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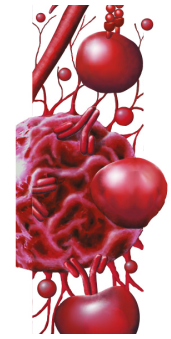

Overview of subcutaneous immunoglobulin 16.5% in primary and secondary immunodeficiency diseases

Roger H Kobayashi*[,1], Jiří Litzman[2], Syed Rizvi[3], Huub Kreuwel[3], Sonja Hoeller[4] & Sudhir Gupta[5]

[1]University of California, School of Medicine, Los Angeles, CA, USA

[2]Department of Clinical Immunology & Allergology, St. Anne's University in Brno, Faculty of Medicine, Masaryk University, Brno, Czechia

[3]Octapharma AG, Paramus, NJ, USA

[4]Octapharma Pharm. ProduduktionsgesmbH, Vienna, Austria

[5]Division of Basic & Clinical Immunology, University of California, Irvine, CA, USA

*Author for correspondence: rhk.immunology@gmail.com

Most primary immunodeficiency diseases, and select secondary immunodeficiency diseases, are treated with immunoglobulin (IG) therapy, administered intravenously or subcutaneously (SCIG). The first instance of IG replacement for primary immunodeficiency disease was a 16.5% formulation administered subcutaneously in 1952. While most SCIG products are now a 10% or 20% concentration, this review will focus on SCIG 16.5% products with a historical overview of development, including the early pioneers who initiated and refined IG replacement therapy, as well as key characteristics, manufacturing and clinical studies. In determining an appropriate IG regimen, one must consider specific patient needs, characteristics and preferences. There are advantages to SCIG, such as stable serum immunoglobulin G levels, high tolerability and the flexibility of self-administered home treatment.

Lay abstract: Primary immunodeficiency diseases, and select secondary immunodeficiency diseases, weaken the immune system, allowing infections and other health problems to occur more easily. Some patients require treatments to boost their immune system, such as immunoglobulin (IG) therapy, which can be either injected via a needle into a vein (intravenously) or inserted underneath the skin (subcutaneously; SCIG). The first instance of IG treatment for primary immunodeficiency disease was a 16.5% SCIG product given in 1952. While most SCIG products are now a 10% or 20% concentration, this review will focus on SCIG 16.5% products with a historical overview of development, including the early pioneers who initiated and refined IG therapy, as well as key characteristics, manufacturing and clinical studies. In determining an appropriate IG regimen, one must consider specific patient needs, characteristics and preferences. There are advantages to SCIG, such as stable serum immunoglobulin G levels, high tolerability and the flexibility of self-administered home treatment.

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The origin of passive immunity had its genesis in the 1890s anchored by the seminal work of Paul Ehrlich, Emil von Behring, Shibasaburo Kitasato and Francesco Cenci with diphtheria and measles. By the 1920s and 1930s, the use of animal serum and human convalescent sera became a key weapon in combating the devastating diseases of the day such as diphtheria, measles, pneumonia, tetanus, influenza and a host of other ailments. In the 1940s, the development of antibiotics and vaccines pushed passive immunity into the background with a few exceptions such as measles and hepatitis. However, doctors recognized that even with antibiotics and vaccinations, there were some individuals who had repeated infections and many who died.

Future Medicine

A fortuitous landmark case described by Colonel Ogden Bruton in 1952 of a youngster with no antibodies and frequent, severe infections led to the first use of immunoglobulin (IG) for the treatment of primary immunodeficiency disease (PIDD). The IG was administered subcutaneously by Bruton and, subsequently, intramuscularly by others. Just as the need to combat severe infections led to the development of animal and human convalescent sera and then to vaccinations and antibiotics, the pain, inadequate dosing and poor compliance of intramuscular (IM) administration of IG (IMIG) led to the manufacturing of safe, effective subcutaneous IG (SCIG) and intravenous IG (IVIG) products.

This discussion will provide a brief but useful review of the history and development of PIDD. The main focus will then shift to 16.5% SCIG, including its development, characteristics, preclinical studies and finally clinical studies in both adults and children. While most SCIG products have unit percentages of either 10% or 20%, two products, Gammanorm (Octapharma AG) and Cutaquig (Octapharma AG), have utilized the original concentration of the Cohn fraction II of 16.5%.

