about available treatments by summarizing the available literature regarding the preferences of patients with chronic immune system disorders for IV infusion, SC infusion or SC injection.

Methods

Data Sources and Search Strategy

Electronic database searches were conducted on 24 February 2021. The included databases were MEDLINE (via the US National Library of Medicine PubMed tool; pubmed.ncbi.nlm.nih.gov), Embase (via embase.com) and the Cochrane Library (via cochranelibrary.com). The searches were designed to capture all studies reporting patient preferences between subcutaneous and intravenous therapy. Search strings are shown in Supplementary Tables 1–3.

Screening

EndNote (Clarivate Analytics; Philadelphia, PA, USA) was used to combine search results and remove duplicates. For all citations identified in the electronic searches, titles and abstracts were screened by two reviewers (PMO and Claire Mulligan, Beacon Medical Communications Ltd, Brighton, UK) to assess the potential relevance of the study according to prespecified eligibility criteria. For potentially relevant citations, full-text articles were obtained and reviewed to confirm inclusion in the SLR. The reference lists of SLRs identified in the database searches were checked for potentially relevant references, which were included in the review.

Eligibility Criteria

Studies were eligible for inclusion in the SLR if they reported primary data on patients' preferences for SC infusion or SC injection versus IV infusion of any therapy, or of hypothetical interventions. Studies were included if they described patient preferences for the treatment of chronic immune system disorders (Supplementary Table 4); other indications were excluded. Both pediatric and adult populations were included.

Relevant studies were limited to those in which the mode of administration, including treatment frequency and setting, was the main difference between comparators (ie

comparisons between therapies with different efficacy or safety profiles were not included). For studies describing relevant patient preferences, preferences for treatment setting (home vs hospital) and reasons given by patients for preferring each mode of administration were also investigated.

All relevant study designs were included, and no date restriction was applied. Articles published in languages other than English were excluded, except where English-language abstracts contained relevant evidence. Relevant conference abstracts indexed in the databases were included unless the studies described were also published as journal articles.

Data Extraction and Analysis

For the included publications, data on patient preferences were extracted into predefined tables. Classification of SC administration as infusion or injection was based on the term used in the relevant publication. Where data were available for subgroups of patients currently using IV or SC therapies, these were extracted separately. Where reasons given by patients for preferring IV or SC administration, these were also extracted. Reasons for preferences were analyzed semi-quantitatively by grouping the reported reasons into categories and calculating the proportion of studies reporting preferences for IV or SC administration in which each category was mentioned as a main driver of preferences or reported by ≥ 20% of patients.

Risk of Bias Assessment

Risk of bias in the included studies was assessed using the McMaster University CLARITY group Risk of Bias Instrument for Cross-Sectional Surveys of Attitudes and Practices.[8]

Results

Study Selection

The study selection process is summarized in Figure 1. In total, 1719 citations were identified in the searches. After removal of 507 duplicates, 1212 citations were screened. Full-text versions of 56 articles, as well as 92 conference abstracts, were assessed for eligibility. Searching the bibliographies of seven identified SLRs[9–13] identified eight additional relevant articles, which were included in the review. In total, 49 studies,[14–62] comprising 38 full papers[14–51] and 11 conference abstracts,[52–62] were included in the review.

Description of the Included Studies

Eighteen studies were identified that compared IV and SC infusion of immunoglobulin (IVIg or SCIg).[14–28,52–54] Of these, four studies were randomized controlled trials (RCTs);[14–17] six were non-randomized interventional studies;[18–22,52] four were observational studies;[23–25,53] and four were surveys.[26–28,54] The indication in the majority of included studies of SCIg (13 studies in total) was immunodeficiency, mostly primary immunodeficiency (PID).[14,15,18–20,23,24,26–28,52–54] The remaining studies comprised four studies of patients with multifocal motor neuropathy (MMN)[16,21,22,25] and two studies of patients with chronic inflammatory demyelinating polyneuropathy (CIDP)[17,25] (one study included both MMN and CIDP groups).[25]

The remaining 31 studies compared administration routes for a range of non-immunoglobulin therapies, and described preferences for IV infusion or SC injection.[29–51,55–62] Of these, 29 studies were patient surveys,[29–50,55–61] of which 22 were straightforward preference questionnaires[29–47,55–57] and seven involved conjoint analyses or discrete choice experiments.[48–50,58–61] The remaining studies were a non-randomized interventional study[51] and a retrospective analysis of treatment choices.[62]

The most common indication in the included studies of non-immunoglobulin therapies was rheumatoid arthritis (RA; 11 studies).[29–36,46,48,58] An additional ten studies involved patients with inflammatory bowel disease (IBD, comprising Crohn's disease [CD], ulcerative colitis or a mixture of the two);[37,38,45,47,49,55,57,59,61,62] two studies were conducted among patients with systemic lupus erythematosus (SLE);[39,51] two among patients with severe asthma;[40,41] and one each among patients with multiple sclerosis (MS),[60] psoriasis[50] and axial spondyloarthritis.[56] Three studies included patients with a range of conditions (most commonly RA or IBD).[42–44]

Risk of Bias

The risk of bias assessment of the included studies is shown in Supplementary Table 5. Most studies had some risk of bias, mostly with regard to whether the included population was representative of the overall patient population.

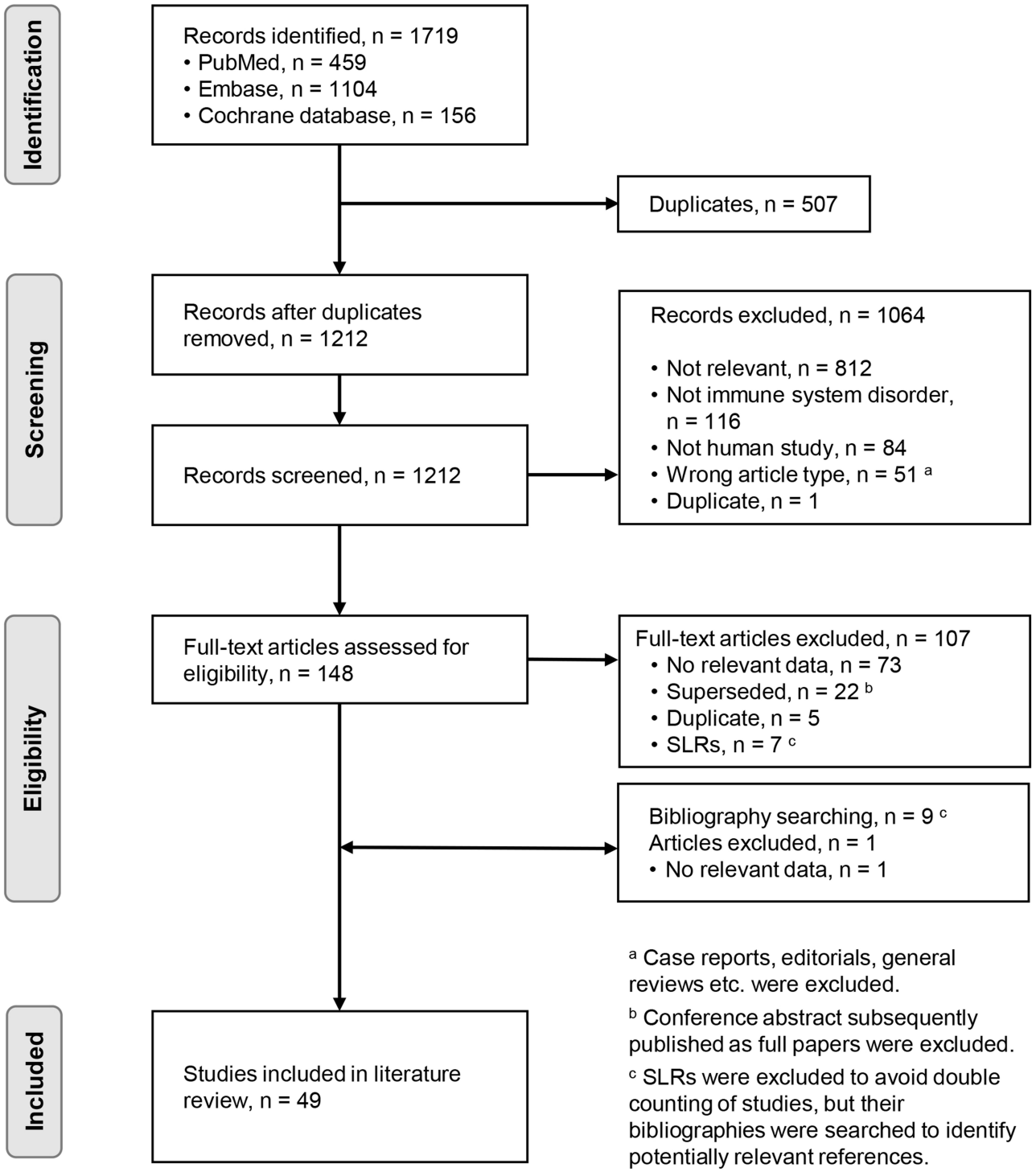

Figure 1 Study selection flow chart.
Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Preferences for IVIg or SCIg

