"The profiling of the patient with Intravenous or Subcutaneous Immunoglobulin Therapy"

Nicolas Mavroudakis, MD, PhD
Centre de référence neuromusculaire
Hôpital Erasme, Brussels

BEL-HIZ-0015

DISCLOSURES

Travel and congress attendance sponsoring from Biogen, CSL Behring, la Croix Rouge, Lilly, Pfizer, Schering, Teva and Octapharma.

Speaker honorarium from CSL Behring.

Served on advisory boards for CSL Behring.

DO WE HAVE TO SHIFT SYSTEMATICALLY AND RAPIDLY OUR PATIENTS FROM INTRAVENOUS TO SUBCUTANEOUS IMMUNOGLOBULINS?

Place of SCIG in the treatment of CIDP?

Profiling of the patient?

BEL-HIZ-0015

CHANGE MAY BE DRIVEN BY:

- **Physicians:**
  - Efficacy
  - Safety
  - Quality of life
- **Patients (associations)**
  - Efficacy
  - Safety
  - Quality of life
- **Exterior factors** (Health policy, hospital financing,…)

BEL-HIZ-0015

FACTORS AFFECTING THE CHOICE OF IVIG VERSUS SCIG IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASE

	IVIG	SCIG
Pharmacokinetics	Wide range of serum IgG levels (peaks & troughs)	Consistent serum IgG levels
Systemic side effects	Common	Infrequent
Infusion site reactions	Infrequent	Common
Location of infusions	Infusion center or home	Anywhere
Patient satisfaction	Often better for needle-phobic patients; preferable in patients with compliance issues	Very flexible; minimizes impact on quality of life

IgG preparations safe for either intravenous or subcutaneous delivery allow healthcare providers and patients significant flexibility in developing an effective treatment plan that is tailored to the individual needs of each patient

A key challenge to clinicians is to help patients decide which route of IgG delivery is best suitable for the patient's individual needs and lifestyle

Skoda-Smith S, Torgerson TR, Ochs HD. Ther Clin Risk Manag. 2010;6:1–10.

BEL-HIZ-0015

WHY I USE SUBCUTANEOUS IMMUNOGLOBULIN (SCIG)

- Treatment for individuals with primary immunodeficiency disease
- Choice is an individual one based on many factors.
- "My preference for most patients", … "many advantages not offered by the intravenous (IVIG) route."
  - **1) independence from hospital-based infusion settings;**
  - **2) an alternative for patients with poor venous access;**
  - **3) better tolerability in those patients who are not able to tolerate IVIG;**
  - **4) flexibility of dosing;**
  - **5) ease of administration;**
  - **6) a very low side-effect profile;**
  - **7) a comparatively more even, almost physiological, IgG level;**
  - **8) less cost to administer than IVIG;**
  - **9) improved quality of life in patients treated with SCIG**

R. S. Shapiro. J Clin Immunol (2013) 33 (Suppl 2):S95–S98

BEL-HIZ-0015

- Highly motivated patients are the most suitable candidates for SCIG
- Others have poor long-term adherence to this approach to treatment
- SCIG may be contraindicated in patients with severe thrombocytopenia, bleeding disorders, or in those on anticoagulation therapy
- Inappropriate for patients with widespread eczema
- Patients with physical limitations may also have difficulty with self-administration of SCIG

R. S. Shapiro. J Clin Immunol (2013) 33 (Suppl 2):S95–S98

BEL-HIZ-0015

SCIG VS IVIG: LET'S GIVE PATIENTS THE CHOICE!

- Pediatric cohort of 143 patients with PID on Ig replacement
- All patients, regardless of the physician and nurse's impression of the "idealness" of the candidates, were offered the choice between hospital-based IVIG and home-based SCIG.

