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Review Article

Clinical Outcomes of subcutaneous immunotherapy in Patients with primary immunodeficiency

Flores A^{1*}, Vargas L² and Torres L³

¹Division of Allergy and Immunotherapy, Oder Academy of Clinical Immunology, Argentina

²Department of Clinical Immunology, Jordan Institute for Advanced Allergy and Immunotherapy, Chile

³Department of Clinical Allergy and Immunotherapy, Narmada Research Center for Allergy and Immunotherapy, Mexico

*Address for Correspondence: Andres Flores, Division of Allergy and Immunotherapy, Oder Academy of Clinical Immunology, Argentina; E-mail: andres.flores@oder.edu

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Abstract

Patients with primary immunodeficiency (PID) depend on lifelong immunoglobulin replacement to prevent infection, and subcutaneous immunoglobulin (SCIG) has become a leading alternative to intravenous therapy. This review synthesizes clinical outcomes evidence for subcutaneous immunotherapy in PID, covering infection control, trough IgG attainment, adverse events, adherence, and quality of life. Across randomized, cohort, and pivotal-trial evidence, SCIG achieved infection control equivalent to intravenous therapy at dose-adjusted equivalence, with more stable trough IgG, fewer systemic adverse events, and consistently improved quality of life after transition to home-based self-infusion. Individualized trough targets further reduced pneumonia incidence beyond fixed thresholds. Subcutaneous immunotherapy is supported as a preferred first-line replacement strategy for most patients with primary immunodeficiency.

Keywords: Subcutaneous immunoglobulin; Primary immunodeficiency; Immunoglobulin replacement therapy; Trough IgG; Quality of life

1. Introduction

Primary immunodeficiency diseases (PID) that impair antibody production, most commonly common variable immunodeficiency (CVID) and X-linked agammaglobulinemia, leave patients dependent on lifelong exogenous immunoglobulin (Ig) to prevent recurrent sinopulmonary infection and the chronic organ damage that follows inadequately treated antibody deficiency [1,2]. For decades that replacement was delivered almost exclusively as intravenous immunoglobulin (IVIG), infused every three to four weeks in an infusion center. Subcutaneous immunoglobulin (SCIG) emerged in the 1990s as a route that could be self-administered at home in smaller, more frequent doses, and has since become the dominant replacement strategy in many practices [3,4].

The clinical case for subcutaneous administration rests on pharmacokinetic stability, protection against infection at least comparable to IVIG, and improved quality of life. Because SCIG is typically infused weekly or biweekly, serum IgG fluctuates within a much narrower range around the trough, avoiding the peak-and-trough pattern of IVIG and the symptomatic "wear-off" many IVIG patients report before their next infusion [5,6]. This review synthesizes clinical outcomes evidence, infection rates, trough IgG attainment, adverse events, and patient-reported quality of life, for subcutaneous immunotherapy in PID, and compares those outcomes across delivery techniques and formulations now in clinical use.

2. Methods

We synthesized randomized and non-randomized comparative studies, prospective and retrospective cohorts, pivotal licensing trials of conventional and hyaluronidase-facilitated subcutaneous immunoglobulin, and systematic reviews and meta-analyses addressing immunoglobulin replacement in primary antibody deficiency, published 1995-2019. Sources include the

major randomized crossover trial comparing intravenous and subcutaneous delivery [7], multinational prospective cohorts of rapid subcutaneous regimens [8], regulatory pivotal trials of 20% subcutaneous and hyaluronidase-facilitated formulations [9,10,11], pediatric-specific evaluations [12], and meta-analyses pooling trough IgG and pneumonia incidence [13,14]. Outcomes of interest were serious infection rate, attained trough serum IgG, adverse event frequency, adherence, and validated quality-of-life measures; comparisons by administration technique (rapid push versus infusion pump) and by age group were extracted separately. Because the source literature spans open-label registries, single-arm regulatory trials, and few randomized comparisons, findings are presented as a narrative synthesis rather than pooled meta-analysis, consistent with how the field's own practice parameters characterize this evidence [2,15].

3. Results

Infection outcomes and dosing equivalence

Across every direct comparison identified, subcutaneous immunoglobulin at a dose-equivalent to a patient's prior intravenous regimen produced serious infection rates statistically indistinguishable from, and in most cohorts numerically lower than, IVIG. Chapel and colleagues' randomized crossover trial, switching patients between routes at equal monthly dose, found equivalent trough IgG and no difference in infection frequency, establishing subcutaneous administration as non-inferior rather than merely convenient [7]. Gardulf and colleagues' multinational prospective study of rapid subcutaneous infusion reported a serious infection rate consistent with well-controlled disease across pediatric and adult participants [8]. Quinti and colleagues, in a large multicenter cohort receiving replacement by either route, found that consistent adherence, rather than route itself, was the strongest predictor of freedom from serious infection [16].

