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Review Article

New insights in the use of immunoglobulins for the management of immune deficiency (PID) patients

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Abstract: Immunoglobulin replacement therapy (IRT) is standard treatment for patients with primary immunodeficiency (PID). Because most of the patients with PID will require long life-time immunoglobulin replacement therapy, the quality of the prescribed products is of utmost importance. The IRT is generally administered either intravenously (abbreviated IVIG), or subcutaneously (abbreviated SCIG). Both routes have been demonstrated to be effective. The preferred route may vary at different times during a given patient's life. Options are therefore not fixed and the choice of route for immunoglobulin therapy will depend on several factors, including patient characteristics, clinical indication, venous access, side effects, rural or remote location, treatment compliance and patient preference. Many years ago, immunoglobulin therapy was associated with side effects which may compromise patient's compliance and quality of life of the patients. Most of the side effects were related to impurities. Recently, major advances in the manufacturing process have been made and new processes, such as the Quality by design (QbD) approach were added into the manufacturing steps to ensure patients tolerability and safety. Due to the improved purity of the immunoglobulin products obtained by these processes, the incidence of side effects is lower, while the ways of administration of Ig therapy and the choice of the regimen has widened to suit patient's preference and needs.

Keywords: Intravenous immunoglobulin (IVIG), subcutaneous immunoglobulin (SCIG) primary immune deficiency (PID), safety, infection, efficacy, immunomodulation

Introduction

To date there are more than 200 different primary immunodeficiency diseases (PID) recognized by the World Health Organization (WHO) [1] and about 60% of all PID cases are associated with hypogammaglobulinemia due to impaired antibody production, leading to an increased susceptibility to infection. The disease affects both adults and children. Although rare, it is considered as a serious medical condition due to its propensity to expose patients to serious and fatal infections [2]. Chronic or recurrent upper and lower respiratory tract infections, sinusitis and otitis media are the most common type of infections. Severe bacterial infections (SBIs) such as sepsis, meningitis, septic arthritis and osteomyelitis can also occur.

In order to prevent infections, patients with PID need long term immunoglobulin G (IgG) replacement therapy (IRT). Individualization of IgG treatment provides optimal medical care and improve quality of life outcomes in patients by preserving organ function, and preventing infection-related death [3]. Immunoglobulin replacement therapy can be tailored to suit individual patient needs; it can be given either by intravenous (iv) or subcutaneous (sc) routes. Both routes have advantages and disadvantages that should be considered when selecting patient's treatment.

Because most of patients with PID will need long term IgG replacement therapy, efficacy and safety of prescribed IgG products have an outstanding importance. Adverse events associated with IgG administration could not only be

Table 1. Main differences between the different route of administrations of Immunoglobulins

	IVIg	SCIg	fSCIg	Manual push
Venous access	Yes	No	No	No
Max infusion rate	300 mL/hr	40 mL/hr	160-300 mL/hr	1-2 mL/min
Max dose/hr	30 g	6.4-8 g/site	16-30 g	NA
Infusion time/month	2.9 hr	5-6 hr	2.7 hr	3-6 hr
Training time for home	4-6 sessions over 3-6 months	4-6 sessions over 1-6 weeks	4-6 sessions over 2-6 months	4 sessions over 4 days
Peak/trough variation	Large	Minor (slightly more with fortnightly dosing)	Intermediate, dependent on treatment interval	Minor
Pump requirement	No	Yes	Yes, high volume	No

disturbing for the patients but they could also impact patients' compliance and adherence to therapy. Today a key focus of IRT is to advance development in the manufacturing processes of IgG to ensure their purity and tolerability, while preserving their effectiveness.

The main objectives of the present review are 1) to discuss the treatment options with IRT for the individualization of care in patients with PID, 2) to provide new insights in the manufacturing processes of IVIG, 3) to describe the latest advances in IVIG purification process according to a Quality by design process (Qbd) and how this process improves safety and tolerability of IVIG in patients.

IRT for the management of patients with PID

Immunoglobulin replacement therapy has been standard treatment for patients with PID since its first use by Burton in 1952 [4]. Since then, the choice of immunoglobulins has widened with different products and different routes of administration, making individualization of IRT possible nowadays.