The 18 studies that compared IVIg with SCIg are described in Table 1,[14–28,52–54] with overall preferences, where reported, summarized in Figure 2A.[14–24,52–54] A single Phase 3 trial – PATH – was identified.[17] In this study patients with CIDP using IVIg were randomized to one of two SCIg doses or placebo for 24 weeks. Among the 85 patients treated with SCIg who completed a preference questionnaire at the end of the study, 61 (72%) preferred SCIg, 21 (25%) preferred IVIg and 3 (4%) had no preference.[17] A total of three randomized

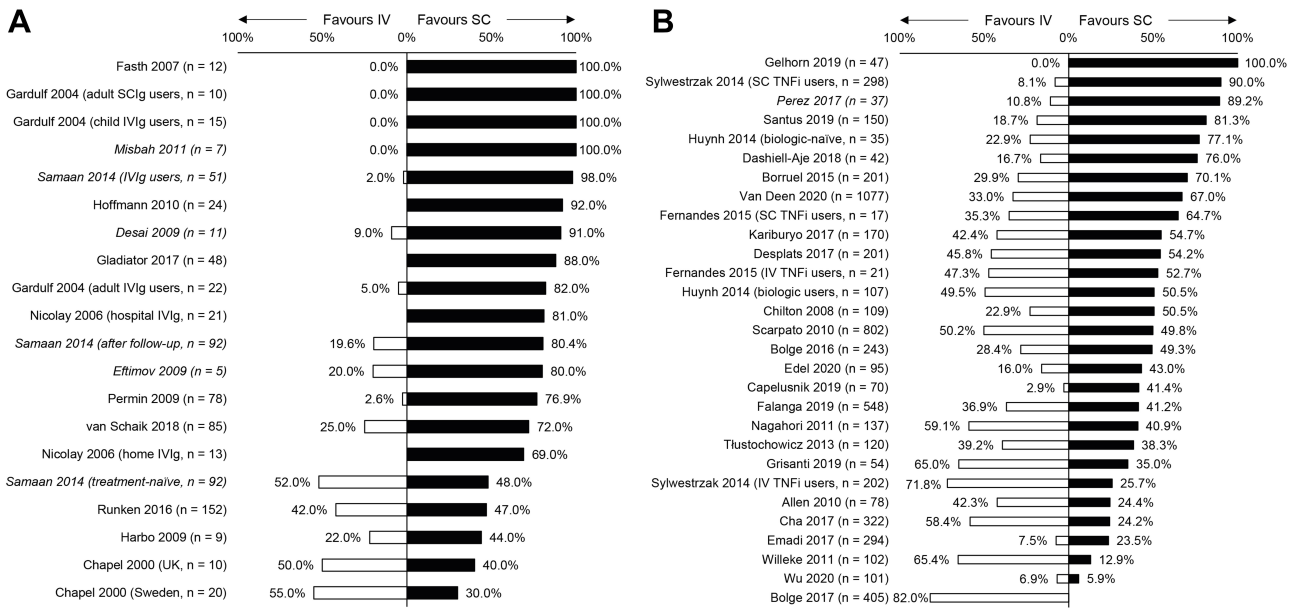

Figure 2 Summary of patient preferences for (**A**) IVIg or SCIg and (**B**) IV infusion or SC injection of non-immunoglobulin therapies. Data are patients' expressed preferences or actual treatment choices (shown in italics). Eight studies in which percentage preferences were not reported were excluded.[25–28,48–50,58] In some studies not all patients expressed a preference, or preferences were not reported for one alternative; therefore, not all lines add up to 100%.

crossover studies were identified.[14–16] In two of these, the majority of patients (56% and 91%) who had used IVIg and SCIg during the study reported preferring SCIg;[14,16] in the third study, 5 of 10 and 11 of 20 patients in cohorts in the UK and Sweden, respectively, preferred IVIg therapy.[15]

Six open-label interventional studies of patients switching from IVIg to SCIg were included.[18–22,52] These studies were typically small (range, n = 5 to n = 48), and comprised two studies of adult patients with MMN[21,22] and four studies of adults or children with PID.[18–20,52] In all seven studies, most patients (76–100%) preferred SCIg therapy.[18–22,52] Preferences among patients switching from IVIg to SCIg were also investigated in two small observational studies, conducted in the UK (n = 8) and Germany (n = 24).[23,25] Both of these studies found strong preferences for SCIg, measured using visual analog scale scores in the UK study[25] and directly elicited preferences in the Germany study, in which 22 of 24 patients preferred SCIg.[23]

A Canadian observational study followed therapy choices made by children with PID (n = 143).[24] Among patients already on IVIg who were offered a choice of treatment, 50 of 51 chose to switch to SCIg, and 44 were still on SCIg after an average follow-up period of 52 months.[24] Of 92 newly diagnosed patients offered a choice between IVIg and SCIg, 44 initially chose SCIg; of these, 42 were still on SCIg after an average of 33 months of follow-up. By contrast, of the 48 newly diagnosed patients who chose IVIg, 35 switched to SCIg during the follow-up period.[24] A further observational study, conducted in Denmark, found that of 78 children and adults with immunodeficiency who used SCIg for 6 months, 77% reported preferring SCIg at the end of the study, compared with 3% who preferred IVIg.[53]

Two similar conjoint analyses investigated patient preferences for multiple attributes of immunoglobulin treatment. In both a US study and an international cohort, adult patients and parents of children with PID significantly preferred self-administration of SCIg to IVIg administered by a healthcare professional ($p < 0.05$ for all groups except US patients).[26,27] By contrast, a Canadian survey of 91 patients receiving hospital IVIg treatment found that although the majority would be willing to switch to home IVIg or home SCIg, respectively, after consulting with their immunologist, participants were significantly more likely to switch to home IVIg than home SCIg ($p = 0.01$).[28] A further survey of patients with PID found a small overall preference for SCIg over IVIg (47% vs 42%).[54]

Preferences for IV Infusion or SC Injection of Non-Immunoglobulin Therapies

The 31 studies that compared IV infusion or SC injection of therapies other than immunoglobulin are summarized in

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Table 1 Summary of Included Studies Comparing IV Infusion to SC Infusion

Study (Country/ Region)	Population	Experience with SC or IV Therapies	Study Design	Patient Preferences
Fasth et al 2007 (Sweden)[18]	Children with PID (n = 12) Median age, 10.9 years (range, 1.7–17.1 years) Female, 2 (17%)	Both SCIg and IVIg during study	Open-label switching study: switch from IVIg (in hospital) to SCIg (at home); 6 months of SCIg treatment	Patient/parent preference at end of study: SCIg, 12 (100%)
Gardulf et al 2004 (Austria, Brazil, Germany, Poland, Spain, Sweden)[19]	Adults and children with PID (n = 47; adults [≥ 14 years, 32 [68%]; children [< 14 years], 15 [32%]) Adults: median age, 33.5 years (range, 14–74 years); female, 12 (38%) Children: median age, 7 years (range, 3–13 years); female, 0	Both SCIg and IVIg during study	Open-label switching study: switch from IVIg (in hospital) to 10 months of treatment with SCIg (at home, after 4–6 training sessions in hospital); 10 adult patients were on SCIg at enrolment	Preferences at end of study Adult patients on SCIg at enrolment (n = 10), 10 (100%) preferred SCIg treatment at home Adult patients on IVIg at enrolment (n = 22): 16 (73%) preferred SCIg treatment at home; 2 (9%) preferred SCIg but no preference for setting; 2 (9%) preferred treatment at home but no preference for treatment; 1 (5%) preferred IVIg in hospital; 1 (5%) had no preferences Children on IVIg at enrolment (n = 15): 15 (100%) preferred SCIg treatment at home
Misbah et al 2011 (UK, Italy, Switzerland)[21]	Adults with MMN (n = 8) Mean age, 57 years (range, 42–66 years) Female, 4 (50%)	Both SCIg and IVIg during study	Open-label switching study: switch from IVIg (in hospital) to SCIg (at home); 24 weeks of SCIg treatment	Choice of ongoing treatment at end of study: SCIg, 7 (100% of patients who completed study)
Samaan et al 2014 (Canada)[24]	Children with PID (n = 143) Mean age: switch to SCIg, 10.7 years; stay on IVIg, 11 years; start on SCIg, 6.0 years; start on IVIg, 8.3 years Female: switch cohort, 43%; new cohort, 41%	In one group, patients switched from SCIg to IVIg; in the other group treatment-naïve patients chose SCIg or IVIg	Retrospective analysis of patient therapy choices between IVIg and SCIg: a) patients already on IVIg (n = 51; average follow-up 52 months); b) newly diagnosed patients (n = 92; average follow-up 33 months) [a]	Patients already on IVIg (n = 51): 50 (98%) chose to switch to SCIg and 44 (88%) remained on SCIg during follow-up Newly diagnosed patients (n = 92): 44 (48%) chose SCIg and 95% remained on SCIg during follow-up; 48 (52%) chose IVIg, of whom 73% switched to SCIg during follow-up; at end of follow-up, 74 (80%) were using SCIg
Hoffmann et al 2010 (Germany)[23]	Patients with PID/SID (n = 82; preferences, n = 24 adult patients) Mean age, 34 years (range, 1–74 years) Female, 46 (56%)	SCIg during study; 73% had received previous hospital IVIg therapy	Observational study: patients receiving SCIg (at home) treatment; preference reported after 9 months of treatment [b]	Preferences at end of study Treatment: prefer SCIg, 22 (92%); no preference, 2 (8%) Setting: prefer home therapy, 20 (83%); prefer clinic/ physician setting, 1 (4%); no preference, 3 (13%)

