EMA workshop on the challenges in drug development, regulation and clinical practice for immunoglobulins
March 5th, 2025

Clinical considerations on the use of IgG in primary immunodeficiencies (replacement therapy)

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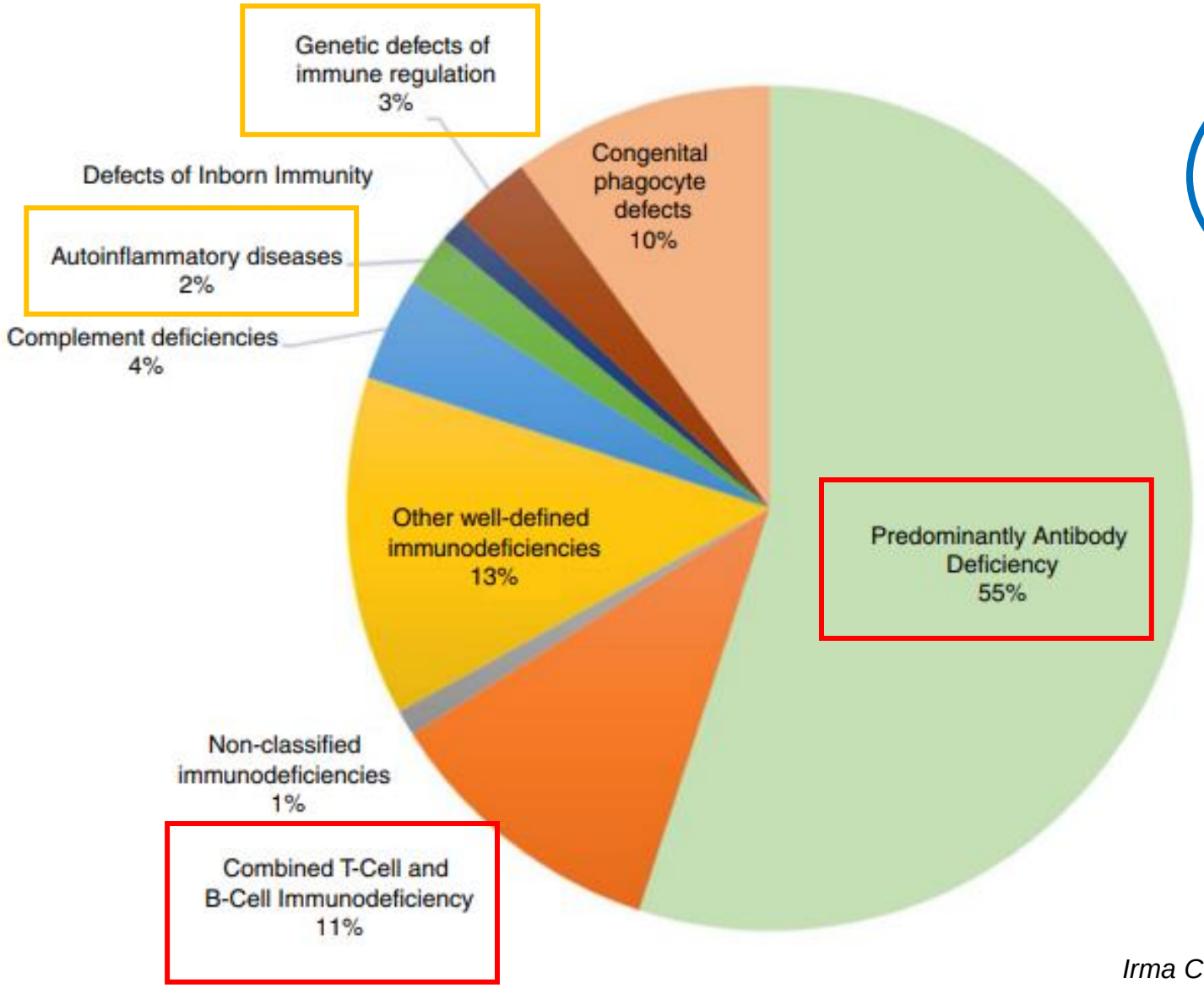
DISCLOSURE/STATEMENTS

The undersigned, Cicalese Maria Pia, as Speaker in this activity

I HERE DECLARE

NO, I have no relevant personal financial relationship in the medical/health field treated in this presentation

Classification of primary immunodeficiencies (PIDs) and their relative frequencies



PIDs are a heterogeneous group of more than 480 diseases that affect adults, children and neonates.

