Review

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The New Formulations of Immunoglobulin Replacement Therapies and Future Aspects

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Abstract

Immunoglobulin replacement therapy (IgRT) stands as the established method of treatment for numerous inborn errors of immunity (IEI). Over the past six decades, there have been notable advancements in the dosing, processing, and administration routes of IgRT for IEI. Intravenous immunoglobulin has proven to be an effective treatment method, typically administered every 3 to 4 weeks. Traditional subcutaneous intravenous immunoglobulin (SCIG) is equally effective in maintaining biological IgG levels, with smaller doses administered daily every 2 weeks. F-SCIG is also equally effective and is typically administered every 3 to 4 weeks, in which patients are first required to administer hyaluronidase and then the gammaglobulin. Compared to less concentrated SCIG products, those with higher concentrations allow for the infusion of a smaller volume, less time spent on infusion, increased interval between infusions, and improved health-related quality of life. In addition, high-concentration products are reported to be similarly effective and well-tolerated by patients compared to lower-concentration SCIG and IVIG bioequivalents. High-concentration SCIG products, such as Cutaquig/Gammanorm (16.5% IgG) and Hizentra, Cuvitru, and Xembify (20% IgG), are available in the market. Overall results demonstrated that high-concentration SCIG products were efficient and well-tolerated, and allowed successful self-administration in individuals with IEI. A precise and personalized approach to IgRT is essential for improving outcomes in patients with IEI. The quest for new IgRT formulations and improved ancillary tools for SCIG aims to lower the occurrence of infections and complications related to them by enhancing adherence to long-term IgRT.

Keywords: Facilitated subcutaneous immunoglobulin, high concentration immunoglobulin, immunoglobulin replacement therapy, inborn errors of immunity, intravenous immunoglobulin, subcutaneous immunoglobulin

Introduction

Immunoglobulin replacement therapy (IgRT) represents the established approach to treating a variety of inborn errors of immunity (IEI), especially those involving common variable immunodeficiency, hypogammaglobulinemia, and/or antibody deficiency. The availability of intravenous immunoglobulin (IVIG) became widespread in the 1980s, while the utilization of subcutaneous intravenous immunoglobulin (SCIG) was introduced later in the same decade by Berger and colleagues. In the 2000s, the first product licensed explicitly for SCIG received approval, and this was succeeded by facilitated SCIG (f-SCIG) in the 2010s. F-SCIG includes human recombinant hyaluronidase and 10% human immunoglobulin G, designed for IgRT in IEI (1). Additionally, SCIG products with the concentrations of 16% and 20% have been recently developed and approved for subcutaneous administration in the current era (Figure 1).

In the past six decades, significant progress has been made in refining the dosing, processing, and methods of administering IgRT for IEI. Intravenous (IV) immunoglobulin has demonstrated its efficacy as a treatment approach, typically given every 3 to 4 weeks. Nonetheless, some patients encounter challenges due to systemic side effects, fluctuations in IgG levels, wear-off effects, difficulties with IV access, hospital visits, and work