Desai et al 2009 (USA)[14]	Adults and children with PID (n = 11) Mean age, 29 years (range, 5–59 years) Sex NR	Both SCIg and IVIg during study	Randomized crossover study: IVIg (not reported, assumed to be in hospital) vs SCIg (at home); 6 months each treatment	Preferences for ongoing treatment at end of study: SCIg, 10 (91%); IVIg, 1 (9%)
Gladiator et al 2017 (Europe and Brazil)[52] [abstract only]	Adults and children with PID (n = 48) Age and sex NR	Both SCIg and IVIg during study	Open-label switching study: switch from IVIg (not reported, assumed to be in hospital) to SCIg (at home); 12 months of SCIg treatment	Preferences at end of study SCIg, 88% (age ≤ 13 years, 84%; age > 13 years, 91%) Prefer home infusion, 88%
Nicolay et al 2006 (USA, Canada)[20]	Adults with PID (n = 44; hospital IVIg, 28; home IVIg, 16) Prior hospital IVIg: mean age, 36.1 years (SD, 13.6 years); female, 11 (39%) Prior home IVIg: mean age, 35.5 years (SD, 13.2 years); female, 6 (38%)	Both SCIg and IVIg during study	Open-label switching study: switch from IVIg (in hospital [n = 21] or at home [n = 13]) to SCIg (at home); 12 months of SCIg treatment	Preferences at end of study Prior hospital IVIg group (n = 21): prefer SCIg, 17 (81%); prefer home therapy, 19 (90%) Prior home IVIg group (n = 13): prefer SCIg, 9 (69%); prefer home therapy, 12 (92%)
Eftimov et al 2009 (Netherlands)[22]	Adults with MMN (n = 5) (second cohort described in paper) Median age, 57 years (range, 47–65 years) Female, 0	Both SCIg and IVIg during study	Open-label switching study: switch from IVIg (at home) to SCIg (at home); 6 months of SCIg treatment	Choice of ongoing treatment at end of study: SCIg, 4 (80%); IVIg, 1 (20%)
Permin et al 2009 (Denmark)[53] [abstract only]	Children and adults with immunodeficiency (n = 79; 78 with data) Age ≤ 12 years, 34; 13–18 years, 10; > 18 years, 34 Female, 33 (42%)	SCIg during study; prior IVIg use NR	Open-label prospective observational study; patients or parents asked about preferences after 6 months of SCIg treatment	Preferences at end of study: prefer SCIg, 60 (77%); prefer IVIg, 2 (3%); no preference/not known, 16 (21%)
van Schaik et al 2018 (multinational)[17]	Adults with CIDP (n = 172; n = 85 treated with SCIg) Mean age, 55.2–58.9 years across groups Female, 36.0%	Both SCIg and IVIg during study	RCT: IVIg re-stabilization period (up to 13 weeks) followed by randomization to SCIg high or low dose, or to placebo; 24 weeks of randomized treatment	Preferences at end of study: SCIg, 61 (72%); IVIg, 21 (25%); no preference, 3 (4%)
Runken et al 2016 (NR)[54] [abstract only]	Patients with PID (n = 152) Age and gender NR	NR	Survey: online questionnaire; preferences measured using 100-point VAS	Prefer SCIg, 47%; prefer IVIg, 42% Patients strongly preferred their current administration route

(*Continued*)

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Table 1 (Continued).

Study (Country/ Region)	Population	Experience with SC or IV Therapies	Study Design	Patient Preferences
Harbo et al 2009 (Denmark)[16]	Adults with MMN (n = 9) Mean age, 49 years (range, 28–63 years) Female, 5 (56%)	Both SCIg and IVIg during study	Randomized crossover study: IVIg (in hospital) vs SCIg (at home); each treatment for a period equal to three IVIg treatment intervals of 18–56 days	Preferences at end of study: SCIg, 4 (44%); IVIg, 2 (22%); no preference, 3 (33%) Choice of ongoing treatment at end of study: SCIg, 5 (56%); IVIg, 4 (44%)
Chapel et al 2000 (UK, Sweden)[15]	Adults with PID (n = 30: UK, n = 10; Sweden, n = 20) Mean age, 44 years (range, 18–67 years) Female, 67%	Both SCIg and IVIg during study	Randomized crossover study: IVIg (at home or in hospital [UK, all in hospital]) vs SCIg (home); 1 year each treatment	Preferences at end of study UK: SCIg, 4 (40%); IVIg, 5 (50%); no preference, 1 (10%) Sweden: SCIg, 6 (30%); IVIg, 11 (55%); no preference, 3 (15%)
Espanol et al 2014 (21 countries outside USA)[26]	Adult patients with PID (n = 216) Caregivers of patients with PID (n = 84, 77 aged 1–20 years) Patients: median age, 36 years; female, 128 (59.3%) Patients with caregiver responses: median age, 9 years; female, 29 (34.5%)	Current IVIg, 53% (64% in hospital); current SCIg, 45% (94% at home); other, 2%	Survey – choice-format conjoint analysis; patient preferences for five treatment attributes: Mode of administration (self-administration or administration by a healthcare professional) Frequency of administration (one, two or four times a month) Location (home versus surgery, doctor's office, clinic or hospital) Number of needle sticks per treatment (one, two or four) Treatment duration (2, 4, or 6 hours)	Both patients and caregivers significantly preferred self-administration to administration by an HCP ($p < 0.05$) Both groups also significantly preferred ($p < 0.05$) administration at home, a lower treatment frequency, lower treatment duration and fewer needle sticks per treatment Mode of administration was the least important treatment attribute Patients currently receiving SCIg and their caregivers had a stronger preference for self-administration and treatment at home than those receiving IVIg (both $p < 0.05$)
Hadden et al 2015 (UK)[25]	Adults with MMN (n = 4) or CIDP (n = 4) Mean age, 57.4 years (SD, 13.7 years) Female, 3 (38%)	Both SCIg and IVIg during study	Observational study: patients switching from IVIg (in hospital) to SCIg (at home); preference questionnaire completed after a mean 31 months of SCIg treatment; preference measured with VAS scale	Very strong preference for SC over IV immunoglobulin (VAS mean 93 [SD 12] where 0 = prefer IVIg, 100 = prefer SCIg)