Irma Cecília Douglas Paes Barreto et al, J Pediatr (Rio J). 2020

Summary of primary antibody deficiencies (PADS)

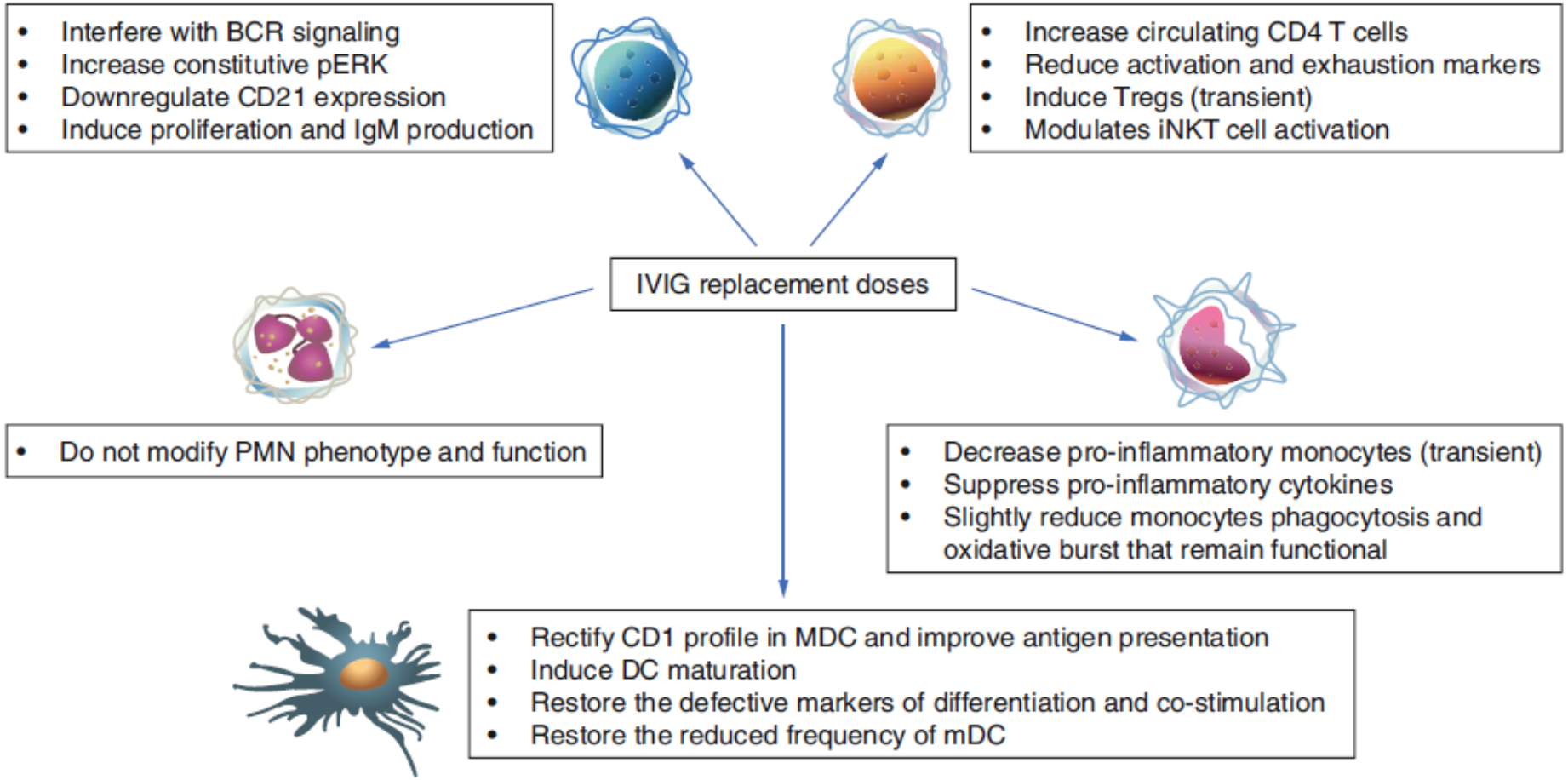
Table 3 **Summary of primary antibody deficiencies**

Disease	Genetic Defects	Age/Sex	Frequency	Clinical Manifestations	Laboratory Evaluation	Management
CVID	Cellular defects such as *TACI, BAFF, ICOS, TWEAK*; cytosolic defects such as *PKCδ, BLK, PLCγ2*; nuclear defects such as *NFκB, STAT1**	Diagnosed typically in adulthood; equally distributed between males and females#	Estimated prevalence of 1:25,000–1:50,000#	Recurrent infections, autoimmunity, malignancy#§	Immunoglobulin levels, vaccine antibody responses, lymphocyte subsets, proliferation to mitogens and antigens, genetic testing*§	Immunoglobulin replacement, prophylactic antibiotics, inactivated vaccines, malignancy and autoimmunity surveillance, immunomodulatory drugs for autoimmunity, PFTs, chest imaging§
HIGM	CD40LG, CD40, AID, UNG¶	Presents in childhood up to the 5th decade of life; X-linked or AR inheritance¶	XHIGM: estimated prevalence of 1:1,000,000 HIGM types 2–4 rarer¶	Recurrent respiratory tract infections, chronic diarrhea, neutropenia, autoimmunity, malignancy¶	Immunoglobulin levels, lymphocyte subsets, vaccine antibody responses, CBC with diff, genetic testing¶	Immunoglobulin replacement, prophylactic antibiotics, malignancy and autoimmunity surveillance, consider HSCT¶
XLA	BTK gene mutations‖**	Toward the end of the first year of life, mostly males ‖##	Incidence of 1:100,000–1:200,000 §§	Recurrent infections, including sinopulmonary infections, conjunctivitis, gastroenteritis, skin infections ‖**	Immunoglobulin levels, lymphocyte subsets, vaccine antibody responses, genetic testing‖**	Immunoglobulin replacement, antibiotic prophylaxis, consider HSCT** ¶¶
THI	Unknown‖‖	In children 6 months to 6 years of life; males more affected than females in a 2:1 ratio***	Incidence of 0.061 per 1000 live births###	Many are asymptomatic; others may demonstrate viral and bacterial respiratory infections, may have atopy or autoimmunity§§§	Ig levels, vaccine antibody responses, lymphocyte subsets§§§‖‖¶¶¶	No therapy for patients who are asymptomatic; antibiotic prophylaxis; consider immunoglobulin replacement for patients with frequent