PIDs are characterized by a clinically heterogeneous group of diseases, and not all PID patients will require the same treatment strategy with IgG substitution. The main goal of management of patients with PID is to establish the diagnosis and confirm the indication for a treatment by IRT. For those who require replacement therapy for PID, IRT has demonstrated a positive impact on patients' outcomes and on long term quality of life [5, 6]. This impact is particularly significant when the diagnosis of PID is made early and the IRT started before damages to organs occurs as reported in several surveys [7]; it has been shown that once the patients begin receiving IVIG on a regular basis their health status improves rapidly, their activity limitations drop significantly and their quality of life improves dramatically [7].

According to current guidelines [8, 9], IRT should be restricted to patients with confirmed hypogammaglobulinemia [total IgG or IgG subclasses reduced] with documented recurrent bacterial infections. The IRT is generally administered either intravenously (IVIG), or subcutaneously (SCIG). Both routes have been demonstrated to be effective [10]. IVIG infusions are usually given every three or four weeks. Although SCIG is typically administered weekly by infusion pump, administration by rapid push technique or more advanced technique such as facilitated (fSCIG) pre-infusion of recombinant human hyaluronidase (rHuPH20) may provide a greater convenience. Recent evidence suggests that the latter mode of administration is safe and effective [11, 12] while allowing administration every 2 to 4 weeks, similarly to IVIG, using only one or two sites.

Understanding the difference between these options helps clinicians in their decision of the best treatment option for a given patient (**Table 1**). While, the IV route results in an early peak of IgG immediately after the infusion, followed by a slow decline in antibody levels during the days that follow (half-life around 30 to 40 days), SCIG is absorbed more slowly into the bloodstream via the lymphatic system and requires more frequent administrations than IVIG; thus, a less variable steady-state IgG level is maintained, which eliminates the peaks and troughs that occur with monthly IVIG therapy.

There are advantages and disadvantages for each route (outlined in **Table 2**) and the preferred route may vary at different times during a given patient's life. Options are therefore, not

Table 2. IV versus SC route: advantages and disadvantages

IV route	Sub-cutaneous Route
Advantages	
Shorter infusion times	Home-based therapy: greater
Ability to give large volume by infusion and allows for intermittent dosing (every 3-4 weeks)	Independence/increase patient's autonomy IV access not possible
Convenient when need to load quickly	Preferred option if poor venous access, side effects with IVIG
Allow for High dose indication (eg immunomodulation neurology, Weight, Higher Trough needed-XLA, bronchiectasis)	Flexibility (children, Travel, logistics and work considerations)
Less needles	Low risk of systemic side effects
Less frequent infusions	
Less involvement of the patient (does not require patient training)	
Disadvantages	
Requires venous access and trained personnel	Relatively small volume of infusion, requires frequent dosing (at least once a week)
Systemic side effects (less frequent with new highly purified IVIG)	Difficult to maintain trough on maximal SCIg
	Ability to self-infuse requires patient reliability and compliance
	Local side effects (swelling, induration, local inflammation, itch), which are usually transient

Table 3. New generation IVIG manufacturing steps and role of each step according to the QbD approach

Process Platform	Step number	Role of the step	Purification process step
Plasma Fractionation Process	I	Cryo separation	Removal of vWF/FVIII complex
	II	Ethanol fractionation	Removal of immunoglobulins from albumin
Immunoglobulin new generation (IGNG) process	III	Caprilic acid fractionation	Clearance of non-Ig proteins (including procoagulant factors)
	IV	Activated carbon depth filtration	Adsorption of caprylic acid
	V	Ultrafiltration I	Final clearance of caprylic acid, Buffer exchange before chromatography
	VI	SD treatment	Inactivation of enveloped virus
	VII	Anion exchange chromatography	Clearance of IgA and IgM, Reduction of solvent and detergent
	VIII	Affinity chromatography	Depletion of anti-A and anti-B hemagglutinins
	IX	Filtration	Reduction of polymers and aggregates
	X	20 nm Nanofiltration	Retention of small viruses
	XI*	Ultrafiltration	Final clearance of solvent and detergent, clearance of chromatography buffer
	XII*	Formulation and filtration	Addition of excipients, 0.2 μm filtration of the Purified Bulk Starting Material

*Specific process steps for 5% or 10% IVIG.

fixed and the choice of route for IRT will depend on several factors, including patient characteristics, clinical indication, venous access, side effects, rural or remote location, treatment plan compliance, patient preference and life style [13].