Primary & secondary immunodeficiency diseases: overview & standard of care

In the 1920s, there were reports describing characteristic clinical syndromes that were later recognized as PIDDs. In 1922, Schultz described four patients with gangrenous throat lesions with severe neutropenia [1]. The patients were all middle-aged women who subsequently died and at autopsy were found to have diminished myeloid cells in the bone marrow. The term Schultz used for the condition was "agranulocytosis" [1]. Ataxia telangiectasia and Wiskott-Aldrich syndrome were initially reported in 1926 [2] and 1936 [3], respectively. Although the Swiss pathologists Glanzmann and Riniker defined the syndrome as "essential lymphocytophtise," they did not make the connection with immunodeficiency [4]. Two Swiss groups from Bern and Zurich had patients with similar presentations and made this essential connection [5,6]. The condition that was initially coined "Swiss-type gammaglobulinemia" was renamed severe combined immunodeficiency (SCID) by the WHO in 1970. The landmark in the history of PIDD was the recognition and treatment of agammaglobulinemia by Colonel Ogden Bruton in 1952 [7].

As of 2021, more than 400 PIDDs, resulting from 430 identified gene defects, have been described [8,9]. The hallmark manifestation of PIDD is an increased susceptibility to recurrent or severe infections due to an inability to produce an adequate immune response to pathogens [10]. Although PIDDs have traditionally been considered rare diseases affecting 1 in 50,000 to 100,000 births, new genetic variant mutations, also categorized as inborn errors of immunity (IEIs), have been discovered that may have a prevalence of 1/1,000 to 1/5,000 births [11,12]. However, no single assay at present will identify all forms of PIDD, which presents a challenge for newborn screening [13]. Globally, over 6 million people are affected by PIDD, and approximately 70–90% remain undiagnosed [14,15]. Further, although classically thought of as a disease of infants and newborns, PIDD, particularly antibody abnormalities, may be much more common in adults.

The most frequently diagnosed, clinically severe PIDD is common variable immune deficiency (CVID), which is characterized by a heterogeneous group of hypogammaglobulinemic syndromes and accounted for 91% of PIDD patients in one United States (US) survey [16]. Many PIDDs present as infections (often of the sinuses, ears and lungs) that are temporarily or partially amenable to antibiotics and, therefore, may go undetected in the primary-care setting [17,18]. As a result of antibiotics and other "modern" interventions, in far too many instances these infections are missed opportunities for early diagnosis. The average time to diagnosis following the onset of symptoms for all diagnoses in a US survey was 15 years (median of 8 years) with almost 3 out of 10 (28%) patients reporting a diagnostic delay of more than 20 years [16]. Delays in proper diagnosis have a major impact on patient health, as almost half (49%) of PIDD patients reported at least one permanent functional impairment as a result of the delay in diagnosis, including impairments to lungs, digestive system function, hearing and mobility [16,18]. The importance of the prompt recognition and management of PIDD has been further characterized by the rate of hospitalizations pre- and post-diagnosis. In one study, 70% of patients reported being hospitalized prior to diagnosis; however, following proper diagnosis, less than half were hospitalized [17].

The standard of care for PIDD is IG replacement therapy, administered either intravenously or subcutaneously. Multiple randomized, controlled clinical trials have demonstrated that IVIG and SCIG reduce infection frequency and severity [10,19–22]. Despite known benefits, some patients discontinue therapy due to side effects or concerns about product safety, inconvenience, cost and/or inability to obtain insurance coverage for treatment. To minimize risk from serious infections and optimize outcomes, it's very important to ensure continuous, regular therapy with consistent dosing. To provide optimal care, one must take into consideration specific patient needs, characteristics and preferences when selecting an IG replacement regimen [17,20].

Table 1. Timeline of the development of current treatments for primary and secondary immunodeficiencies.

Year	Event	Ref.
1890	Immunization of rats with tetanus/diphtheria toxin by Kitasato and von Behring, leading to the formation of blood serum that protected rabbits infected with tetanus/diphtheria from infection	[32,33]
1901	Von Behring awarded the first Nobel Prize in Physiology and Medicine for "his work on serum therapy, especially its application against diphtheria"	[31]
1907–1940	Convalescent sera from animals and humans introduced for treatment of diseases caused by bacteria, viruses, toxins and allergens	[31,38]
1940	Development of cold ethanol fractionation of plasma by Edwin Cohn and team	[39,40]
1952	Recognition of agammaglobulinemia by Colonel Ogden Bruton and treatment with SCIG 16.5%	[7]
1953	Preferred use of intramuscular immunoglobulin 16.5% for the treatment of primary immunodeficiency by Janeway and colleagues	[41,42]
1960	First intravenous immunoglobulin prepared by Behringwerke in Germany by proteolytic cleavage by pepsin	[31,33]
1995	Approval of Gammanorm SCIG 16.5% in Europe	[43]
2006	Approval of Vivaglobin SCIG 16% in the United States	[44]
2018	Approval of Cutaquig SCIG 16.5% in the United States and Canada	[45]

SCIG: Subcutaneous immunoglobulin.