Mohamed et al 2012 (USA)[27]	Adult patients with PID (n = 252) Parents of children with PID (n = 66) Patients: mean age, 50.2 years (SD, 13.8 years); female, 189 (75.0%) Parents: mean age, 44.0 years (SD, 7.2 years); female, 55 (83.3%)	Patients: IVIg, 59.9%; SCIg, 40.1%; at home, 60.3%; hospital/clinic, 39.7% Children: IVIg, 43.9%; SCIg, 56.1%; at home, 77.3%; hospital/clinic, 22.7%	Survey – choice-format conjoint analysis; patient preferences for five treatment attributes: Mode of administration (self-administration or administration by a healthcare professional) Frequency of administration (one, two or four times a month) Location (home versus doctor's office, clinic or hospital) Number of needle sticks per treatment (one, two or four) Treatment duration (2, 4, or 6 hours)	Preferences for aspects of treatment Participants preferred self-administration of SCIg to IVIg administered by an HCP ($p < 0.05$ for parents; $p > 0.05$ for adult patients) Preferences for all other aspects of treatment were statistically significant ($p < 0.05$) toward fewer treatments, treatment at home, fewer needle sticks and shorter treatment duration For both patients and parents, mode of administration was the least important treatment attribute For patients, treatment frequency, number of needle sticks and treatment duration were the most important attributes For parents, treatment frequency was the most important attribute, followed by number of needle sticks and location
Reid et al 2014 (Canada)[28]	Patients receiving immunoglobulin treatment (n = 91, including hypogammaglobulinemia [n = 41], antibody deficiency [n = 13] and SCID [n = 6]) Mean age, 23 years (SD, 15 years) Female, 35 (39%) Surveys completed by patients (41), parents (39) or both (5)	All patients on hospital IVIg	25-question survey, including questions on patient choices in the event that home IVIg or home SCIg became available IVIg vs SCIg preferences were assessed using McNemar tests	Patient choices if home IVIg became available: 64% would switch from hospital to home treatment after consulting with their immunologist ($p = 0.006$) Patient choices if home SCIg became available: 78% would switch from hospital to home treatment after consulting with their immunologist ($p < 0.001$) IVIg vs SCIg Patients were significantly more likely to switch to home IVIg than to home SCIg ($p = 0.01$)

Notes: [a]Mean vs median not reported. [b]Although not explicitly stated, the 24 patients responding to the preference questions are assumed to have prior experience of IVIg.

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; HCP, healthcare provider; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; NR, not reported; PID, primary immunodeficiency; RCT, randomized controlled trial; SCID, severe combined immunodeficiency; SCIg, subcutaneous immunoglobulin; SD, standard deviation; SID, secondary immunodeficiency; TTO, time trade-off; VAS, visual analog scale.

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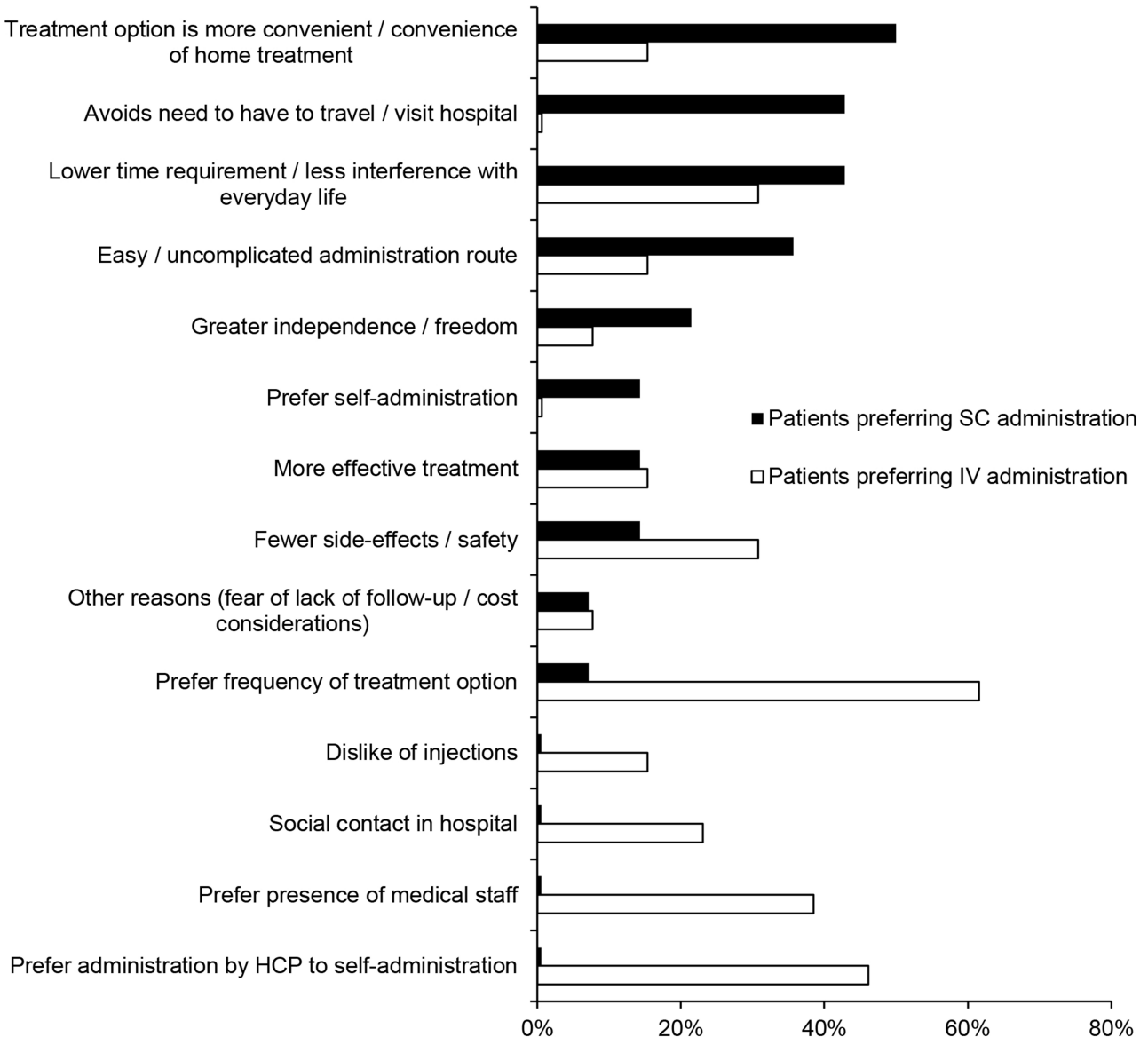

Figure 3 Summary of reported reasons for preferring SC or IV administration. Data are the proportion of studies reporting preferences for SC or IV administration (n = 14 and n = 13, respectively) in which each category was mentioned as a main driver of preferences or reported by ≥ 20% of patients.

Table 2[29–47,51,55–57,59,61,62] and, where overall preferences were reported, in Figure 2B.[29–47,51,55–57,59,61,62] Two clinical studies of patient preferences for IV infusion compared with SC injection were identified.[51,62] The first was an open-label switching study, conducted in the USA, in which patients with SLE treated with IV infusions of belimumab (n = 43) switched to SC belimumab, administered using an autoinjector.[51] After 8 weeks of treatment, 32 of 42 patients (76%) expressed a preference for the autoinjector over IV administration.[51] The second was a retrospective analysis of treatment choices made by children with CD and their families when initiating TNFi therapy (n = 37).[62] Most chose SC adalimumab (89%), with 11% opting for IV infliximab.[62]

Among the 23 surveys of preferences for IV infusion or SC injection, 12 studies enrolled patients with RA, or populations in which most patients had RA.[29–36,42,46,48,58] Of these, eight studies found that more patients preferred SC injection than preferred IV administration.[29–33,46,48,58] IV infusion was preferred to SC injection in two studies,[34,42] while two studies reported an even split of preferences.[35,36]

Table 2 Summary of Included Studies Comparing IV Administration to SC Injection

Study (Country/ Region)	Population	Current or Previous Use of SC or IV Therapies	Study Design and Comparators	Results
Gelhorn et al 2019 (USA)[40]	Adult patients with severe asthma (n = 47) Mean age, 49.9 (13.1) years Female, 74.5%	Currently on biological therapy, 29 (62%); previous experience of biological therapy, 6 (13%); biologic-naïve, 26%	Survey: telephone interview; questionnaire including preference for SC injection vs IV administration for hypothetical therapy	Preferences for administration route 100% of patients preferred SC injection to IV Preferences for who administers medication 54% of patients preferred administration by HCP in a clinic; 24% self-administration at home; 22% administration by caregiver at home
Sylwestrzak et al 2014 (USA)[44]	Adults with TNFi indications (n = 500) [a] Mean (SD) age: IV TNFi users, 49.8 (16.0) years; SC TNFi users, 49.4 (12.2) years; Female: IV TNFi users, 69.3%; SC TNFi users, 67.1%	IV TNFi users, 40.4%; SC TNFi users, 59.6%	Survey: telephone interview including preference for SC injection or IV infusion of TNFi therapy	Preferences for administration route IV TNFi users (n = 202): prefer IV, 71.8% (strongly, 54.5%); prefer SC, 25.7% (strongly, 18.3%) SC TNFi users (n = 298): prefer SC, 90.0% (strongly, 70.8%); prefer IV, 8.1% (strongly, 5.0%) Overall $p < 0.001$ Preferences among patients with prior experience of other administration route IV TNFi users (n = 48): prefer IV, 65% (strongly, 58%); prefer SC, 35% (strongly, 23%) SC TNFi users (n = 61): prefer SC, 82% (strongly, 62%); prefer IV, 18% (strongly, 10%) Preferences for home treatment IV TNFi users (n = 202): prefer home treatment, 46.0% (strongly, 23.3%) SC TNFi users (n = 298): prefer home treatment, 96.3% (strongly, 94.3%)
Perez et al 2017 (Spain)[62] [abstract only]	Children (< 18 years) with CD (n = 37) Age and sex NR	All patients were initiating TNFi therapy	Retrospective study of patients and families choosing a TNFi therapy	Chose IV infliximab, 4 (11%); chose SC adalimumab, 33 (89%)
Santus et al 2019 (Italy)[41]	Adult patients with severe asthma (n = 150) Mean (SD) age, 48.8 (12.1) years Female, 52.7%	48 patients (32.0%) were using SC biologic; 6 patients (4.0%) had prior experience of SC biologic	Survey: paper questionnaire including preference for SC injection or IV infusion of biological therapy	Preferences for administration route Prefer SC, 81.3%; prefer IV, 18.7% Current SC biologic users: prefer SC, 48/48 (100%) Current and prior SC biologic users: prefer SC, 49/54 (91%); prefer IV, 5/54 (9%)