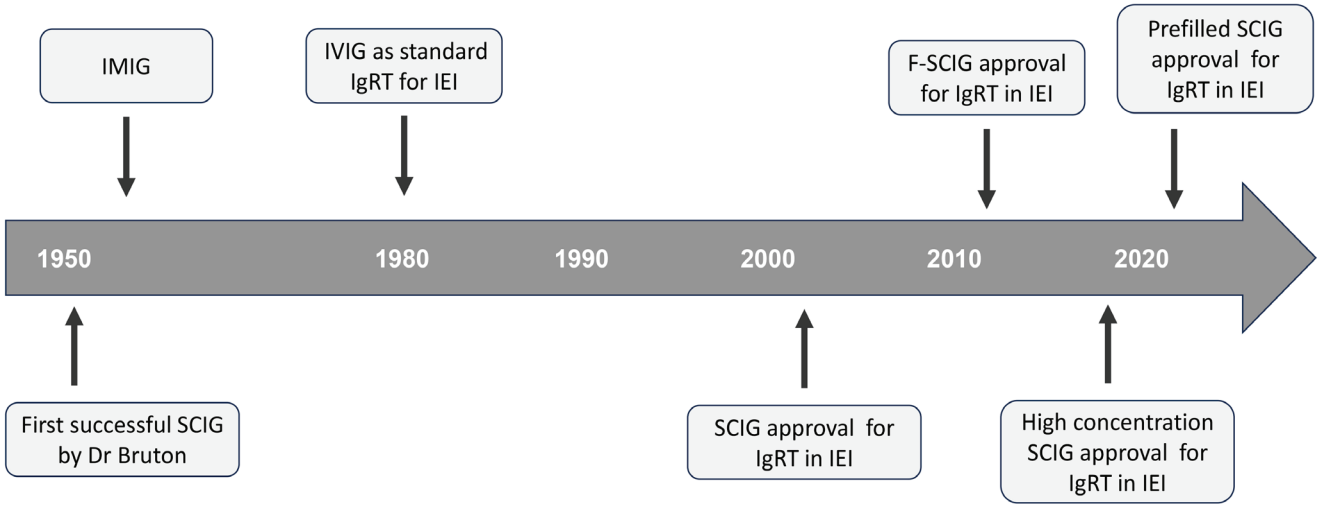

Figure 1. History of immunoglobulin replacement therapy for inborn errors of immunity during the past decade.
F-SCIG: Fasciliated SCIG, IEI: Inborn errors of immunity, IgRT: Immunoglobulin replacemnet therapy, IMIG: Intramuscular immunoglobulin, IVIG: Intravenous immunoglobulin, SCIG: Subcutaneous immunoglobulin

or school schedule disruptions (2). Conversely, traditional SCIG is equally effective in maintaining the desired IgG levels, with smaller doses administered daily to every 2 weeks, depending on the specific product used. SCIG is recognized for its lower incidence of systemic side effects; however, it does tend to result in more frequent local site reactions (3). Facilitated SCIG (f-SCIG) is equally effective and is typically administered every 3 to 4 weeks. In this method, patients must first receive hyaluronidase and then infuse the gammaglobulin.

In any form of IgRT, whether it is IVIG or SCIG, there is an expectation that all licensed products and methods should effectively shield IEI patients from infections while causing only manageable minor side effects. Furthermore, in today's context, there is an increasing emphasis on the importance of IgRT positively impacting a patient's quality of life and satisfaction with the treatment. From the perspective of patients, the ideal IgRT with SCIG is characterized by using fewer needles and having longer intervals between infusions, as outlined in the International Patient Organization for Primary Immunodeficiencies (IPOPI) Patient Needs and Outlooks Survey (4). Therefore, the current review primarily concentrates on newer formulations of IgRT, specifically 16.5% and 20% SCIG, in the context of IEI and its future implications.

High Concentration SCIG in Patients with IEI

Compared to less concentrated conventional or traditional SCIG products, those with higher concentrations allow for the infusion of a smaller volume, reduced time for infusion, increased interval between infusions, and improved health-related quality of life (HRQoL). Moreover, high-concentration products are reported to be equally effective and well-tolerated by patients when compared to SCIG and IVIG bioequivalents with lower concentrations (5). Due to differences in bioavailability, a prerequisite for Food and Drug Administration (FDA) approval requires raising the dose by 40-50% when switching from IVIG to high-concentration SCIG therapy (5). As these IgRT treatments, including high-concentration SCIG, are typically used over the long term, patients and physicians must consider various factors related to the patient and the infusion. These factors may include the specific diagnosis, comorbidities, the chosen route of administration, the administration site, infusion frequency, dosage, the infusion setting, treatment tolerability, patient preferences, and the patient's ability to self-administer, all while aligning with the patient's lifestyle.

Currently, high-concentration SCIG products, such as Cutaquig/Gammanorm (16.5% IgG) and Hizentra, Cuvitru, and Xembify (20% IgG), are available in the market (Table 1) (6-10). Regarding the volume received, for these two concentrations, 1 gram of immunoglobulin is contained in 6 mL of 16.5% SCIG, whereas it is 5 mL for 20% SCIG. An important distinguishing factor between SCIG concentrations is viscosity, which refers to the force required for injection. The final infusion force, determined by factors like needle diameter, injection rate, tissue back pressure, and product viscosity, often necessitates using a pump for support during infusion.