THI: transient hypogammaglobulinemia of infancy.

Ashley T. Nguyen et al, Allergy Asthma Proc 2024

Potential mechanisms of action of immunoglobulins in PIDs



Iftekhar Mahmood et al., Immunotherapy 2024

Use of immunoglobulins in PIDs

• Indication: IVIG is indicated as replacement therapy for PIDs with absent or deficient Ab production (PIDs with minimal-to-low total IgG levels in circulation, and with normal level but documented specific Ab deficiency).

• Frequency of treatment: IVIG is a continuous replacement therapy for PIDs (no interruption).

• Dose: starting dose of 400–600 mg/kg every 3–4 weeks. Less frequent treatment, or use of lower doses, is not substantiated by clinical data.

• IgG trough levels: can be useful in some diagnoses of PIDs for guiding dosing strategies, but should not be a consideration in access to IVIG therapy.

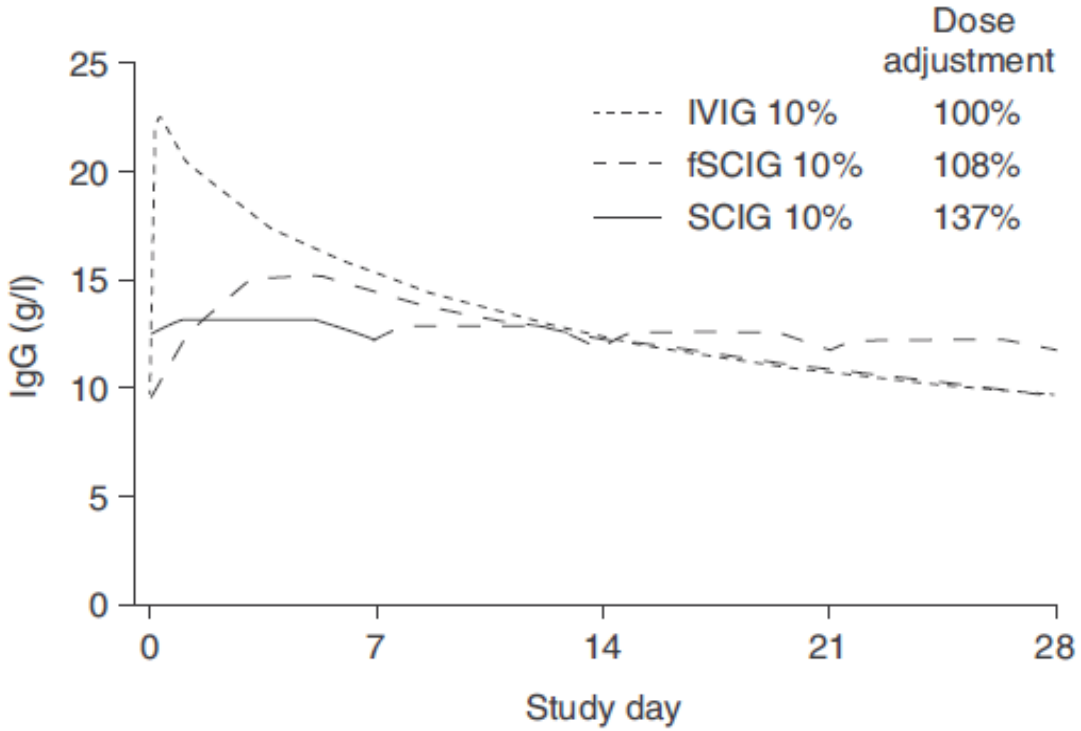
• Site of care: the decision to infuse IVIG in a hospital, hospital outpatient, community office or home-based setting must be based upon the clinical characteristics of the patient.

• Route: route of administration must be based on patient characteristics. Most patients with PIDs are appropriate candidates for IVIG and a subset for SCIG therapy.

• Product: IVIG or SCIG are not generic drug products and various approved Ig products are not interchangeable. A change of product should occur only with the active participation of the prescribing physician. While the common active component of Ig products is IgG, IgG concentrations and formulations can vary significantly.