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Table 2 (Continued).

Study (Country/ Region)	Population	Current or Previous Use of SC or IV Therapies	Study Design and Comparators	Results
Huynh et al 2014 (Denmark)[33]	Patients with RA (n = 142) Mean (SD) age, 57 (14) years Female, 77%	35 patients (24.6%) were biologic-naïve; 107 (75.4%) were treated with IV or SC biologic	Survey: questionnaire including preference for SC injection at home or IV infusion at clinic	Preferences for administration route Biologic-naïve patients: 27/35 (77%) preferred SC at home; 8/35 (23%) preferred IV at clinic ($p < 0.01$) Patients using biologics: 54/107 (50.5%) preferred SC at home; 53/107 (49.5%) preferred IV at clinic Preference by current administration route Patients on IV (n = 41): 85% preferred IV ($p < 0.0001$) Patients on SC (n = 66): 71% preferred SC ($p < 0.001$)
Dashiell-Aje et al 2018 (USA)[51]	Patients with SLE treated with belimumab (n = 43) Mean (SD) age, 46.2 (12.2) years Female, 88%	41 of 43 patients were using IV belimumab [b]	Open-label switching study: switch from IV belimumab to SC belimumab using autoinjector; questionnaire completed after 8 weeks	Preferences after 8 weeks (n = 42): prefer autoinjector, 32 (76%); prefer IV, 7 (17%)
Borruel et al 2015 (Spain)[59] [abstract only]	Patients with CD (n = 201) Mean (SD) age, 38.9 (12.3) years Female, 44.3%	NR; patients were candidates for biological therapy	Survey: discrete choice analysis including preferences for SC injection or IV infusion of biologics	Preferences for administration route Prefer SC, 70.1%; prefer IV, 29.9% Preferences for setting among patients preferring SC (n = NR) Prefer home treatment, 68.7%; prefer hospital treatment, 31.3%
Van Deen et al 2020 (Canada, UK, USA)[61] [abstract only]	Patients with IBD (n = 1077) Age and sex NR	NR	Survey: conjoint analysis of different medication attributes including route of administration	SC every 8 weeks vs IV every 8 weeks: prefer IV, 33%; prefer SC, 67% SC every 2 weeks vs IV every 8 weeks: prefer IV, 51%; prefer SC, 49% Experience with SC or IV medication was a strong predictor of preferences for SC or IV, respectively
Fernandes et al 2015 (Portugal)[57] [abstract only]	Adult patients with CD Infliximab group (n = 21): mean (SD) age, 40.4 (10.4) years; female, 43% Adalimumab group (n = 17): mean (SD) age, 35.6 (10.9) years; female, 71%	All patients using SC or IV TNFi therapy	Survey: questionnaire including preference to change to alternative administration method	Patients receiving IV infliximab (n = 21): prefer SC, 53%; prefer IV, 47% Patients receiving SC adalimumab (n = 17): prefer SC, 65%; prefer IV, 35%

Kariburyo et al 2017 (global)[38]	Adult patients with IBD (n = 170) Mean age: no discussion, 50.0 years; with discussion, 42.1 years Female: no discussion, 69.0%; without discussion, 65.1%	All patients were biologic-naïve; 83 (48.9%) had discussed biologics with their physician	Survey: online questionnaire including preference for SC injection or IV infusion	Prefer IV, 42.4%; prefer SC, 54.7% Patients who discussed biologics with physician: prefer IV, 39.8%; prefer SC, 59.0% Patients who had no discussion: prefer IV, 44.9%; prefer SC, 50.5%
Desplats et al 2017 (France)[30]	Adult patients with RA receiving IV abatacept or IV tocilizumab (n = 201) Mean (SD) age, 58.4 (12.6) years Female, 81.1%	All patients were using IV therapy Majority had previous SC therapy experience (etanercept, 58.5%; mean [SD] number of previous SC treatments, 1.2 [0.9])	Survey: questionnaire including preference for continuing IV therapy or switching to SC	Prefer to continue IV, 45.8%; prefer to switch to SC, 54.2% Patients who preferred to switch to SC were more likely than those wishing to continue on IV to have another ongoing SC treatment (15.9% vs 4.3%; p = 0.016)
Chilton et al 2008 (UK)[46]	Adult patients with RA (n = 109) Median age, 65 years Female, 79%	No prior TNFi use	Survey: questionnaire including preference for adalimumab, etanercept or infliximab	Prefer IV infliximab every 2 months, 25 (23%); prefer SC etanercept twice weekly, 4 (4%); prefer SC adalimumab every 2 weeks, 51 (47%); no preference, 29 (27%)
Scarpato et al 2010 (Italy)[35]	Adult patients with RA (n = 802) Mean (SD) age, 55.6 (13.1) years Female, 76.9%	Patients using SC or IV drugs were excluded	Survey: paper questionnaire including preference for SC injection at home or IV infusion in hospital	Preferences for administration route Prefer IV at hospital, 50.2%; prefer SC at home, 49.8% Preferences for setting Patients preferring IV (n = 403): 81% prefer hospital administration Patients preferring SC (n = 399): 65% prefer home treatment
Bolge et al 2016 (USA)[29]	Adult patients with RA (n = 243) Mean (SD) age, 52.5 (13.1) years Female, 85.2%	Patients were naïve to biologics, but had discussed biological therapy	Survey: online questionnaire about aspects of biological therapy including SC injection vs IV infusion	Prefer SC, 49.3% (strongly, 26.3%); prefer IV, 28.4% (strongly, 11.9%)

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Table 2 (Continued).

Study (Country/ Region)	Population	Current or Previous Use of SC or IV Therapies	Study Design and Comparators	Results
Edel et al 2020 (Israel)[31]	Adult patients with RA (n = 95) Mean (SD) age, 63.4 (11.9) years Female, 73%	Current SC, 52 (55%); current IV, 24 (25%); current oral, 15 (16%)	Survey: questionnaire including preference for oral, IV or SC treatment	Preferences for administration route Prefer oral therapy, 41%; prefer SC, 43%; prefer IV, 16% Patients who have previous experience with preferred administration route Preferring SC, 40/41; preferring IV, 14/15; preferring oral, 18/39 Preference by current administration route Current SC, 34/52 prefer SC; current IV, 13 of 24 prefer IV; current oral, 13 of 15 prefer oral (all $p < 0.001$)
Capelusnik et al 2019 (Argentina)[56] [abstract only]	Patients with ASA (n = 70) Median (IQR) age, 46.5 (38–57) years Female, 21%	NR	Survey: questionnaire including preferences for administration route and setting	Preferences for administration route Prefer oral, 51%; prefer SC, 41%; prefer IM, 4%; prefer IV, 3% Preferences for setting Prefer home treatment, 90%; prefer self-administration, 79%
Falanga et al 2019 (Italy)[39]	Adult patients with SLE (n = 548) Mean (SD) age, 43.1 (11.6) years Female, 95.6%	28.3% of patients had had a previous prescription for biological therapy (SC vs IV NR)	Survey: online questionnaire including preference for SC injection or IV infusion	Preferences for administration route Prefer SC, 41.2%; prefer IV, 36.9%; do not know, 21.9% Preferences by past experience of biologics No: prefer SC, 40.2%; prefer IV, 33.8%; do not know, 26.0% Yes: prefer SC, 43.9%; prefer IV, 44.5%; do not know, 11.6% (overall $p = 0.001$ vs 'No')
Nagahori et al 2011 (Japan)[55] [abstract only]	Patients with IBD (n = 137) Age and sex NR	All patients were biologic-naïve	Survey: online questionnaire including preference for SC injection or IV infusion	Prefer IV, 81 (59.1%); prefer SC, 56 (40.9%)
Tłustochowicz et al 2013 (Poland)[36]	Adult patients with RA (n = 120) Median age, 52 years (range, 20–75) [c] Female, 76.7%	All patients were receiving biologics: IV, 58 (48.3%); SC, 62 (51.7%)	Survey: paper questionnaire including preference for SC injection or IV infusion of biological therapy	Prefer IV, 39.2%; prefer SC, 38.3%; no preference, 22.5%