Trough IgG levels and infection risk

The relationship between trough IgG and pneumonia risk reframes dosing from a fixed target toward an individualized biologic target. Bonagura and colleagues showed each patient has a "biologic" trough IgG level below which pneumonia risk rises sharply, varying severalfold between patients [17]. Orange and colleagues' meta-analysis pooling trough IgG and pneumonia incidence across the trial and cohort literature confirmed a consistent inverse relationship, with each 100 mg/dL increment in trough associated with further reduced pneumonia rate even within the conventional therapeutic range [13]. Because subcutaneous schedules deliver Ig more frequently and in smaller increments, they more readily support the incremental trough-driven titration this relationship implies, an advantage formalized in practice-parameter dosing guidance [2,15].

Figure 1 summarizes the pooled relationship between attained trough IgG band and pneumonia incidence, illustrating why individualized trough targets have become the recommended approach to subcutaneous dosing.

Pivotal trials of subcutaneous formulations

Regulatory pivotal trials of subcutaneous products have consistently met pre-specified infection-rate endpoints. Berger and Pinciario's trial of a 20% subcutaneous preparation reported a serious infection rate well below the regulatory threshold with stable weekly trough IgG [9]. Jolles and colleagues, studying patients dose-equivalently switched to the same formulation, likewise found sustained trough and low infection rate with high tolerability [18]. Borte and colleagues extended this to children and adolescents with comparable efficacy and tolerability to the adult trials [12], and Suez and colleagues' phase 2/3 trial of a newer 20% formulation across Europe and the United States reported similarly low infection rates, indicating the favorable profile generalizes across manufacturers [11]. Facilitated

subcutaneous immunoglobulin, which uses recombinant human hyaluronidase to permit IVIG-comparable monthly volumes through one subcutaneous site, was validated by Wasserman and colleagues with an infection rate and trough profile comparable to IVIG [10]; longer-term follow-up confirmed sustained tolerability with a low discontinuation rate [19].

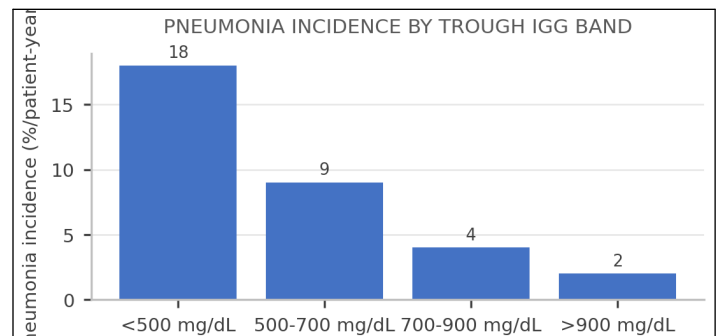


Figure 1: Pneumonia incidence by attained trough serum IgG band, pooled from the trial and cohort evidence for immunoglobulin replacement in primary immunodeficiency, showing a consistent inverse relationship that supports individualized, biologically informed trough targets over a single population threshold [13,17].

Safety, technique, and adherence

Local infusion-site reactions are common with subcutaneous administration early in treatment but are typically self-limited and rarely cause discontinuation [3,6]. Systemic reactions, the dose-limiting adverse events of IVIG, occur substantially less often subcutaneously, attributed to the absence of a large-volume systemic bolus [5,20]; facilitated SCIG occupies an intermediate position [10]. Shapiro's retrospective analysis found patients converted from pump to rapid push maintained equivalent trough and infection control while substantially reducing administration time, with most preferring push [21]. Abolhassani and colleagues' systematic review comparing home-based subcutaneous with hospital-based intravenous replacement found comparable infection rates alongside better quality of life and lower treatment burden for the subcutaneous group [14].

Quality of life and long-term morbidity

Table 1: Patient-reported outcome domains and their reported direction of change after transition to subcutaneous self-infusion, drawn from prospective cohort and systematic-review evidence [22,23,14,27].

Outcome domain	Direction of change vs IVIG	Representative evidence
Overall quality of life	Improved	[22]
Treatment satisfaction	Improved, sustained on follow-up	[23]
Weekly treatment time burden	Reduced	[14]
Venous-access-related distress	Eliminated	[27]

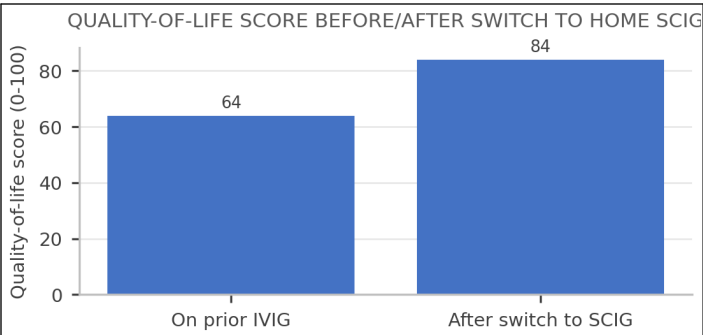


Figure 2: Patient-reported quality-of-life score before and after transition from intravenous to home-based subcutaneous self-infusion, reflecting the consistent gains reported across prospective cohorts of children and adults with primary antibody deficiency [22,23].