Zhaoyang Li et al, Immunotherapy 2024

Representative PK profiles for various IgG therapies



- Absorption
- Volume of distribution
- Clearance (renal and metabolic)
- Half-life and accumulation

Figure 2. Representative PK profiles for various IgG therapies [21]. IVIG and fSCIG data shown at a 28-day dosing interval; SCIG data shown at a 7-day dosing interval; SCIG dotted line shows weekly dose extrapolated over 21 additional days.
fSCIG: Hyaluronidase-facilitated subcutaneous immunoglobulin G; IgG: Immunoglobulin G; IVIG: Intravenous immunoglobulin; PK: Pharmacokinetics; SCIG: Subcutaneous immunoglobulin.

Iftekhar Mahmood et al., Immunotherapy 2024

Comparison of dosing strategies and PK between IVIg and scIg

Comparison parameters	IVIG 10%	SCIG 20%	fSCIG 10%
Infusion frequency	Every 3–4 weeks	Daily to every 2 weeks (pump administration) Daily to every 3 to 4 days (manual administration)[a]	Every 2–4 weeks
Infusion volume[b]	Large (700 ml)	Small (5–10 ml for daily infusion). Smaller volume allows gradual absorption and achievement of steady-state levels	Large (280–560 ml every 4 weeks)
Infusion time	3–5 h/dose every 3–4 weeks	~1 h/dose every 1–2 weeks (pump administration) 5–10 minutes/dose every 1–2 days (manual administration)[a]	3–5 h/dose every 3–4 weeks
Use of high doses	Possible	Limited by volume and number of sites	Possible
Infusion route	IV, requires venous access	SC, no requirement for venous access	SC, no requirement for venous access
Pharmacokinetics	Rapid rise in IgG levels and then gradual decline, ultimately reaching baseline levels	Slower increase in IgG levels compared with IVIG, but decline in levels is slow with subsequent stable levels	Faster increase in IgG levels compared with SCIG
	High peak/trough fluctuation	Low peak/trough fluctuation or higher trough than IVIG and fSCIG	Intermediate trough level, dependent on treatment interval
	100% bioavailability	Generally 60–70% bioavailability[c]	>90% bioavailability[c]
Local adverse events	Rare	Frequent, but mild to moderate	Similar to SCIG; mild and common and diminish with continued use
Systemic adverse events	Frequent	Rare	Similar to SCIG; milder than for IVIG
Administration	Skilled personnel needed	Self-administration is possible	Self-administration is possible
Level of patient satisfaction	Preferred by patients who do not want frequent dosing	Preferred by patients who want independence and who are willing to self-administer	Preferred by patients who have poor venous access or when frequent SCIG infusions are problematic
Cost	High	Low	Low

[a]Manual administration is by hand using a conventional syringe and butterfly needle and offers quicker administration times compared with an infusion pump due to lower infusion volumes [11].
[b]In these examples, indicative infusion volume is based on an individual weighing 70 kg and is dependent on the formulation of the medication.
[c]Bioavailability relative to IVIG.
fSCIG: Hyaluronidase-facilitated subcutaneous immunoglobulin; IgG: Immunoglobulin G; IVIG: Intravenous immunoglobulin; SCIG: Subcutaneous immunoglobulin.

Zhaoyang Li et al, Immunotherapy 2024

Dosing of ‘conventional’ SCIG

- Convenience to both patients and healthcare professionals
- Preferred over IVIG in pts at thrombotic risk or with poor or difficult venous access (e.g., infants and small children), or adults with compromised venous access or in need to preserve access (e.g., chemotherapy) or in previous systemic reactions to IVIG.
- PIDs pts typically initiate SCIG by switching from another IVIG, treatment is initiated 1 week after the last IVIG
- Dose and dosing frequency ranges from daily to every 2 weeks. Weekly dose established by converting the monthly IVIG dose into equivalent weekly dose and increasing using a dose adjustment factor (1.3–1.5). In the EU, no dosing conversion factor.
- Higher IgG trough levels beneficial to PIDs pts; higher doses used for the treatment of serious bacterial infections.
- EMA guidelines in SmPCs recommends for PIDs: ‘The dosage regimen should achieve a sustained level of IgG. A loading dose of at least 0.2–0.5 g/kg (200–500 mg/kg) body weight may be required, to be divided over several days, with a maximal daily dose of 0.1–0.15 g/kg. After steady-state IgG levels, maintenance doses administered at repeated intervals to reach a cumulative monthly dose of the order of 0.4–0.8 g/kg (400–800 mg/kg). Trough levels should be measured in order to adjust the dose and dosage interval. The dosage may need to be individualized for each patient dependent on PK and clinical response’.
- Caveats: absorption is slow compared with IVIG, large doses (> 500 mg/kg) and large volume cannot be administered.