Grisanti et al 2019 (USA)[42] [survey 1]	Adult patients with AS, PsA or RA (n = 243) [d] Mean (SD) age, 59.8 (12.8) years Female, 76%	44% of patients were biologic-naïve	Survey: paper questionnaire including preference for SC injection or IV infusion of biological therapy	Preferences for administration route Of 54 biologic-naïve patients expressing a preference, 65% preferred IV to SC therapy Preference by current administration route Patients currently on SC therapy (n = NR): prefer SC, 50%; prefer IV, 17% Patients currently on IV therapy (n = NR): prefer IV, 58%; prefer SC, 13%
Adlard et al 2018 (France, Germany, UK, USA)[60] [abstract only]	Adult patients with MS (n = 140) Age range, 21–60 years	NR	Survey: conjoint analysis of preferences for frequency and administration route of MS DMTs	Part-worth preference score: oral administration, 0.475; IV, 0.191; SC, 0.186; overall $p < 0.001$
Allen et al 2010 (UK)[45]	Adult patients with IBD (n = 78) [e] Mean age, 44 years Sex NR	Prior infliximab, 10 (13%)	Survey: questionnaire including preference for IV infliximab in hospital every 8 weeks or SC adalimumab at home every 2 weeks	Prefer IV infliximab, 33 (42%); prefer SC adalimumab, 19 (24%); no preference, 26 (33%) Previous IV infliximab users (n = 10): prefer IV infliximab, 6 (60%)
Cha et al 2017 (South Korea)[37]	Adult patients with IBD (n = 322); CD, 46.0%; UC, 54.0% Mean (SD) age, 39.7 (14.2) years Female, 32.6%	157 (48.8%) using TNFi therapies; administration route NR	Survey: questionnaire including preference for IV (in hospital, every 8 weeks) or SC (at home, every 2 weeks) TNFi	Prefer hospital IV every 8 weeks, 58.4%; prefer home SC every 2 weeks: 24.2%
Emadi et al 2017 (Qatar)[32]	Patients with RA (n = 294) Mean age: men, 51 years (range, 24–75); women, 48 years (range, 16–84) Female, 75.9%	Current oral therapy, 195 (66.3%); current SC, 64 (21.8%); current IV, 35 (11.9%)	Survey: questionnaire including preference for oral, IV or SC treatment	Preferences for administration route Prefer oral therapy, 69.0%; prefer SC, 23.5%; prefer IV, 7.5% Preference by current administration route Current SC patients: 37/64 (58%) prefer SC Current IV patients: 22/35 (63%) prefer IV
Willeke et al 2011 (Germany)[34] [abstract only; article in German]	Adult patients with RA (n = 102) Mean (SD) age, 59 (11) years Female, NR	All patients were receiving IV rituximab	Survey: questionnaire including preference for SC injection or IV infusion of biological therapy, or for oral therapy	Prefer IV infusion, 65.4% (every 6–9 months, 63.4%; every month, 2.0%); prefer tablets only, 21.5%; prefer SC every 2 weeks, 12.9%

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Table 2 (Continued).

Study (Country/ Region)	Population	Current or Previous Use of SC or IV Therapies	Study Design and Comparators	Results
Wu et al 2020 (Brazil)[47]	Adult patients with IBD (n = 101) [f] Mean (SD) age, 43.6 (13.5) years Female, 75.3%	All patients were biologic-naïve	Survey: questionnaire including preferences for mode of administration and for treatment profiles based on infliximab and adalimumab	Preferences for administration route Prefer oral, 87.1%; prefer IV, 6.9%; prefer SC, 5.9% Preference for treatment profiles Prefer hospital IV every 8 weeks, 54.5%; prefer home SC every 2 weeks, 45.5%
Bolge et al 2017 (USA, Canada)[43]	Adult patients with autoimmune conditions treated with IV biologics (n = 405) [g] Mean age, 50 years (19.3% were aged 65 years or older) Female, 72.8%	All patients were using IV biologics Most patients (68%) had not been able to choose their therapy	Survey: telephone interviews including questions on SC injection vs IV infusion	Prefer IV medication to SC injection, 82%
Boeri et al 2019 (USA)[49]	Adult patients with moderate-to-severe UC (n = 200) Mean (SD) age, 42.1 (14.7) years Female, 59.0%	Past or present experience: SC injection, 81 (40.5%); IV infusion, 52 (26.0%)	Survey: discrete choice analysis including preferences for frequency and administration route of UC treatment	Patients preferred oral administration to SC or IV; no significant difference between SC and IV
Bolt et al 2019 (Japan)[50]	Adult patients with psoriasis (n = 306) Mean (SD) age, 53.4 (10.7) years Female, 17.6%	NR	Survey: discrete choice analysis including preferences for SC injection or IV infusion of psoriasis treatments	Preferences for administration route SC injections vs IV infusion: coefficient, 0.0762; $p = 0.014$ Patients with mild disease, 0.1243; $p = 0.005$; moderate or severe disease, 0.0315; $p = 0.477$ Preferences for setting Treatment administered by a healthcare professional in a clinical setting, rather than at home: coefficient, 0.3970; $p < 0.0001$
Husni et al 2016 (USA)[58] [abstract only]	Adult patients with moderate-to-severe RA (n = 510) Mean age, 56.4 years Female, 64.7%	Receiving biological therapy, 45.1% (administration route NR)	Survey: discrete choice analysis including preferences for SC injection or IV infusion of RA treatments	Patients were more likely to select SC than IV administration (OR, 1.69) Preference for oral therapy vs IV: OR, 2.30

Louder et al 2016 (USA)[48]	Adult patients with RA (n = 380) Mean (SD) age, 54.9 (9.3) years Female, 81.6%	Patients using biologics were excluded 136 (35.8%) had received injection or infusion of non-RA medication in previous 180 days	Survey: choice-based conjoint analysis including preferences for frequency and administration route of RA therapies	Frequency selected: oral, 75.4%; SC self-injection, 49.2%; IV infusion, 26.3% Utility: oral, +99.3; SC self-injection, +7.3; IV infusion, −106.6 Route of administration was the most important attribute

Notes: [a]IV group: RA, 92; CD, 78; PsA, 23; AS, 15; psoriasis, 12; other, 15. SC group: RA, 151; CD, 77; PsA, 50; psoriasis, 50; AS, 17; other, 14. [b]Two patients switched from SC belimumab using a pre-filled syringe. [c]Assumed to be median; reported as "average". [d]RA, 81%; PsA, 13%; AS, 5%. [e]UC, 40; CD, 28; indeterminate colitis, 10. [f]UC, 82; CD, 19. [g]RA, 204; CD, 145; UC, 62; psoriasis, 47; PsA, 41; AS, 9.

Abbreviations: AS, ankylosing spondylitis; ASA, axial spondyloarthritis; CD, Crohn's disease; DMT, disease-modifying therapy; IBD, inflammatory bowel disease; IM, intramuscular; IQR, interquartile range; IV, intravenous; MS, multiple sclerosis; NR, not reported; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SC, subcutaneous; SLE, systemic lupus erythematosus; TNFi, tumor necrosis factor inhibitor; TTO, time trade-off; UC, ulcerative colitis.