SCIG (16.5%) in Patients with IEI

SCIG 16.5% is produced through IgG extraction, viral removal/inactivation, and stabilization processes, which ensure the drug's tolerability. A Phase 3, prospective, open-label, single-arm, pivotal study involving adult and

Table 1. Characteristics of high-concentration subcutaneous immunoglobulin products (6-10)

Characteristics	Octanorm 16.5% (Cutaquig)	IgPro20 (Hizentra)	IGSC 20% (Xembify)	Ig20Gly (Cuvitru)
Protein	165 g/L (16.5%)	200 g/L (20%)	200 g/L (20%)	200 g/L (20%)
IgG	≥96%	≥98%	≥98%	≥98%
Pharmacokinetics AUC (area under curve SCIG/ IVIG)	98-107% with 1.5 of dose adjustment factor	77-120% with 1.5 of dose adjustment factor	68% Dose adjustment factor not used	82-88% with 1.37 of dose adjustment factor
IgA	≤20 µg/mL	≤50 µg/mL	Not defined	≤280 µg/mL
Stabilized by		L-proline	Glycine	Glycine
Polysorbate 80	31±3.7 µg/mL	10-30 µg/mL	≤10-40 µg/mL	None
Sodium	<30 mmol/L	<1 mmol/vial	None	None
Osmalality	310-380 mOsmol/kg	380 mOsmol/kg	280-404 mOsmol/kg	280-292 mOsmol/kg
Ph	5-5.5	4.8	4.1-4.8	4.6-5.1
Store at	+2 °C to +8 °C	room temperature (<25 °C)	+2 °C to +8 °C	Room temperature (<25 °C)
Infusion site	not limited	up to 4	up to 6	Not limited
Volume/site	15-50 mL/site 1st 2 infusion:10-25 mL /site (adjusted by age)	25-50 mL/site 1st infusion: 15 mL/site	25 mL/site	<18 years of age: 5-15 mL/site Adults: preferably <30 mL/site
Infusion rate	15-50 mL/hour/site 1st 2 infusion:10-25 mL/hour/ site (adjusted by age and increased every 10 minutes)	25-50 mL/hour/site 1st infusion: 15 mL/hour/site	25 mL/hour/site	Adjusted according to the patient's tolerability 1st 2 infusions: Starting at 10 mL/hour/site and up to 20 mL/hour/site, increased every 10 minutes
Infusion intervals	Daily-every 2 weeks	Daily-every 2 weeks	Daily-every 2 weeks	Daily-every 2 weeks

pediatric patients revealed that the administration of SCIG 16.5% enabled patients to maintain elevated plasma IgG levels and effectively prevent infections (11). The study found no severe bacterial infections and minor infections occurred at a rate of 3.3 per patient per year for both adult and pediatric populations, with a rate of 3.1 for the pediatric population alone (11,12). Moreover, these trials concluded that the administration of SCIG 16.5% resulted in high tolerability with fewer systemic side effects and self-administration flexibility at home (13,14). However, it is essential to note that further real-life data comparing these two patient groups are needed to gain a comprehensive understanding of their experiences.

SCIG (20%) in Patients with IEI

IgPro20, Ig20Gly, and IGSC 20% represent three unique SCIG solutions that have recently gained approval and are currently accessible in the global market as high-concentration 20% SCIG products (8-10).

To assess the effectiveness and safety of IgPro20, a summary of seven open-label Phase 3 prospective multicenter studies was conducted, involving a total of 125 patients, encompassing both pediatric and adult populations. These studies included 15,013 infusions in total. The reported infection rates and rates of serious bacterial infections were 3.10 and 0.03 events per patient per year, respectively. Administering 20% SCIG increased serum IgG trough levels for patients who transitioned from IVIG and maintained IgG levels for those who switched from SCIG. All adverse events (AEs) were mild/moderate (events/infusion: 0.094-0.773) and were local site reactions (15). The findings from these seven studies collectively suggest that IgPro20 therapy is both effective and well-tolerated for long-term treatment.

A comprehensive analysis of pooled data, focusing on the safety and tolerability of subcutaneous Ig20Gly in primary immunodeficiency diseases, was conducted based on information gathered from two Phase II/III studies in North America and Europe. In total, 122 patients, including adults and pediatric individuals, received 6676 Ig20Gly infusions, and no severe adverse events causally related to the treatment were reported. However, 27 patients did report 165 mild systemic adverse events that were causally related (16). These findings are consistent with the idea that Ig20Gly is well-tolerated among a diverse population of patients with primary immunodeficiency diseases. Another recent retrospective study, which included pediatric and adult patients initiating Ig20Gly treatment, was conducted at two medical centers. This study examined various aspects, including administration parameters, tolerability, and usage patterns over 12 months. The results demonstrated that Ig20Gly was well-tolerated and allowed for successful self-

administration in individuals with IEI, including elderly patients and newly starting IgRT.