Zhaoyang Li et al, Immunotherapy 2024

Recombinant human hyaluronidase (rHuPH20)-facilitated SCIGs (fSCIGs) 10%

- rHuPH20 facilitates the absorption of SCIG
- fSCIG 10% approved for the treatment of PIDs in adults and children aged ≥2 years in the USA, and in patients of all ages with PIDs in Europe
- Dual vial unit, one vial containing 10% IgG (100 mg/ml) and the other 160 U/ml rHuPH20, which depolymerizes hyaluronan in the extracellular matrix, transiently increasing the permeability of sc tissue to IgG → increased bioavailability.
- Pros: high-volume sc Ig administration (up to 600 ml/infusion site over 2–3 h) over a short time and higher infusion rates and reduced dosing frequency *vs* conventional SCIG.
- AUC of fSCIG 10% *vs* conventional SCIG is 20% higher, and the weekly AUC-based bioavailability of fSCIG 10% is 93.3% of IVIG. 1:1 dose conversion from IVIG to fSCIG 10%, or vice versa, with no adjustment required for bioavailability.
- The initiation of fSCIG 10% treatment requires an initial dose ramp-up to achieve target dose and volume (25% of the target full dose in week 1, 50% in week 2, 75% in week 4 and 100% in week 7). Then, an fSCIG 10% dose of 300–600 mg/kg at 3- to 4-week intervals should be administered.

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IgG dosing guided by target IgG trough levels

- The use of serum IgG trough levels in guiding the dosing of patients with PIDs is widespread, but guiding dosing in PIDs based on IgG trough levels alone not proven to be adequate.
- Pneumonia incidence with IVIG maintenance of 5 g/l IgG trough levels (0.113 cases per patient - year) five-fold higher than in patients with 10 g/l trough levels (0.023 cases per patient - year) → risk of pneumonia could be reduced by achieving higher IgG trough levels.
- In an evidence-based review of 25 studies in which patients with PIDs were administered IVIG or SCIG, it was revealed that IgG trough levels were higher with SCIG administration than with IVIG administration, but both routes of administration provided protection from serious bacterial infections.
- In a meta-analysis (24 studies) assessing IgG trough levels and efficacy of IVIG (13 pts) and SCIG (11 pts) treatment for PIDs, for every 1 g/l increase in IgG trough level, a linear trend for decreased incidence of infection was observed in SCIG-treated patients ($p = 0.03$).
- Serum IgG trough levels are a highly relevant surrogate marker for therapeutic efficacy of IgG in PIDs.
- Interpatient variability in the ‘protective threshold’ that drives the ultimate dosing and dosing optimization strategy for individual patients.

Zhaoyang Li et al, Immunotherapy 2024

Dosing strategies in specific populations

- Considerable variation in body composition between individuals (children, neonates, adults, geriatric and obese), to balance treatment benefits and the potential risk of adverse events.
- For all the approved Ig therapies, no recommendation for dose adjustment for specific populations (clinical data of dose levels in pediatric or obese patients with PIDs still lacking)
- Body mass composition may affect how IgG is absorbed, distributed and eliminated (differences in the PK profiles of IgG)
- Additionally, given the high cost of IgG therapies and increased infusion time, administering higher doses than necessary has implications for healthcare resource utilization and patient burden
- There is some evidence indicating that initial loading doses of IVIG (typically 2 g/kg over 2–5 days) should be based on ideal body weight rather than adjusted body weight in obese patients with PIDs.
- In Ig-naïve PIDs pts, the lower the baseline IgG levels, the higher the loading and maintenance doses required and the longer the time to achieve the target levels. They are frequently initiated on IVIG, but can be initiated directly on SCIG.

Zhaoyang Li et al, Immunotherapy 2024

Open issues

Dosing strategies in specific populations and IgG-naive pts

Variability in PK→ individualized dosing strategies

IgG dosing guided by target IgG trough levels

Immunogenicity (anaphylaxis/non neutralizing Abs)

Passive transfer of autoantibodies → misdiagnosis of AI disease

Zhaoyang Li et al, Immunotherapy 2024
Murat Özer et al, Scandinavian J of Immunology, 2024

frontiers | Frontiers in Immunology

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Infectious outcomes of a standardized subcutaneous immunoglobulin dose reduction strategy in primary immune deficiencies amid global shortage