Ten studies enrolled patients with IBD.[37,38,45,47,49,55,57,59,61,62] The results of these studies were mixed, with five reporting that patients preferred SC injection,[38,45,57,59,61,62] three describing an overall preference for IV infusion[37,45,55] and two finding similar preferences for the two options.[47,49]

Both of the included surveys of patients with severe asthma found strong preferences for SC injection over IV infusion, with 81.3% and 100% of patients preferring the SC administration route.[40,41]

A discrete choice experiment survey conducted among patients with psoriasis found that patients preferred SC injections to IV infusions (p = 0.014); this preference was significant only for patients with mild disease (p = 0.005) and not for those with moderate or severe disease (p = 0.477).[50] An Italian survey of patients with SLE (n = 548) and an Argentinian survey of patients with axial spondyloarthritis (n = 70) also found a preference for SC injection over IV infusion (41.2% vs 36.9% and 41% vs 3%, respectively).[39,56] A further two surveys, of patients with MS and of patients with a range of autoimmune conditions, both found that patients preferred IV administration to SC injections.[43,60] The final study, conducted among patients using TNFi therapies, found an overall preference for SC injections.[44]

Preferences According to Current Therapy

Nine studies described preferences among patients naïve to IV or SC therapies. Of these, five studies found patients to prefer SC injection,[29,33,38,46,47,62] two found patients to prefer IV infusion,[42,55] and two found similar preferences for the two administration routes.[35,47]

A total of 23 studies described preferences among patients currently using IV or SC therapies. Of these, nine studies assessed preferences among patients currently using SCIg (seven studies),[17–22,52] those currently using IVIg (one study),[24] or a mixture (one study).[54] All seven studies of current SCIg users or patients who had switched from IVIg to SCIg as part of the study found that the majority (69–100%) of patients preferred the SCIg route.[17–22,52] In another study, patients already on IVIg were offered a choice between staying on IVIg and switching to SCIg: 50 of 51 patients chose to switch.[24] The final study, conducted in a mixed population of SCIg and IVIg use, reported that patients strongly preferred their current administration route.[54]

Table 3 Reported Reasons for Preferences

Study (Country/Region)	Main Reasons Given for Patient Preferences
Allen et al 2010 (UK)[45]	Prefer IV (n = 33): dislike of idea of self-injecting, 67%; less frequent dosing, 42%; convenience, 36%
	Prefer SC (n = 19): convenience of injecting at home, 79%; no requirement to visit hospital, 63%; less complicated, 53%
Bolge et al 2017 (USA, Canada)[43]	Prefer IV (n = 332): dislike of self-injection, 43%; less frequent dosing, 34%; administered by professional, 24%; staff interaction at infusion center, 16%; easier to remember doses, 14%
Capelusnik et al 2019 (Argentina)[56] [abstract only]	Prefer SC (n = 29): easy application, 44.8%; efficacy, 27.6%; safety, 13.8%
Cha et al 2017 (South Korea)[37]	Prefer hospital IV every 8 weeks (n = 188): do not like idea of self-injecting, 73%; prefer frequency, 7%
	Prefer home SC every 2 weeks (n = 78): convenience of injecting at home, 73%; no requirement to visit hospital, 8%
Chilton et al 2008 (UK)[46]	Patients preferring IV were more likely than those choosing SC to identify contact with other patients and availability of staff as advantages (both $p < 0.001$)
	Preferring SC was associated with identifying not needing to travel to hospital as an influential factor ($p < 0.001$)
	Route of administration was not statistically significantly associated with treatment choice
Desplats et al 2017 (France)[30]	Prefer IV (n = 92): fear of lack of follow-up with SC route, 72%; lack of medical presence with SC route, 61%; keeping social relationships, 41%; prefer frequency, 33%; fear of adverse events, 28%
	Prefer SC (n = 109): avoid organization difficulty with hospital administration, 72%; greater autonomy, 39%; economic considerations, 22%; technical difficulties with IV infusions, 14%
Falanga et al 2019 (Italy)[39]	Patients preferring IV reported that advantages included feeling safe and calm during the infusion, thanks to the assistance of medical staff who are responsible and can intervene in case of side effects.
	Patients preferring SC reported that advantages included the higher comfort and convenience of managing medication at home, and avoiding hospital, with more time for a possible job
Gladiator et al 2017 (Europe and Brazil)[52] [abstract only]	Prefer SCIg (n = 42): highest proportion of "like"/"like very much" responses: "ability to fit treatment into my own schedule" (96%) and "ability to self-administer without medical supervision" (94%)
Huynh et al 2014 (Denmark)[33]	Prefer IV (n = 62): safer, 65%; easy to manage, 50%; minimize time, 31%; social contact, 24%
	Prefer SC (n = 80): minimize time, 63%; easy to manage, 43%; more comfortable with self-injections at home, 38%
Nagahori et al 2011 (Japan)[55] [abstract only]	Prefer IV (n = 81): medical staff availability, 83%; prefer frequency, 54%; dislike self-administration, 35%
	Prefer SC (n = 56): simple administration, 79%; home administration, 32%; difficulty visiting clinic, 27%
Reid et al 2014 (Canada)[28]	Patients preferred IVIg infusions over SCIg infusions because they take less time ($p = 0.005$) and did not believe that SCIg infusions 2 times per week are less traumatic than IVIg once per month ($p = 0.003$)
Runken et al 2016 (NR)[54] [abstract only]	The top reason for preferring IVIg was decreased infusion frequency; the main reason for preferring SCIg was decreased side effects
Santus et al 2019 (Italy)[41]	IV administration was associated with less frequent treatment, faster symptom reduction and greater effectiveness
	SC administration was seen as allowing more time for daily activities, with greater convenience and less time managing asthma, but with some practical hassles associated with treatment administration

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Table 3 (Continued).

Study (Country/Region)	Main Reasons Given for Patient Preferences
Scarpato et al 2010 (Italy)[35]	Prefer IV at hospital (n = 403): safety of hospital administration, 77%; reassuring effect of doctor's presence, 67%; prefer frequency, 61%; convenience of hospital treatment, 56%; convenience of administration route, 45%
	Prefer SC at home (n = 399): difficulty of reaching hospital, 97%; convenience of home treatment, 81%; convenience of administration route, 55%; level of interference with everyday life, 42%; easy to use, 36%
van Schaik et al 2018 (multinational)[17]	Prefer IVIg (n = 21): works better, 52%; greater independence, 33%; less time needed, 33%; prefer frequency, 33%; fewer side effects, 33%
	Prefer SCIg (n = 61): greater independence, 85%; less time needed, 61%; prefer frequency, 49%; fewer side effects, 48%; works better, 33%
Wu et al 2020 (Brazil)[47]	Prefer IV (n = 55): dislike of self-application, 53%; fear of SC injection, 27%
	Prefer SC (n = 46): prefer to take medication at home, 57%; more freedom, 54%

Note: The top five reasons reported by ≥ 5% of respondents are listed.
Abbreviations: IV, intravenous; IVIg, intravenous immunoglobulin; SC, subcutaneous; SCIg, subcutaneous immunoglobulin.

Of 14 reports of preferences for IV infusion or SC injection among current users of relevant non-immunoglobulin therapies, 13 found that patients preferred their current treatment.[30–34,41–44,57] Seven studies reported that patients receiving treatment by IV infusion preferred the IV administration route.[31–34,42–44] Similarly, in six studies patients using SC therapies expressed a preference for that option.[31–33,41,44,57] The exceptions were two surveys, conducted in France and Portugal.[30,57] In the French study, 54.2% of 201 patients with RA using IV biologics expressed a preference to switch to SC injections.[30] Similarly, in the Portuguese survey, 11 of 21 patients with CD using IV infliximab reported preferring to change to SC adalimumab.[57]

Patient Preferences for Frequency and Setting Separate from Those for Administration Route

Only nine of the included studies separated preferences for treatment at home versus in hospital from choices about administration route.[19,20,23,35,40,44,50,59] Four studies reported that patients separately preferred SCIg over IVIg, and home treatment over hospital administration.[19,20,23,56] A further study found that among patients with CD who preferred SC injection over IV infusion, the majority (68.7%) preferred home treatment over hospital administration.[59] By contrast, two surveys, which investigated multiple aspects of treatment for psoriasis and severe asthma, found patients to prefer SC injection over IV infusion, and also to prefer administration by a healthcare professional in a clinical setting.[40,50] Two final studies found that patient preferences varied between those currently using or preferring SC TNFi therapies, who preferred home administration, and those receiving or preferring IV TNFi agents, who preferred hospital treatment.[35,44] In two studies, a minority of patients (18% and 44%) preferring SC injections indicated that they would prefer the injections to be performed by a nurse.[30,33]

All ten studies that separately assessed preferences for administration route from those for treatment frequency found patients to prefer less frequent treatment options.[26,27,29,33,36,40,48,50,60,61]

Reasons for Treatment Preferences

A total of 16 studies reported patients' main reasons for preferring particular administration routes (Table 3 and Figure 3).[17,28,30,33,35,37,39,41,43,45–47,52,54–56] The main reasons given by patients for preferring IV infusion were the lower frequency of IV infusions compared with SC administration, the presence of healthcare professionals and resulting feelings of safety, and a dislike of self-injecting. By contrast, patients preferring SC treatment cited the convenience and comfort of home treatment and the avoidance of having to attend hospital, as well as the reduced time requirement and greater independence associated with SC administration.