Unlike PIDDs, secondary immunodeficiency disorders (SIDs) result from nonhereditary factors such as infectious agents, medications, metabolic diseases and environmental conditions [23,24]. It is estimated that SIDs are approximately 30-times more common than PIDDs, and the prevalence is increasing for a variety of reasons [25]. The continued expansion of new therapies for autoimmune, inflammatory and malignant disease, many targeting B cells, may be associated with the rise in SIDs [25–27]. Therapies such as rituximab with long-term steroid treatment, often in combination with other treatments, may contribute to the increased development of SIDs [25–27]. In addition, chronic infectious diseases (especially viral infections) may be associated with the development of SIDs [28]. It is important to recognize the unmet needs in this growing patient population, including risk factors for SIDs, improved screening, monitoring and treatment strategies. The goal for the use of IVIG and SCIG for the treatment of SIDs is the same as that for PIDDs, the prevention of infection.

Historical development: subcutaneous & intravenous immunoglobulin replacement

The landmark recognition of PIDD was the discovery of agammaglobulinemia by Colonel Ogden Bruton in 1952 [7]. Bruton observed that a young male patient had been admitted to the hospital 19-times between the ages of 4 and 9 years for recurring infections. In nine instances, pneumococcal bacteremia was documented and promptly responded to antibiotic treatment. However, antibodies against pneumococci were not present. After several failed attempts to discern an explanation for this phenomenon using standard laboratory evaluations, Bruton heard that a new piece of laboratory electrophoresis equipment was available, based on the pioneering work by Tiselius and Kabat, that could separate serum proteins into different fractions [29]. He reasoned that, following so many infections, the patient should have a high level of gammaglobulin. However, the unexpected result was that no gammaglobulin was detectable, which had never been seen before [7,30,31]. Later on, Bruton recalled, "things began to click then: no gammaglobulins; can't build antibodies. . . . This seems so simple now that it seems to me hardly worth repeating, but I thought, well, if he doesn't have any gammaglobulins, maybe we could try treating him with gammaglobulin" [30]. Bruton's patient was given SCIG replacement at "20 cc. containing 3.2 g of gamma globulin" [7]. There was improvement in the clinical picture after the first dose of SCIG, and the electrophoresis repeated 4 days later exhibited a normal gammaglobulin gradient. The patient was then prescribed a monthly SCIG regimen and "suffered no attack of sepsis" [7].

Although Bruton's was a landmark discovery, it was actually a logical progression in a long period of developments beginning with the recognition of innate and adaptive immunity in the late 19th and early 20th centuries, leading to the current, stunning discovery of genetically determined immunodeficiency (Table 1) [30,31]. In 1890 Emil von Behring and Kitasato published their work showing that immunization of rats with tetanus toxin (and in another study with diphtheria toxin) led to the formation of antibodies, which, if transferred into rabbits infected with tetanus (or diphtheria), protected them from infection [32]. This antitoxin activity was specific, and tetanus antitoxin activity could not neutralize diphtheria toxin and *vice versa*. The single-authored paper by von Behring describing protection against diphtheria and its toxin by antisera was then published shortly thereafter [33]. Consequently, von

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Behring was awarded the first Nobel Prize in Physiology and Medicine for "his work on serum therapy, especially its application against diphtheria." Unfortunately, Kitasato was not given the Nobel Prize because, at that time, the Nobel Prize could not be shared. Therapy with antisera became a common practice at the beginning of the 20th century, and not only in diphtheria and tetanus; animal antisera were introduced in the treatment of staphylococcal, streptococcal and meningococcal diseases. Before the advent of widespread vaccination, the prevention of measles was also pioneered using animal sera, human convalescent plasma and globulin products obtained from human placenta [34–37].