		Switch cohort		New cohort	
		Switching to SCIg	Staying on IVIg	Starting on SCIg	Starting on IVIg
Sex male: n (%)		29 (57 %)		55 (59 %)	
Age at diagnosis in years		7.2		7.1	
Age of patients when given choice of treatment in years		10.7	11	6.0	8.3
PID diagnosis: n	Common variable immunodeficiency	37		39	
	Isolated IgG deficiency	3		27	
	IgG class 2 deficiency	3		4	
	Combined immunodeficiency	2		3	
	Di George syndrome	1		4	
	HyperIgE	0		3	
	Other	5*		12[□]	

*=1X-linked agammaglobulinemia, 2 X-linked lymphoproliferative disorder, 1 NEMO, 1 Rothman-Thompson syndrome

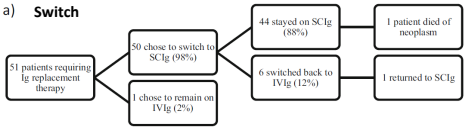
□=1 X-linked agammaglobulinemia, 3 humoral deficiency not otherwise specified, 3 ataxia-telangiectasia, 1 tricho-hepato-intestinal syndrome, 1 polysaccharide antibody deficiency, 1 ALPS-like syndrome with IgG deficiency, 1 congenital dyskeratosis, 1 hyperIgM

PID: primary immunodeficiency

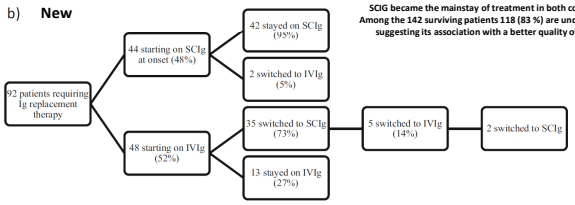
K. Samaan et al, J Clin Immunol (2014) 34:611–614

BEL-HIZ-0015

a) **Switch**



b) **New**



SCIG became the mainstay of treatment in both cohorts
Among the 142 surviving patients 118 (83 %) are under SCIG, suggesting its association with a better quality of life

K. Samaan et al, J Clin Immunol (2014) 34:611–614

BEL-HIZ-0015

WHAT TO CONSIDER WHEN STARTING SCIG THERAPY

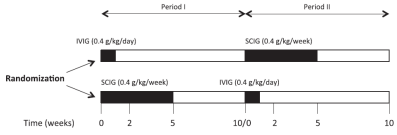
- Successful SCIG therapy depends on several key factors:
  - patients' commitment to therapy
  - education and support they receive
- Self administration of SCIG is not a difficult process, but many variables need to be considered before starting therapy:
  - patient's ability to perform the infusion
  - the infusion regimen itself (frequency and volume of infusions, number of sites)
  - the necessary ancillary supplies (infusion sets with needles of the appropriate length and gauge)
- Patients' input regarding their therapy must be considered, evaluated, and addressed to design a **regimen that ensures maximum compliance**
- Patients may be reluctant to consider SCIG therapy because of concerns about their ability to learn and perform the procedure, the time involved.
- Listening to patients and working with them to design and plan an individualized treatment regimen is essential in ensuring success.
- Although the permutations for infusions are not endless, it is possible to plan a patient-specific regimen that will meet each patient's needs.

M.E M. Younger et al Journal of Infusion Nursing. Vol 38, 1, 2015: 70 - 79

BEL-HIZ-0015

SUBCUTANEOUS IMMUNOGLOBULIN AS FIRST-LINE* THERAPY IN TREATMENT-NAIVE PATIENTS WITH CIDP

- Randomized, single-blind, cross-over study with a total duration of 20 weeks during the period from September 2013 to November 2015.



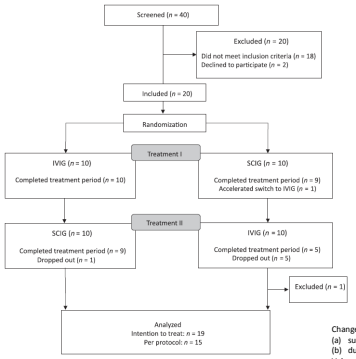
- Twenty patients fulfilling the clinical and electrophysiological criteria for CIDP were included
- Treated with either SCIG (0.4 g/kg/week) for 5 weeks or intravenous immunoglobulin (IVIG) (0.4 g/kg/day) for 5 days.
- After 10 weeks, patients were switched to the opposite treatment arm and followed for a further 10 weeks.
- All participants were evaluated at weeks 0, 2, 5 and 10 during both therapies.
- Primary outcome was combined isokinetic muscle strength (cIKS). Secondary outcomes were disability, clinical evaluation of muscle strength and the performance of various function tests.