Santamaria and colleagues conducted a multicenter, open-label, single-arm clinical trial to assess the effectiveness, pharmacokinetics, safety, and tolerance of IGSC 20% in individuals with IEI. A total of sixty-one participants, including children, were enrolled in the study. The reported rates of serious bacterial infections and hospitalizations per person per year were both 0.017. The mean trough total IgG concentrations were comparable to those achieved with the previous IgG replacement therapy. Notably, no severe adverse events related to the investigational product were observed, although the overall rate of adverse events, including local infusion site reactions, was 0.135 (17). These findings align with those of other products, indicating that IGSC 20% exhibits efficacy and maintains a high level of safety and tolerance in individuals with IEI (18).

Future Aspects of SCIG in Patients with IEI

The practice of patients or their caregivers administering SCIG therapy at home offers several benefits, including enhanced patient adherence, reduced treatment-related challenges, increased convenience, and lowered expenses. An area with potential for future enhancements lies in the options for delivering SCIG, such as using prefilled syringes or on-body injectors.

The perceived benefits of prefilled syringes for available formulations include their ability to provide accurate dosages, maintain sterility, and shorten the treatment duration. They also provide patients with increased choices, enhanced convenience, and ease of use. Ig20Pro has already been approved for prefilled syringe use by the FDA in the first quartile of 2023 and is expected to be available on the market in a few months (19). The growing availability of prefilled syringes can enhance both the quality of life and cost-effectiveness of treatment, especially when tailoring treatment regimens for specific patient groups, such as the elderly and children, particularly those with disabilities due to IEI. Kafal et al. (20) have proposed that medication errors and drug wastage will be prevented if SCIG is applied with prefilled syringes. These are important issues for patients and healthcare providers since immunoglobulin supplies are limited and production is costly.

A recently developed Investigational Wearable Infusor device has the capability to administer subcutaneous IgG replacement therapy, specifically IgPro20, to patients suffering from PID. The trial demonstrates that this device can effectively provide IgG replacement therapy, resulting in comparable IgG levels in patients compared to a standard device (21). This wearable drug delivery system streamlines the process of medication administration. It can alleviate some of the difficulties associated with self-injection, such as the complexity of infusion preparation, needle anxiety, and pain concerns. Substantial advancements in artificial intelligence and technological devices will improve the infusion experience of IEI patients with high-concentration SCIG.

Other than the subcutaneous route, the feasibility of topical administration of nebulized immunoglobulin has been evaluated in animal studies, and results are promising with jet and mesh nebulizers (22). A recent small pilot study on nebulized IVIG (10%) was conducted on three pediatric male patients suffering from frequent otitis media due to antibody deficiency. The patients were reported to be tolerating inhaled IVIG well, with no adverse events and a decreased number of upper respiratory tract infections during 2 years of follow-up period (23).

Besides SCIG, IVIG at home is a commonly used option for IgRT in the States. Rastegar et al. (24) have recently proposed that there may be value in increasing referrals for IVIG home infusion due to decreased healthcare utilization, cost savings, and improved clinical outcomes of their cohort. Such studies may divert health policymakers to maximize the benefits of IVIG home infusion while minimizing potential risks and promoting extensive usage and access.

Conclusion

A precise and personalized approach to IgRT is essential for improving outcomes in patients with IEI. The quest for new IgRT formulations and improved ancillary tools for SCIG aims to lower the occurrence of infections and complications related to them. Furthermore, these approaches enhance patient adherence and the effectiveness of SCIG by reducing the disease or treatment burden experienced by IEI patients. It is important to note that the key to a favorable prognosis in such patient groups lies in early diagnosis and effective treatment of IEIs. Despite significant efforts, many patients are not diagnosed until irreversible damage from multiple infections has led to chronic impairments and disabilities, which could have been alleviated with early and efficient IgRT.

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References

1. Duff C, Ballow M. Nuts and bolts of subcutaneous therapy. Immunol Allergy Clin North Am. 2020;40:527-37.
2. Wasserman RL. Immunoglobulin replacement for primary immunodeficiency: Indications for initiating and continuing treatment. Allergy Asthma Proc. 2021;42:489-94.
3. Karakoç Aydıner E, Kıykım A, Barış S, Özen A, Barlan I. Use of subcutaneous immunoglobulin in primary immune deficiencies. Turk Pediatri Ars. 2016;51:8-14.