The impetus to develop techniques for plasma fractionation on a large scale was largely due to the efforts of the US Navy during World War II in an attempt to control shock in severely wounded soldiers [31,38]. Due to the overwhelming need for albumin, the National Research Council charged Edwin Cohn and his team in Boston with isolating stable protein fractions with different biologic uses from human blood. Their efforts were successful [39,40]. Cohn and his coworkers developed a separation procedure of plasma dividing serum using alcohol at low concentrations in low temperature. The gammaglobulin from fraction II consisted of 165 mg/ml protein (or 16.5%) and was a "slightly opalescent, colorless solution when prepared from ordinary plasma and a brownish color when prepared from placental blood" [41]. Thus, the first resulting separated fraction II serums had a 16.5% concentration. Such separated serum fractions were initially used to prevent and treat infectious diseases (e.g., measles, hepatitis, mumps, poliomyelitis and pertussis). Cohn's team also reported that all antibodies were contained in the gammaglobulin fraction. These studies most likely had an influence on Bruton's first documented use of gammaglobulin to treat a patient with agammaglobulinemia in 1952 [7].

Although the first patient was treated by the subcutaneous route [7], IMIG was preferred by Janeway and colleagues in Boston and soon became the standard of care in the US [42,46,47]. The adoption of IMIG in the United Kingdom (UK) in 1971 also provided the impetus to establish IMIG as the early administration method worldwide [48]. Local pain at the injection site, adverse events (AEs) and relatively low dosing volumes were major limitations of IMIG and frequently led to poor patient compliance [47].

In the late 1970s, faced with patients who were noncompliant with prescribed schedules of IMIG injections, Berger and colleagues introduced the use of a small, battery-powered pump to slowly administer IMIG 16.5% in PIDD patients by a subcutaneous route [49,50]. Administration of IMIG 16.5% at rates of 1–2 ml/hour allowed diffusion into the subcutaneous tissues and adsorption into the bloodstream with low rates of pain/swelling and no systemic reactions [49]. Slow subcutaneous infusions were also found to promote tolerance of IG in patients who had anaphylactic reactions to IMIG injections [47,51].

It was understood that intravenous administration was a possibility to increase the administered dose; however, attempts to give IMIG intravenously resulted in severe adverse reactions [52]. Notably, following a small test dose of 16.5% IMIG given intravenously, Janeway developed severe gastrointestinal symptoms, chills, fever and shock, requiring hospitalization for 2 days [31]. These reactions were mainly caused by the anti-complement activity of polymers included in IG derivates. The recovery rate from AEs was reportedly less than 50% [53,54]. In addition, the transmission of hepatitis B and C was reported [55–57]. However, by the late 1970s and early 1980s, manufacturing processes mitigated/attenuated much of the severe side effects, and IVIG became the standard of therapy for immunoglobulin G (IgG) replacement, which is expanded upon below. Reactions, venous access, inconvenience and costs, together with the European experience, provided the impetus toward subcutaneous infusions.

Even after the introduction of safe IVIG preparations in the 1980s, in Sweden the widespread availability of IMIG 16.5% for subcutaneous use, which was less expensive, better tolerated and preferable to most patients, resulted in the persistent use of IMIG preparations by the subcutaneous route in that country [58]. In addition, hepatitis contamination of an early IVIG product further reinforced the practice, as did regimens for rapid infusion, the use of multiple sites and the availability of home-based treatment [57–60]. The IMIG utilized in Sweden was a mercury-free, human 16.5% preparation (Ganunaglobulin Kabi, KabiVitrum) [58].

Despite these advantages, the need to increase the administered dose ultimately led to various methods of preparing IVIG that were tolerable and included specific pathogen reduction steps. As discussed above, IMIG preparations were not suitable for intravenous administration as a result of serious systemic AEs [31,52–54]. The majority of these AEs were most likely due to complement activation by aggregates or the presence of kallikrein and the activation of kinin pathways [47,52]. The subsequent development of IVIG preparations in which aggregation of the IgG was minimized by low pH and/or the inclusion of stabilizers obviated many of these issues, and it was later demonstrated that monomeric IG preparations can inhibit complement activation or deposition [61,62].

The first IVIG was prepared by Behringwerke in Germany in the early 1960s by proteolytic cleavage by pepsin [38]. However, this product did not contain intact IgG molecules, only Fab fragments, with absent Fc fragment activity. Also, the half-life was short (approximately 1 day), so it was not suitable for replacement treatment. During the late 1960s and 1970s, new IVIG products were prepared by various approaches (proteolytic enzymes, chemical modification—beta-propion lacton, Ph4+ pepsin, reduction and alkylation) that produced unmodified IgG monomer molecules for widespread use [38]. The intravenous route of infusion allowed the administration of higher doses of IG (~400 mg/kg every 4 weeks was recommended for replacement in the 1970s and 1980s; this regimen has continued to the present day). Direct comparisons demonstrated the superiority of IVIG over IMIG [63,64]. Today, IVIG still plays a significant role in the replacement treatment of patients with PIDD, SID and various autoimmune and inflammatory syndromes in which high doses are required (as much as five-times the replacement dose for PIDD) [10].