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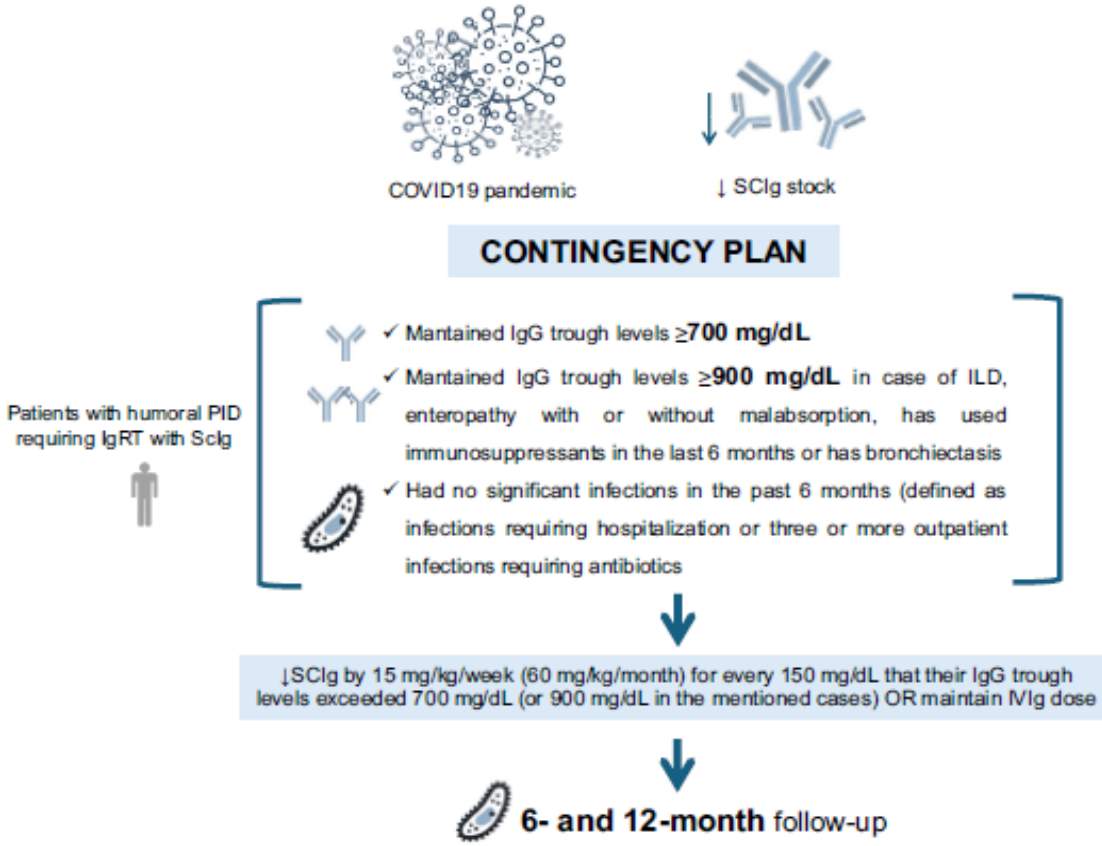

FIGURE 1
Contingency plan for subcutaneous immunoglobulin (SCIg) dose adjustment in humoral primary immunodeficiency (PID) patients during the COVID-19 pandemic in the Unit for Primary Immunodeficiencies from the University and Polytechnic Hospital La Fe. IgRT, immunoglobulin replacement therapy; IVIg, intravenous immunoglobulin.

- Adult PID patients on SCIg for at least 6 months, with IgG trough levels ≥ 700 mg/dL and no significant infections in the past 6 months
- Dose reduction of 15 mg/kg/week (60 mg/kg/month)
- Clinical and laboratory data, and infectious events at 6- and 12-month F-U, were analyzed.
- 31 pts (CVID 54.83%, IgG subclass deficiency 9.67%, other PIDs 35.48%
- No significant change in severe or mild infections before and at 6- and 12-months post-dose adjustment
- The dose reduction saved an average of 5,550 euros per patient annually.

Moral Moral ET AL, Frontiers in immunology 2024

Safety and efficacy of a novel mini-pool intravenous immunoglobulin therapy in children with primary immunodeficiency

Vox Sanguinis ISBT International Society of Blood Transfusion

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- A new method for preparing lipid-enveloped virus-inactivated immunoglobulin solution from mini-pools of domestic recovered plasma (mini-pool intravenous polyvalent immunoglobulin [MP-IVIG]) was established.
- Safety and efficacy of MP-IVIG for STD-IVIG preparations as a replacement therapy in a cohort of 21 paediatric patients with PID.
- MP-IVIG has equivalent safety and efficacy to those of standard intravenous immunoglobulin preparations.

Insights into Patient Experiences with Facilitated Subcutaneous Immunoglobulin Therapy in Primary Immune Deficiency: A Prospective Observational Cohort

Table 1 Immunoglobulin replacement therapy administration practices of patients with primary immunodeficiency before and after facilitated subcutaneous immunoglobulin

	Baseline				
	IVIG (n = 22) median min–max	SCIG (n = 6) median min–max	fSCIG (n = 155) median min–max	p-value fSCIG vs IVIG	p-value fSCIG vs SCIG
mg/kg/infusion	500 230–700	120 110–180	500 220–700	**0.029**	**< 0.001**
g/kg/4 weeks	0.50 0.45–0.86	0.51 0.47–0.77	0.53 0.38–0.80	0.874	1
g/infusion	20 5–40	10 5–20	25 5–45	0.065	**0.008**
mL/infusion	250 50–600	100 50–200	250 50–450	1	**0.003**
mL/site	250 50–600	75 45–200	250 50–450	0.969	**0.002**
number of sites	1 1–1	1 1–2	1 1–1		
infusion site per patient (antecubital/abdominal/thigh)	22/0/0	0/6/0	0/28/1		
infusion interval days	30 15–30	7 5–7	28 15–30	0.981	**< 0.001**
duration of infusion (hour)	4 1.5–6	1 1–1.5	2.5 0.5–5	**< 0.001**	**< 0.001**
needle diameter (G)	24 22–25	24 23–24	24 24–25	**< 0.001**	**0.039**
needle length (mm)	25 9–25	15.5 12–20	12 9–15	**< 0.001**	**0.004**

IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin; fSCIG, facilitated subcu ous immunoglobulin

Data pooled from analyses of 29 patients, encompassing a total of 155 administrations, were juxtaposed with individual historical periods, denoting each patient's prior experience with immunoglobulin treatment (SCIG or IVIG), as indicated in respective columns

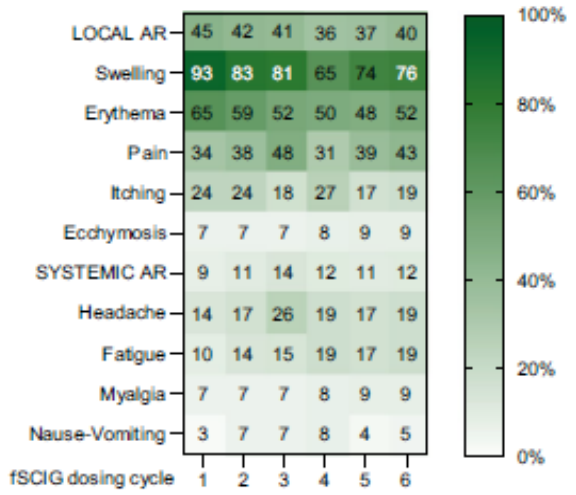

Fig. 1 Heatmap data of for ARs related to fSCIG administration during first 6 cycles of infusions. Percentages are shown on the relevant box for each. AR, adverse reaction; fSCIG, facilitated subcutaneous immunoglobulin

Table 2 Local and systemic adverse reactions during treatment with Facilitated Subcutaneous Immunoglobulin Therapy

Dosing Cycle	#1 n = 29	#2 n = 29	#3 n = 27	#4 n = 26	#5 n = 23	#6 n = 21	TOTAL n = 155
LOCAL							
Swelling	27	24	22	17	17	16	**123**
Erythema	19	17	14	13	11	11	**85**
Pain	10	11	13	8	9	9	**60**
Itching	7	7	5	7	4	4	**34**
Ecchymosis	2	2	2	2	2	2	**12**
SYSTEMIC							
Headache	4	5	7	5	4	4	**29**
Fatigue	3	4	4	4	3	3	**21**
Myalgia	2	2	2	2	2	2	**12**
Nause-Vomiting	1	2	2	2	1	1	**9**

#: number of dosing cycle, n: number of application per patient

Statistical analysis involved the use of the Friedman test, followed by post-hoc analyses using the Durbin-Conover method. Significant differences were not detected in dosing cycle

Ezgi Yalcin Gungoren et al, Journal of Clinical Immunology 2024

Immunoglobulin replacement therapy in patients with primary and secondary immunodeficiencies: impact of infusion method on immunoglobulin-specific perceptions of quality of life and treatment satisfaction

Table 2 Average time (mean) for preparation before each infusion, infusion time, and post-infusion time for IVIG and SCIG. (IVIG $n=376$, SCIG $n=598$)

	IVIG ($n=376$)	SCIG ($n=598$)	*P* value
Preparation time before each infusion (minutes			
Mean score	63.40	22.32	$p<0.001$
Standard deviation	100.83	15.85	
Infusion time (minutes)			
Mean score	237.77	119.07	$p<0.001$
Standard deviation	102.63	105.70	
Post-infusion time (minutes)			
Mean score	31.27	9.04	$p<0.001$
Standard deviation	182.78	6.08	

Note: table based on available data for $n=376$ out of a total IVIG $n=392$ patients

Table 3 Impact of immunoglobulin infusions on work or school[1]

"Does any part of the treatment regimen cause you to miss work/school?"	Total	IVIG	SCIG	*P* value
Base: All respondents	($n=990$)	($n=392$)	($n=598$)	
Yes	18%	28%	11%	<0.001
No	82%	72%	89%	
"How much time of work/school per month do you typically miss?"				
Base: Those who miss work/school	($n=174$)	($n=108$)	($n=66$)	
Less than 1 h	2%	0%	6%	NS
Between 1–3 h	11%	10%	14%	NS
Half a day to one full day	34%	44%	20%	<0.001
1–2 days	18%	20%	15%	NS
More than 2 days	24%	20%	30%	NS
Not sure	9%	6%	15%	NS

[1]Responses to the question "Does any part of the treatment regimen cause you to miss work/school?". Those who responded "yes" were asked the follow-up question "How much time of work/school per month do you typically miss?"