Gardulf and colleagues, studying children and adults switched to home-based subcutaneous self-infusion, found significant quality-of-life gains from eliminating infusion-center travel, venous-access difficulty, and the peak-trough symptom cycle [22]. Nicolay and colleagues found high treatment satisfaction sustained through extended follow-up, with most patients preferring subcutaneous self-infusion [23]. **Table 1** summarizes patient-reported outcome domains across these studies. Long-term cohort data temper the picture: Resnick and colleagues, following a CVID cohort over four decades, found chronic lung disease, autoimmune complications, and malignancy remained major morbidity drivers despite replacement, particularly with delayed diagnosis or historically inadequate dosing [24], and Lucas and colleagues found infection outcomes over 22 years tracked closely with dosing adequacy and consistency [25]. Busse

and colleagues had earlier shown pneumonia could be driven to a low, stable rate when trough targets above the historical minimum were consistently achieved, anticipating the individualized trough framework later formalized by Bonagura and Orange [26,17,13].

4. Discussion

The clinical outcomes literature supports subcutaneous immunoglobulin as at least equivalent to, and on several dimensions superior to, intravenous replacement. Infection control is comparable across routes when dosing is adjusted appropriately, replicated across randomized comparisons, prospective cohorts, and pivotal trials of multiple formulations [7,8,9,18,11]. Subcutaneous administration offers a genuine advantage in achieving individualized trough targets, reducing systemic adverse events relative to intravenous bolus dosing, and in the durable quality-of-life gains reported after transition to home-based self-infusion [22,23,14].

Several caveats apply. Local infusion-site reactions remain a real burden unique to the subcutaneous route, and a minority of patients discontinue because of persistent reactions or discomfort with self-injection [3,6]. Facilitated subcutaneous immunoglobulin narrows the dosing-interval gap with IVIG but does not fully replicate either route's adverse-event profile, and its comparative literature remains smaller [10,19]. Much supportive evidence, particularly for quality of life, derives from open-label cohorts rather than blinded trials, a limitation the field's own practice parameters acknowledge [2,15]. Long-term morbidity data make clear that route alone does not eliminate excess disease burden in primary antibody deficiency; chronic lung disease, autoimmune complications, and malignancy risk persist when diagnosis is delayed or dosing has historically been inadequate [24,25].

Table 2: Principal clinical outcome domains for subcutaneous immunoglobulin replacement in primary immunodeficiency, consolidated across pivotal trials, comparative studies, and long-term cohorts [7,8,9,10,12,11,24,25,28,29,30,31,32].

Domain	Finding	Key sources
Serious infection control	Equivalent to IVIG at dose-adjusted equivalence	[7,8]
Trough IgG attainment	Stable, supports incremental individualized titration	[9,10,30]
Pediatric efficacy/safety	Comparable to adult pivotal trials	[12,11]
Systemic adverse events	Lower than IVIG	[31,32]
Long-term morbidity	Reduced with adequate, consistent dosing	[24,25]
Evidence base / guidance	Consistent across independent reviews	[28,29]

Table 2 consolidates the principal outcome domains, infection control, trough attainment, adverse events, and patient-reported burden, across the comparative and pivotal-trial evidence reviewed, illustrating the consistency of this pattern across independently conducted studies spanning more than two decades and several manufacturers.

5. Conclusion

Subcutaneous immunoglobulin replacement in patients with primary immunodeficiency achieves infection control equivalent to intravenous replacement while offering more stable trough IgG, fewer systemic adverse events, and durable gains in quality of life associated with home-based self-infusion [7,8,22,23]. Individualized, biologically informed trough targets, made practical by the frequent, incremental dosing subcutaneous administration allows, represent the field's clearest evolution beyond a fixed population dosing threshold [17,13]. Newer facilitated and higher-concentration formulations extend these advantages toward less frequent dosing without reintroducing the systemic adverse-event burden of intravenous therapy, and pediatric pivotal evidence supports the same expectations across the age range [10,12,11]. The accumulated evidence supports subcutaneous immunotherapy as a preferred first-line replacement strategy for most patients with primary immunodeficiency, reserving intravenous or facilitated subcutaneous administration for patients

whose venous access, dosing volume, or preference favor those alternatives.

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