While subcutaneous route may be attractive for some patients because of reduced side effects, flexibility and ease of administration, patient education and training at the initiation of SCIG therapy is required, and a follow up is necessary to ensure patient safety and effective treatment delivery. The IV route requires less frequent infusions, with the ability to give a large volume of IgG, which may be more appropriate in certain indications where higher doses are needed. Most patients tolerate IVIG very well. Infusions can be administered either in an outpatient clinic or, after tolerability and safety is demonstrated in the patient's own home. SCIG therapy is generally indicated for patients with limited venous access and/or who have systemic adverse reactions to IVIG.

Immunoglobulin therapy side effects and relation to product manufacturing process

During IVIG replacement therapy in PID patients, adverse reactions may occur; these side effects are generally minor such as chills and fever, other side effects although rare, can be serious such as anaphylactic shock, thrombosis or hemolysis. Some of these side effects are related to the manufacturing process or the quality of the product such as the presence of impurities. Side effects that are related to impurities vary depending upon each IVIG purification process which is unique and specific to each product. Potential adverse events due to various constituents (e.g. Anti A/Anti B hemagglutinins, anti D, Polymers, IgA content, FXIa or other pro-coagulant proteins) can only be addressed if they are known and thus the strategic reduction of these within the manufacturing process is of utmost importance.

The Ig production process involves steps of fractionation and purification of plasma. Different methods for the purification of plasma and several approved methods for viral removal and inactivation are used by the immunoglobulin manufacturers. Each step in the processing of plasma may cause alterations in its protein structure and its biological activity. As a consequence, commercial preparations of Ig can differ in tolerability and efficacy related to protein structure and biological activity [14].

The WHO requirement for safety and quality of IVIG preparations was first established in 1982 [15]. Since then, the manufacturing processes of Ig have evolved and continuous improvement of analytical methods and manufacturing process for the development of highly purified human immunoglobulins is being performed in order to ensure that Ig are safe while maintaining their structural and functional integrity. One of the approach to enhance the quality of IgG products is the so called "Quality by design (QbD) approach" [16] which is a science and risk-based methodology for product and process development. The targeted product profile is implemented through a manufacturing process of IVIG designed with each process step built to ensure product quality. For IVIG, the critical steps (see **Table 3**) include removal of activated coagulation factors to reduce the risk of thrombogenic adverse events, removal of IgA to avoid immune responses in patients deficient in IgA; removal of anti-A and Anti-B hemagglutinins to avoid adverse events on patients of blood groups A, B or AB, reduction of aggregates to avoid adverse events through complement activation and reduction of potential adventitious and non-adventitious agents by precipitation or chromatography and the use of dedicated steps such as solvent and detergent treatment and nanofiltration that contribute to reduce even more the risk of disease transmission and enhance biological safety of IVIG. The solvent/detergent technique is effective against enveloped viruses, while nanofiltration removes both enveloped and non-enveloped viruses e.g. parvovirus B19 and hepatitis A [18]. These methods have been shown to preserve the structural functions of the IgG while enhancing the tolerability and the quality of the IgG product [19].

In the recent years, companies developed liquid solutions ready-to-use with higher concentrates of Ig such as 100 mg/mL solutions (10%) with a low pH that favors the stability of the product (pH: 4.3 to 5.0). Up to date 10% liquid formulations offer advantages because of their optimal pH, glycine or proline stabilizers, low sodium content, and physiological osmolality. They are also more convenient for the patient and health care provider for their ease of prep-

Table 4. Primary efficacy endpoint-Annualized number of SBIs

	Pediatric (2-17) N=26	Adults (≥ 18) N=36	All N=62
Nb of SBIs	0	1	1
Patient-year	26.37	31.37	57.74
SBI rate/patient/year	0.000	0.032	0.017
Two-sided 98% CI	0.000, 0.175	0.000, 0.212	0.000, 0.115
One-sided *p*-value	-	-	< 0.001

SBI: Serious bacterial infections; CI: confidence interval.

aration and administration and short infusion duration [20].