Note Total $N=990$, IVIG $n=392$, SCIG $n=598$)

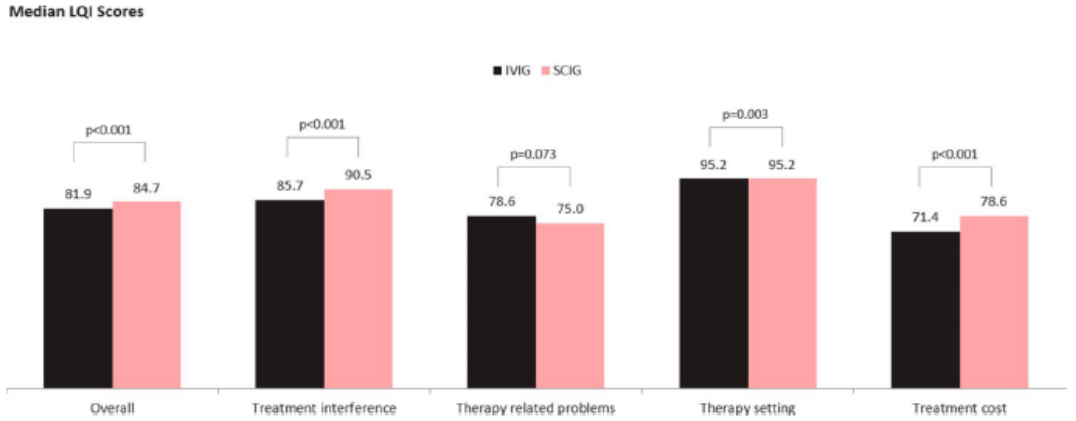

Fig. 1 Median LQI Scores – Total and by LQI sub-domain: IVIG vs. SCIG. Note: figure based on available data for $n=376$ out of a total IVIG $n=392$ patients and $n=598$ SCIG patients. The inferential p-values are based on the full distribution, and not on medians alone

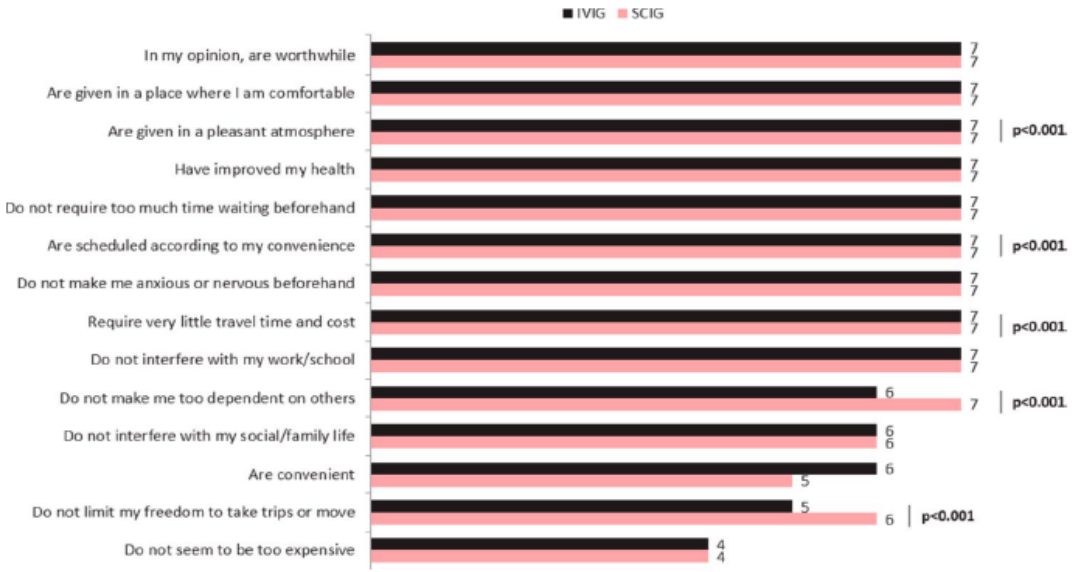

Fig. 2 Item/ attribute specific LQI median scores: IVIG vs. SCIG. Note: IVIG $n=392$, SCIG $n=598$. The inferential p-values are based on the full distribution, and not on medians alone

Rajiv Mallick et al Allergy, Asthma & Clinical Immunology 2025

Conclusions

- Human plasma-derived immunoglobulin G (IgG) products are used as replacement therapy to restore and maintain stable and optimum concentrations of IgGs for the clinical management of patients with PIDs.

- The dosing strategy for immunoglobulin G (IgG) for treating PIDs requires individualization based on serum IgG trough levels, clinical response and the patient's past experiences with Ig therapies.

- Monitoring serum IgG levels has been an integral part of diagnosing PIDs and determining or adjusting IgG dosing scheme in patient care to meet individual needs. The frequency and dose(s) of intravenous immunoglobulin and subcutaneous immunoglobulin (SCIG; including hyaluronidase-facilitated SCIG) require rigorous evaluation to provide optimum therapeutic benefit to patients with PIDs.

- The use of SCIG treatment, irrespective of patients receiving prior intravenous immunoglobulin or being treatment naive, may lead to similar outcomes. Model-based simulations indicate the need for loading doses to attain a protective IgG threshold in Ig-naïve patients with PIDs when initiating SCIG.

- Substantial variability in the pharmacokinetics (PK) and clinical response to IgG therapy have led to the proposal of individualized therapy for maximizing therapeutic benefit.

Thank you very much