Current overview of 16.5% subcutaneous immunoglobulin

A new era of IG replacement treatment was opened following the introduction of rapid infusion of SCIG in Sweden and the UK in the 1990s [58–60,65,66] and the US in 2005 [67]. In 2000, an international crossover study demonstrated the non-inferiority of SCIG as compared with IVIG [68].

There are distinct clinical advantages to SCIG, such as stable serum IgG levels [69,70], high tolerability with fewer systemic side effects [71,72] and the flexibility of self-administered home treatment [58,60,73]. Self-administration at home can improve compliance and quality of life and may reduce the frequency of hospitalizations [58,60,73]. Several studies have also shown an economic advantage and cost reductions with the use of SCIG [65,74,75]. The utilization of SCIG has become even more convenient and popular with the optimization of administration devices such as portable pumps. The first SCIG product approved in the US was Vivaglobin 16% (CSL Behring) in 2006, a pasteurized, polyvalent human normal immunoglobulin for subcutaneous infusion indicated for the treatment of patients with PIDD [44]. In January 2011, Vivaglobin was discontinued in the US due to the delay in supply and the presence of side effects [76]. Two additional 16% SCIG products Subcuvia (Baxalta, Inc.) and Subgam (Bio Products Laboratory) were also approved for use in Europe but were not approved in the US [77,78]. Neither of these SCIG 16% products are currently available.

A number of 10% and 20% SCIG preparations are now available in the US and Europe [79]; however, the first commercially available 16.5% IG directly prepared for subcutaneous treatment (as opposed to intramuscular derivates administered subcutaneously) was Gammanorm (Octapharma AG) licensed in Europe in 1995 [43]. Gammanorm is currently indicated in Europe for replacement therapy in adults and children for PIDD and SID.

More recently, another SCIG 16.5% product, Cutaquig (Octapharma AG), was approved for use in the US, Canada, Europe and Australia [45]. Cutaquig is currently indicated for replacement therapy in PIDD in children who are 2 years and older and adults in the US and Europe. In addition to these indications, it is also indicated for SID in adults in Canada, Europe and Australia. An overview of the manufacturing process for Cutaquig and Gammanorm is provided below.

Manufacturing of subcutaneous immunoglobulin 16.5%

As described above, Cutaquig 16.5% is a recently approved SCIG product manufactured by a process similar to that of the IVIG product Octagam (Octapharma AG) [80]. Cutaquig is a ready-to-use, highly purified and concentrated polyvalent SCIG manufactured from a pool of human fresh-frozen plasma, where single donations are screened using licensed/approved third-generation immuno-assays and nucleic acid testing for pathogens. Pathogen-safety precautions include a rigorous selection process of plasma donors, screening of donations and plasma pool and quality control measurements of the final product. In order to optimize a broad range of antibodies directed against common bacterial and viral infections, it's vital to have a large donor pool. Cutaquig is purified using a combination of cold ethanol fractionation, ultrafiltration and chromatography and is stabilized with maltose [80].

Cutaquig was developed at a concentration of 16.5% to optimize administration, including the delivery of appropriate volumes at a viscosity suitable for safe and tolerable use in all patients. It is important to note that 10 g of SCIG 16.5% is equal to 60 ml, while 10 g of SCIG 20% is equal to 50 ml. Therefore, there is only a 10 ml difference between the weekly infusion volume of an SCIG 16.5% and an SCIG 20%.

Injectability (i.e., force required for injection) is a major performance parameter and affects the ease of administration by patients, family members and/or healthcare professionals. As patients are often responsible for self-administration, the ease of preparation and infusion is important. Glide force results showed that for Cutaquig

10.2217/imt-2021-0313

Table 2. Subcutaneous immunoglobulin injectability study results.