Discussion

This SLR identified 49 studies that described patient preferences for IV or SC administration of treatments for chronic immune system disorders. The included studies covered a range of indications and comparisons between both IVIg and SCIg, and IV infusion and SC injection of non-immunoglobulin therapies. Overall, the literature suggests that patients with chronic immune system disorders are more likely to choose SC administration over IV infusion, although the results of individual studies varied. Preferences toward SC administration were most consistent in the studies comparing methods of immunoglobulin administration (ie IVIg vs SCIg). These observations speak to the importance of developing and maintaining a diverse suite of treatment options for patients, such that the unique preferences of any individual patient can be accommodated. Patients who favored IV infusions frequently cited the relative infrequency of treatment and feelings of safety due to hospital administration as desirable attributes. By contrast, patients preferring SC therapies tended to like the convenience and independence associated with self-injection at home.

No clear trends were identified according to indication, including whether the disease in question might be expected to affect patients' ability to self-inject. The most common indication in the included studies was immunodeficiency (mostly PID), for which 11 of 13 studies found an overall preference for SCIg over IVIg.[14,15,18–20,23,24,26–28,52–54] This is consistent with studies of patients with arthritis (in nine of 11 studies reporting an overall preference this was in favor of SC administration),[29–34,42,46,48,56,58] asthma[40,41] and SLE[39,51] (for both two of two studies favored SC administration). The preference toward SC therapies was slightly weaker in studies of patients with IBD, but an overall preference for SC treatment was still seen in the majority of studies (5 of 8 studies reporting an overall preference).[37,38,45,55,57,59,61,62]

Preference toward SC therapies was seen in studies of both adult and pediatric populations. Notably, all of the seven studies of preferences in specific populations of children found an overall preference for SC therapies.[18,19,24,26,27,53,62] Of these, six studies compared IVIg and SCIg for the treatment of PID.[18,19,24,26,27,53] The final study reviewed treatment choices among children with CD (or their families).[62] Interestingly, while 89% of the group offered a choice (n = 37) opted for SC adalimumab over IV infliximab, 72% of those in a parallel group (n = 29) who were not given a choice were treated with IV infliximab. This highlights the potential for treatment preferences to differ between patients and physicians, which may have implications for treatment satisfaction and HRQoL.[62]

There was a clear tendency for patients to prefer their current treatment administration route over administration routes with which they did not have experience. The exceptions to this were two studies that found patients currently using IV therapies would prefer to switch to SC alternatives.[24,30] One of these studies, reported by Samaan et al, illustrates the importance of experience in patients' decision making.[24] A group of IVIg-experienced children strongly preferred to switch to SCIg, and most (88%) remained on SCIg after an average follow-up period of 52 months. By contrast, when a further cohort of children, newly diagnosed with PID and naïve to immunoglobulin replacement therapy, were offered a free choice of IV or SC administration, approximately half selected each administration route. However, by the end of an average of 33 months' follow-up, 80% were using SCIg.[24] Consistent with these observations, preferences expressed by patients as part of clinical studies tended to favor SC administration more strongly than the results of surveys. This difference may reflect many survey respondents not having experience of self-injecting or administering treatment at home. For these patients, training in the use of self-administered therapies is important, as are homecare support structures and patients having sufficient information to make informed treatment choices.

It remains challenging to compare patients' preferences between IV and SC administration, given there are differences in treatment setting and frequency as well as in route, and the relative importance of different aspects may vary among patients. For example, some patients might consider treatment twice-weekly by SC injection to be too frequent, even though in principle they prefer SC administration to IV infusion. There were only limited data in the literature on preferences for treatment administration route separate from treatment setting. Where such data were identified they were consistent with patients preferring SC administration to take place at home, and IV administration to take place in hospital, with the exception of two studies in which both SC injection and administration by a healthcare professional in a clinic were preferred.[40,50] Many of the reasons patients gave for preferring IV treatment were related to receiving treatment in hospital, while many of the reasons given for preferring SC administration were related to receiving treatment at

home. It is possible that some patients' preferences for hospital versus home treatment may change following the SARS-Cov-2 pandemic. During the pandemic, home treatment (including immunoglobulin replacement for myasthenia gravis)[63] and remote consultations[64,65] were widely used in place of hospital visits; in the case of remote consultations, two surveys have suggested that around half of patients would be open to continuing with this approach at least some of the time.[64,65]

The findings of this review are consistent with previously published SLRs, most of which focused on specific patient groups. SLRs reported by Jones et al and Abolhassani et al found preferences for SCIg over IVIg among patients with primary immunodeficiency.[9,12] A recent SLR of patient preferences for RA treatments, described by Durand et al, included five studies that compared SC injection with IV infusion;[10] in four of the five, patients preferred SC administration.[10] As in this review, patients' preferences tended to reflect their current treatment route.[10] In addition, a more general SLR reported by Stoner et al found patients in four of the six studies preferred SC therapy over IV administration.[13]

In addition to managing patients' clinical condition, a major goal of treatment is to improve patients' HRQoL. A recent study has shown that, over an entire population of patients with PID, IVIg and SCIg use are associated with similar HRQoL.[68] Personal preferences may therefore be an important part of matching each patient to the more appropriate therapy, potentially maximizing HRQoL for each individual. Inconvenience, travel and a lack of flexibility are frequently cited as reasons for preferring home treatment to hospital IV therapy,[30,33,69] suggesting that patients' work schedules, or distance from hospital, may play a part. Conversely, patients preferring hospital IV therapy frequently describe feelings of safety with hospital treatment, underlining the importance of psychological factors.[33] Patients' individual preferences may also be influenced by other clinical factors. For example, a recent survey of patients with SLE found that use of non-steroidal anti-inflammatory drugs was associated with an increased likelihood of choosing SC injection over IV infusion.[70] Understanding how other aspects of patients' treatment may affect the choice of the most appropriate therapy for each patient may be important for maximizing HRQoL.

This review has several limitations. First, all of the studies comparing IV infusion to SC infusion assessed preferences for IVIg versus SCIg; no data were identified comparing SC infusion of other therapies with IV alternatives. Second, the comparison between IV infusion and SC injection covers a range of different treatments and indications, but all except two of the included studies were surveys, and the evidence from clinical studies is limited. Third, no studies comparing SC infusion and SC injection were identified, although this reflects the lack of therapies that might potentially be administered by both of those routes. Fourth, the included evidence was limited to studies published in English; although no citations were excluded on the basis of language (for one study published in German, data were extracted only from the English-language abstract), the possibility of additional relevant literature published in other languages cannot be excluded. Fifth, the review was limited to chronic immune system disorders; accordingly, evidence from recent studies of IV and SC versions of several oncology therapies was therefore excluded. This focus was chosen because patient preferences for oncology therapies, which are taken for a limited period of time, typically in the context of multiple hospital visits, were considered not to be readily comparable with those for treatments for chronic disorders. Sixth, the multitude of variables that contribute to patients' preferences cannot be accounted for in this review. For example, SC infusion by automated pump has been shown to be preferred to rapid push administration using a syringe.[71] As the individual characteristics of the IV, SC infusion, and SC injection administration routes evolve, so too may patient preferences. Seventh, many of the results come from clinical trial data. Patients entering a clinical trial may have an inherent bias toward preference for a study medication that cannot be extrapolated to routine clinical care. Eighth, several recent studies have investigated the relative efficacy and safety of SC and IV therapies.[66,67] Although not the focus of this SLR, differences in efficacy or safety would be expected to influence patients' preferences for particular treatment options. Ninth, many of the included studies were not designed to assess preferences among patients who were necessarily representative of the overall patient populations, and most had some risk of bias. Caution should therefore be taken when extrapolating from these results to other patient groups; however, given the similarity of findings across indications a systematic bias toward preferences for one administration route or another can be considered to be unlikely.

Conclusion

The goal of treatment for chronic immune system disorders is to improve patients' disease state, functionality and HRQoL. It is important that the method of treatment administration does not add to the burden of their disease, which in many cases can be substantial. Overall, while there is some variability among individual studies, patients with chronic immune system disorders – particularly those using immunoglobulin therapy – tend to be more likely to choose SC administration than IV infusion. Patients tend to prefer their existing therapy, and some choices may reflect lack of experience of alternatives. Many patients may therefore benefit from training and support structures, and from being provided with the information they need to make informed decisions. Patients' choices appear to reflect the frequency and setting of treatment options as much as differences in administration route – the relative importance of the lower frequency of IV infusions and the convenience of home SC administration may vary among patients. The results of this SLR may help inform discussions about the available treatments, and decisions as to the most appropriate choice of therapy for individual patients.

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