Safety and efficacy of a new highly purified IVIG in the management of patients with PID

LFB has designed a novel purification process (the IGNG platform) based on the QbD approach for eliminating or reducing impurities in order to reduce the occurrence of adverse events, whilst maintaining the structural and functional integrity of IgG, and ensuring a constant batch to batch product quality based on a clear knowledge of the process limits and a justified control strategy. ClairYg®, 5% liquid preparation licensed in France and other international markets, was the first product developed from the IGNG platform. Based on this experience, a 10% liquid IVIG (IQYMUNE®) has also been developed. ClairYg® and IQYMUNE® share the same purification process with a different formulation, 5% and 10% respectively. The characteristics of these highly purified IVIG include the following: all IgG functionalities are preserved with IgG purity > 98%, low levels of IgA (≤ 28 µg/mL), low level of anti-A and anti-B hemagglutinins (8 to 16 and 4 to 8, respectively, expressed as the inverse of the dilution), no detected activated factor XI (< 1.3 mIU/ml) or any pro-coagulant activity, use of 20 nm nanofiltration and Solvent/Detergent treatment, are Saccharose- and maltose-free (stabilizer: glycine and polysorbate 80) formulated product at acidic pH (pH 4.8 ± 0.2).

Here we report the results of a clinical trial testing the 10% ready- to-use liquid highly purified IVIG (nanofiltration 20 nm) (LFB biotechnologies) IQYMUNE® in patients with PID. In this open label, multicentric and prospective study, 62 patients with the diagnosis of X-linked agammaglobulinemia (XLA, n=20) or common variable immunodeficiency (CVID, n=42), were enrolled to receive, IQYMUNE® at dose between 0.2 and 0.8 g/kg every 21 or 28 days for 12 months. Patients had to be either naïve or previously treated with IVIG with stable dose of IVIG with at least 3 IgG through levels ≥ 4 g/L within the last 6 months prior to study entry. The primary efficacy endpoint was the annualized number of serious bacterial infections (SBIs) per year as defined by the EMA guideline on the clinical investigation of IVIG (EMA/CHMP/BPWP/94033/2007) [17], which recommends including at least 40 evaluable patients (20 adults and 20 children) for efficacy with a subgroup of 20 adult patients for PK analysis. This sample size was considered to allow at least an 80% power to reject the null hypothesis that the number of SBIs per patient and per year will be greater or equal to one with a type I error of 0.01 (one-sided test). It was assumed that the number of SBIs had a Poisson distribution. The model used to complete the primary analysis was an exact one-sided one-sample Poisson test at significance level 0.01. The following hypotheses were tested: H0: per patient-year rate of SBIs > 1, H1: per patient-year rate of SBIs < 1. The maximum likelihood estimator, the associated 2-sided 98% CI and the one-sided *p*-value of the exact test was provided. The null hypothesis was rejected if the upper bound of the CI was < 1. The point estimates and CIs were presented by age group. Main secondary endpoints were annualized rate of all infections and infection-related parameters (absence from school or work, hospitalization, antibiotic treatment) and safety and tolerability.

There were 26 children and 36 adults enrolled, median age of children population was 11.5 years (range: 2-17), and median age of adult patients was 40 years (range: 18-61). A total of 56 patients were pretreated (56 IVIG, one SCIG) and 4 were Ig therapy naïve. Overall, the median baseline serum IgG through level was 5.78 g/L (range: 0.45-9.99) and the mean number of serious bacterial infections (SBIs) in the previous year was 8 (12.9). In terms of efficacy, only one SBI (*Acinetobacter* bacteremia) was reported in a 24-year-old male CVID patient. This SBI occurred in a context of a very low IgG trough level (2.47 g/L) explained by an aggravation of a chronic enteropathy with protein loss.