Sample	Viscosity (mPa*s) 20°C	Mean glide force (N)		
		Setting 1 (25G 2 ml/min)	Setting 2 (25G 1.5 ml/min)	Setting 3 (23G 2 ml/min)
Cutaquig	11.3	11.1 ± 0.6	10.0 ± 1.4	6.6 ± 0.8
20% SCIG 1	15.2	13.4 ± 0.6	11.8 ± 0.4	7.7 ± 0.6
20% SCIG 2	16.1	14.9 ± 1.6	13.0 ± 0.0	8.2 ± 0.6

Data courtesy of Octapharma AG.
G: Gauge; mPA*s: Millipascal second; N: Number; SCIG: Subcutaneous immunoglobulin.

infusion, a force of up to 11 newtons (N) is needed using either 23G or 25G needles at given infusion rates (Table 2) [80]. For comparison, marketed 20% SCIG products were investigated in the same settings. The flow of Newtonian liquids through a needle is characterized by the Poiseuille law [81]; the final force is dependent on needle diameter, injection rate and SCIG product viscosity. In all three investigational settings, the use of Cutaquig was associated with less injection force than the 20% SCIG products, with differences up to 21% (SCIG 1) and 34% (SCIG 2) [80]. With tissue back-pressure involved, which is known to be linearly dependent on product viscosity [82], the difference would most likely be even greater. These data demonstrate that Cutaquig is easier to administer than SCIG products with higher concentrations. Such a difference can be particularly relevant for elderly patients or those with decreased grip strength and/or dexterity as well as tissue fragility/resistance [71,83].

The excipient maltose is used as the stabilizer for Cutaquig at a target concentration of 7.4% to achieve osmolality and assure IgG stability. The pH value is an important characteristic, as it influences the tolerability, performance and stability of the product—specifically, the content of IgG monomers/dimers/polymers released during shelf-life. The pH value for Cutaquig is between 5.0 and 5.5, and it has a physiological osmolality of 310–380 mOsmol/kg. Cutaquig also has a low level of accompanying plasma protein like immunoglobulin A (IgA) and a low isoagglutinin titer, similar to Octagam [45,80].

As demonstrated by the assessment of key biochemical safety-related parameters, the shelf-life of Cutaquig is 36 months when stored at 36°F to 46°F (+2°C to +8°C) and protected from light [45,80].

The manufacturing process for Gammanorm and key product characteristics are similar to those of Cutaquig [43,79]. The main differentiation from Cutaquig is the use of a glycine stabilizer (vs maltose for Cutaquig). In addition, Gammanorm has a shelf-life of 3 years when stored at 36°F to 46°F (+2°C to +8°C) [79].

Clinical experience: efficacy & safety of subcutaneous immunoglobulin 16.5%

A previous review published in *Immunotherapy* by Gardulf provides a comprehensive review of the clinical experience of Gammanorm [76]. In short, clinical experience with Gammanorm has demonstrated that it is effective and well tolerated in adults (including pregnant women) and children with a range of primary immunodeficiencies, as well as in adults with secondary immunodeficiencies. In addition, experimental use in adults with certain immune-mediated conditions, including demyelinating diseases such as Lewis–Sumner syndrome, polymyositis and postpolio syndrome, chronic idiopathic demyelinating polyneuropathy and multifocal motor neuropathy, indicates that Gammanorm may be beneficial; however, it is not currently licensed for these indications. Local tissue reactions may be experienced with Gammanorm during the first 8–10 weeks but are usually mild and transitory [76].

A recently completed prospective, open-label, single-arm, Phase 3 study of Cutaquig involving adult and pediatric patients was conducted at 18 centers in Europe and North America [71,72]. A total of 75 patients were enrolled in the study, including 38 children with a median age, per group, of 4.2 years (ages 2–5 years), 7.9 years (ages 6–11 years) and 14.1 years (ages 12–16 years), and 37 adults with a median age of 47.5 years (range: 17–75 years). Six patients (3 adolescents and 3 adults) withdrew voluntarily from the study for personal reasons; no withdrawal was due to AEs. A total of 75 patients (37 adults and 38 children) completed the study. The majority of patients (86.9%) had a diagnosis of CVID [71,72].

All patients in the study were on a stable regimen of IVIG prior to transitioning to SCIG; the majority of patients received IVIG every 4 weeks (47 patients; 77.0%). Individual doses for SCIG were based on the previous IVIG dose that was calibrated using a dose conversion factor (DCF) of 1.3, which was standard at the time of the protocol creation to compensate for differences in bioavailability between the two infusion methods [84].

Table 3. Clinical efficacy results with Cutaquig 16.5%.