4. https://ipopi.org/ipopi-pid-patient-needs-outlooks-survey
5. Epland K, Suez D, Paris K. A clinician's guide for administration of high-concentration and facilitated subcutaneous immunoglobulin replacement therapy in patients with primary immunodeficiency diseases. Allergy Asthma Clin Immunol. 2022;18:87.
6. CUTAQUIG, Immune globulin subcutaneous (Human) – hipp, 16.5% solution [prescribing information]. 2020; Vienna, Austria: Octapharma.
7. GAMMANORM, Immune globulin subcutaneous (Human) – hipp, 16.5% solution [prescribing information]. 2020; Vienna, Austria: Octapharma.
8. HIZENTRA, Immune globulin subcutaneous (Human), 20% Liquid [prescribing information]. 2020; Bern, Switzerland: CSL Behring AG.
9. CUVITRU, Immune globulin subcutaneous (Human), 20% solution [prescribing information]. 2019; Lexington, MA: Baxalta US Inc.
10. XEMBIFY, Immune globulin subcutaneous (Human) – klhw, 20% solution [prescribing information]. 2019; Research Triangle Park, NC, USA: Grifols Therapeutics LLC.
11. Latysheva E, Rodina Y, Sizyakina L, Totolian A, Tuzankina I. Efficacy and safety of octanorm (cutaquig®) in adults with primary immunodeficiencies with predominant antibody deficiency: a prospective, open-label study. Immunotherapy. 2020;12:299-309.
12. Kobayashi RH, Mandujano JF, Rehman SM, Kobayashi AL, Geng B, Atkinson TP, et al. Treatment of children with primary immunodeficiencies with a subcutaneous immunoglobulin 16.5% (cutaquig® [octanorm]). Immunotherapy. 2021;13:813-24.
13. Gupta S, Kobayashi RH, Litzman J, Cherwin L, Hoeller S, Kreuwel H. Subcutaneous immunoglobulin 16.5% for the treatment of pediatric patients with primary antibody immunodeficiency. Expert Rev Clin Immunol. 2023;19:7-17.
14. Kobayashi RH, Litzman J, Rizvi S, Kreuwel H, Hoeller S, Gupta S. Overview of subcutaneous immunoglobulin 16.5% in primary and secondary immunodeficiency diseases. Immunotherapy. 2022;14:259-70.
15. Jolles S, Rojavin MA, Lawo JP, Nelson R Jr, Wasserman RL, Borte M, et al. Long-term efficacy and safety of Hizentra® in patients with primary immunodeficiency in Japan, Europe, and the United States: a review of 7 phase 3 trials. J Clin Immunol. 2018;38:864-75.
16. Suez D, Kriván G, Jolles S, Stein M, Gupta S, Paris K, et al. Safety and tolerability of subcutaneous immunoglobulin 20% in primary immunodeficiency diseases from two continents. Immunotherapy. 2019;11:1057-65.
17. Santamaria M, Neth O, Douglass JA, Krivan G, Kobbe R, Bernatowska E, et al. A multi center, open label, single arm trial to evaluate the efficacy, pharmacokinetics, and safety and tolerability of IGSC 20% in subjects with primary immunodeficiency. J Clin Immunol. 2022;42:500-11.
18. Rosenbach K, Park M, Sanchirico M, Nwose O, Paris K. Real-world evidence of tolerability of 20% subcutaneous immunoglobulin treatment. J Clin Immunol. 2023;43:912-20.
19. https://www.fda.gov/media/78466
20. Kafal AR, Vinh DC, Langelier MJ. Prefilled syringes for immunoglobulin G (IgG) replacement therapy: clinical experience from other disease settings. Expert Opin Drug Deliv. 2018;15:1199-209.
21. Wasserman RL, Cunningham-Rundles C, Anderson J, Lugar P, Palumbo M, Patel NC, et al. Systemic IgG exposure and safety in patients with primary immunodeficiency: a randomized crossover study comparing a novel investigational wearable infusor versus the Crono pump. Immunotherapy. 2022;14:1315-28.
22. Chang KH, Park BJ, Nam KC. Aerosolization performance of immunoglobulin G by Jet and Mesh Nebulizers. AAPS PharmSciTech. 2023;24;24:125.
23. Brodszki N. Add-on or alone? Inhaled nebulized immunoglobulin reduces upper airway infections: 24 months of real-life experience. Immunotherapy. 2020;12:389-394.
24. Rastegar J, Brown VT, John I, Dixon SW, Rodman E, Ellis JJ, et al. Home versus outpatient hospital intravenous immunoglobulin infusion and health care resource utilization. J Am Pharm Assoc (2003). 2023;63:1566-73.e1.