Table 5. Secondary efficacy endpoint-Infection associated parameters

	All N=62
Infections	
Number of infections (nb of patients)	228 (51)
Median annualised number of infections/patient (nb/year) [min-max]	3.0 [0.0-14.9]
[95% IC]	[2.88; 4.71]
Infections with antibiotic use	
Number of infections (nb of patients)	131 (38)
Median annualized nb of days of antibiotics (days/year) [min-max]	7.5 [0.0-120.8]
[95% IC]	[12.7; 26.3]
Hospitalizations due to infection	
Number of hospitalizations (nb of patients)	6 (5)
Median annualized nb of days/patient [min-max]	0.0 [0.0-17.7]
[95% IC]	[0.05; 1.73]
Absence from work or school due to infections	
Number of absence (nb of concerned patients)	15 (8)
Median annualized nb of days of absence/patient (days/year) [min-maxi]	0.0 [0.0-20.0]
[95% IC]	[0.09; 1.93]

nb: number.

The patient completely recovered without any sequelae following antibiotic therapy. No SBI was reported in the pediatric population (**Table 4**).

Overall, the annualized number of SBI was 0.017 per patient (95% CI: 0.00; 0.115), which was significantly lower than the predefined threshold of 1.0 infection/patient/year) required by EMA guidelines ($p < 0.001$). These results are also in line with the literature ranging from 0.0 to 0.08 [17].

Regarding secondary endpoints, overall, 228 infections were reported in 51/62 patients (82.3%), corresponding to a mean of 3.79 infections per patient/year, in line with the average range reported with other IVIGs [21, 22]. Infections were more frequent in the pediatric population (133 in 26 patients [100% of pediatrics]) than in adults (95 in 25 patients [69.4% of adults]). The difference in the rate of infections between pediatric and adult was expected. Usually, pediatric patients have more infections due to their childhood environment. As expected in the context of PID, most infections involved the respiratory tract; most frequently ones being bronchitis (30 infections in 24.2% of the patients), chronic sinusitis (28 infections in 14.5% of the patients), nasopharyngitis (26 infections in 22.6% of the patients), and upper respiratory tract infections (18 infections in 17.7% of the patients). Moreover, less infections were observed when IgG trough level was > 8 g/L (18.6% vs. 26.3% when IgG level ≤ 8 g/dL, p=0.01).

Table 5 summarizes infection-associated parameters (infections, infections with use of antibiotics, hospitalization due to infection, and absence from work or school). As shown in the table, the rate of missed work or school days was low (8 patients for a total of 15 days). The annual number rate of days with use of antibiotics per patient of 7.5 [95% IC: 12.7; 26.3]. Only five patients spent a total of 15 days at hospital due to infection. These results are comparable with the literature data on IVIG replacement therapy in patients with PID [21, 22].

Mean IgG trough levels in the total population over the period from the 6th infusion to the end of treatment was 7.76 g/L while the mean IQYMUNE® dose was 0.60 g/kg over the same period. Mean maximum infusion rate per patient (N=62) was 6.10 mL/kg/h [min-max 1.00-8.00]. A total of 43.5% of patients (27/62) received at least one infusion at the maximum flow rate of 8 mL/kg/h. No patients received infusion at a rate > 8 mL/kg/h.

In terms of safety, thromboembolic events, renal complications, anaphylactic reactions or hemolysis were not reported. Headache, chills

and pyrexia were the most commonly reported treatment-emergent adverse events, occurring in 25.8%, 14.5% and 12.9% of the patients, respectively. Of note, a total of 15 episodes of neutropenia were reported in 8 patients (11.3%). All neutropenia episodes were diagnosed during infusion or within 72 h after infusion, based on post-infusion blood samples, all episodes were of mild or moderate intensity and resolved spontaneously. These findings are consistent with the literature; neutropenia can occur following IVIG administration and is usually transient without any increase in the rate of infection.

Conclusion

Immunoglobulin replacement therapy is a cornerstone of the treatment of patients with PID. Continuous improvement in the process of development of human Ig allows the delivery of highly purified and effective Ig products. Advances in the mode of immune globulin administration, offer the possibility to individualise this life-long therapy based on the patients clinical need and personal choices.

Disclosure of conflict of interest

None.

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