	Adults	Pediatrics	Total
Number of subjects (efficacy period)	37	38	75
Total number of subject-years	35.5	35.0	70.5
Infections			
Annual rate [number of SBIs† per subject-year (upper one-sided 99% CI)]	0 (0.13)‡	0 (0.13)‡	0 (0.06)‡
Annual rate [number of other infections per subject-year (two-sided 95% CI)]	3.4 (2.2, 5.4)	3.1 (2.0, 4.8)	3.3 (2.4, 4.5)
Systemic antibiotic use			
Number of subjects (%)	25 (67.6%)	24 (63.2%)	49 (65.3%)
Annual rate [days on treatment per subject-year (two-sided 95% CI)]	32.1 (17.2, 60.1)	62.6 (31.0, 126.4)	47.2 (28.4, 78.6)
Days out of work/school/kindergarten/day care due to infections			
Number of days	72	180	252
Annual rate [days per subject-year (two-sided 95% CI)]	2.0 (0.7, 5.7)	5.2 (2.8, 9.4)	3.6 (2.1, 6.0)
Hospitalization due to infections	0	4	4
Number of days	0	29	29
Annual rate [days per subject-year (two-sided 95% CI)]	0 (0.1)‡	0.8 (0.3, 2.6)	0.4 (0.1, 1.3)

†Defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis and visceral abscess.
‡Calculation for the upper limit of two-sided 95% or one-sided 99% CI was based on standard Poisson model for zero counts.
SBIs: Serious bacterial infections.
Adapted with permission from Octapharma [45].

The study design had two phases with weekly SCIG infusions; Phase 1 was a 12-week wash-in/wash-out period and Phase 2 was the 52-week primary observation period. To assess the bioavailability of total IgG after IVIG and SCIG administration, a pharmacokinetic (PK) substudy was also conducted.

Following administration of Cutaquig over the study period, patients maintained high trough levels of plasma IgG (a median of 11.5 g/l before the infusion at week 28). As a result, Cutaquig was highly effective at preventing infections, with no serious bacterial infections (SBIs) observed and a rate of 3.3 per patient/year for other infections. Previously published infection rates for a 20% SCIG product resulted in an annual infection rate per patient of 5.18 (95% CI: 4.305, 6.171 [85]); however, efficacy results may vary due to differences in patient populations and study designs. Importantly, infection rates observed in Cutaquig were commensurate with those reported for other SCIGs. Further confirmation of the efficacy of Cutaquig was demonstrated by low episodes of fever, hospitalizations and absences from school/work (Table 3).

A key advantage of SCIG over IVIG is that subcutaneous delivery of IG is associated with fewer systemic AEs; however, local reactions at subcutaneous injection sites are common [71,72,84]. These reactions are rarely severe and are tolerated by most patients. In a review by Orange *et al.*, the reporting rate varied from 0.028 to 0.697 per infusion, demonstrating that the majority of patients tolerate SCIG well [86].

In the Phase 3 Cutaquig study, the rate of infusion site reactions per infusion was 0.23 [71,72]. Reactions were almost exclusively mild or moderate and their incidence decreased over time. The rate of systemic AEs was low (proportion of related AEs per infusion was 0.27). The low incidence of related AEs and infusion site reactions in this study demonstrates the overall safety and tolerability of Cutaquig. Results from the PK study suggested that patients could be dosed weekly or every other week [71,72].

In a separate study by Latysheva and colleagues, similar efficacy and safety of Cutaquig were observed in 25 PIDD patients [87]. No SBIs were observed. The rate of overall infections was 2.30 (95% CI: 1.25–4.20) per person-year in the treatment period, which further underscores the safety and tolerability of Cutaquig.

Innovations & future directions

The self- or caregiver-assisted administration options of SCIG improve patient adherence, reduce treatment burden, increase convenience and decrease cost. Therefore, it is likely that the popularity and use of SCIG will continue to expand. One key area of potential future improvements may be in SCIG-delivery options such as prefilled syringes or on-body injectors [88]. The feasibility of topical administration of a nebulized liquid formulation of IG has been demonstrated in animal studies [89]. A recent small pilot study with three male pediatric patients demonstrated positive clinical results, and reduced upper respiratory infections, with inhaled, nebulized IG [90]. Because SCIG requires self-administration, studies to investigate ease of administration and infusion duration are essential, particularly to serve the needs of the elderly, as well as those with physical disabilities and young children.

Substantial technological advancements have been made in the identification of PIDDs, also known as IEIs. As a result of advances in molecular medicine, improved identification and phenotyping of patients, as well as

10.2217/imt-2021-0313

identification of the genes that are fundamentally required for immunity, will continue to increase [11,12]. These advances will further reveal critical roles for specific genes involved in immune responses, as well as new targets for SCIG, IVIG and other immunotherapies.

The successful work that has been conducted by both professional and patient organizations to increase awareness of PIDD, SID and other immune-mediated conditions that can benefit from IG replacement has been, and continues to be, substantial. However, ongoing efforts to identify patients with immune-mediated conditions must continue and will benefit from progressive improvements in communication technologies. The key to a positive prognosis in this patient population is early diagnosis and treatment. Despite monumental efforts, many patients are still not diagnosed until well after irreversible damage from multiple infections has resulted in chronic impairments and disabilities that could have been avoided with early IG therapy.

Conclusion

In reviewing the historical background for the use of SCIG 16.5% for PIDD, SID and other immune-mediated conditions, one can appreciate that it has been propelled by pioneers with scientific curiosity, ambition and a passion to improve the lives of patients. The science of immunology is an inspiring legacy from a small group of investigators with an overwhelming desire to conquer disease and provide therapeutic options in spite of immense challenges.

The approval of Cutaquig 16.5% for adult and pediatric patients represents an important advance and extends the choice of treatments available for patients with PIDD, as well as with SID. There are distinct clinical advantages to SCIG, including high tolerability, stable serum IgG levels and the flexibility to self-administer treatment at home. While it is difficult to predict what the future may hold, the urgent need to identify patients with immune-mediated conditions and innovate therapeutic options is ever present.

Executive summary

Primary & secondary immunodeficiency diseases

- In the 1920s, there were reports describing characteristic clinical syndromes that were later recognized as primary immunodeficiency diseases (PIDDs).
- As of 2021, more than 400 PIDDs, resulting from 430 identified gene defects, have been described.
- It is estimated that secondary immunodeficiency diseases are approximately 30-times more common that PIDDs, and the prevalence is increasing for a variety of reasons.

Historical development: subcutaneous immunoglobulin 16.5%

- The landmark in the history of PIDD was the recognition and treatment of agammaglobulinemia by Colonel Ogden Bruton in 1952 with a subcutaneous infusion of a 16.5% immunoglobulin (IG).
- Although the first patient was treated by the subcutaneous route, intramuscular administration of IG became the standard of care in the United States in the 1960s and 1970s.
- In the late 1970s, faced with patients who were noncompliant with prescribed schedules of intramuscular IG injections, pumps were developed to administer intramuscular IG by a subcutaneous route.
- A new era of IG replacement treatment was opened following the introduction of rapid infusion of subcutaneous IG (SCIG) in Sweden and the United Kingdom in the 1990s and the United States in 2005.

Current overview of subcutaneous immunoglobulin 16.5%

- There are distinct clinical advantages to SCIG, such as stable serum immunoglobulin G levels, high tolerability with fewer systemic side effects and the flexibility of self-administered home treatment.
- The first SCIG product approved in the United States was a 16% formulation, but it was discontinued in 2011.
- The first commercially available SCIG 16.5% was Gammanorm (Octapharma AG), licensed in Europe in 1995.
- More recently, another 16.5% product, Cutaquig (Octapharma AG), was approved for use in adults and children in the United States, Canada, Europe and Australia.

Clinical efficacy of subcutaneous immunoglobulin 16.5%

- A recently completed prospective, open-label, single-arm, Phase 3 study of Cutaquig involving adult and pediatric patients was conducted at 18 centers in Europe and North America.
- Following administration of Cutaquig over the study period, patients maintained high trough levels of plasma immunoglobulin G (a median of 11.5 g/l before the infusion at week 28).
- As a result, Cutaquig was highly effective at preventing infections, with no serious bacterial infections observed and a rate of 3.3 per patient/year for other infections.

Safety & tolerability of subcutaneous immunoglobulin 16.5%

- In the Phase 3 Cutaquig study, the rate of infusion site reactions per infusion was 0.23.
- Reactions were almost exclusively mild or moderate and their incidence decreased over time.

- The rate of systemic adverse events was low (0.23 related adverse event per patient). The low incidence of related adverse events and infusion site reactions in this study demonstrates the overall safety and tolerability of Cutaquig.

Innovations & future directions

- Substantial technological advancements have been made in the identification of PIDDs; as a result of advances in molecular medicine, improved identification and phenotyping of patients, as well as identification of the genes that are fundamentally required for immunity, will continue to increase.
- The self- or caregiver-assisted administration options of SCIG improve patient adherence, reduce treatment burden, increase convenience and decrease cost; it's likely the popularity and use of SCIG will continue to expand.

Conclusion

- The use of SCIG 16.5% for PIDD and secondary immunodeficiency disease has been propelled by pioneers with scientific curiosity, ambition, and an overwhelming desire to improve the lives of patients.
- The approval of Cutaquig 16.5% for adult and pediatric patients represents an important advance and extends the choice of treatments available for patients with PIDD and secondary immunodeficiency disease.

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