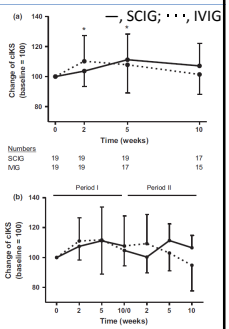
Markvardsen LH et al. Eur J Neurol. 2017 Feb;24(2):412-418.

* SCIG is not registered as first line treatment in CIDP

BEL-HIZ-0015

STUDY FLOW CHART





Changes of combined isokinetic muscle strength (cIKS) during treatment with (a) subcutaneous immunoglobulin (SCIG) and intravenous immunoglobulin (IVIG) (b) during the first and second period of treatment with SCIG versus IVIG. Values are mean SD, *P < 0.05 vs. baseline.

Markvardsen LH et al. Eur J Neurol. 2017 Feb;24(2):412-418.

* SCIG is not registered as first line treatment in CIDP

IVIG, intravenous immunoglobulin

SCIG, subcutaneous immunoglobulin

BEL-HIZ-0015

SWITCH FROM INTRAVENOUS TO SUBCUTANEOUS IMMUNOGLOBULIN

- Eight consecutive patients, four with MMN* and four with CIDP, **already on long-term, hospital-based IVIG** were switched to home-based SCIG
- **Selected on the basis of their requirement for relatively low treatment doses, problems experienced with IVIG, and their willingness to switch to SCIG**
- After a mean of 33 months [standard deviation: 19] receiving SCIG, 7 patients remained neurologically stable
- King's College Hospital, London

R. D. M. Hadden, F Marreno. *Ther Adv Neurol Disord* 2015, Vol. 8(1) 14–19

* SCIG is not registered as line treatment in MMN

BEL-HIZ-0015

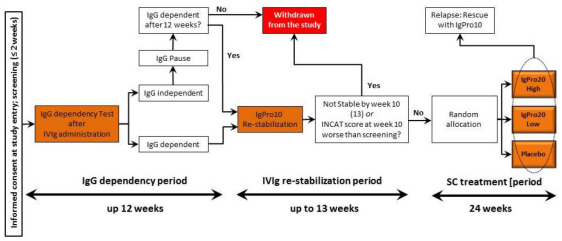
- The main reasons for wishing to switch from IVIG to SCIG were:
  - adverse effects / consequences attributable to IVIG treatment:
    - nausea or headache, n = 2
    - poor intravenous access (2 patients)
    - distance from home to hospital (2 patients)
    - missing work to attend hospital (1 patient)
    - unacceptable fluctuations in weakness as IVIG wore off (1 patient)
    - neutropenia, n = 3
    - allergy requiring antihistamine or hydrocortisone, n = 1

    (Several patients had more than one reason)
- All the above reasons were successfully resolved after switching.
- In seven of the eight patients, SCIG gave improved tolerability and patient satisfaction with similar efficacy compared with IVIG.

R. D. M. Hadden, F Marreno. *Ther Adv Neurol Disord* 2015, Vol. 8(1) 14–19

BEL-HIZ-0015

PATH STUDY DESIGN



IgG=immunoglobulin G. INCAT=Inflammatory Neuropathy Cause and Treatment. IVIg=intravenous immunoglobulins. SC=subcutaneous.

BEL-HIZ-0015

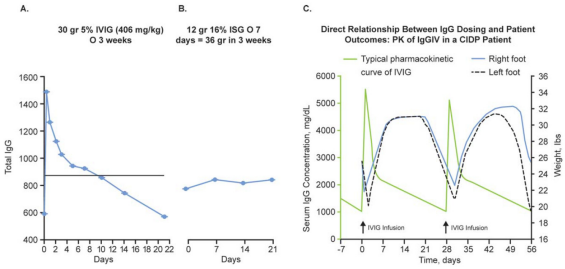
OPTIMIZING IGG THERAPY IN CHRONIC AUTOIMMUNE NEUROPATHIES: A HYPOTHESIS DRIVEN APPROACH

- The doses and treatment intervals are usually chosen empirically due to a paucity of data from dose–response studies.
- Clinical observations suggest that, in some cases, the effects of each dose of IVIG may be transient, **wearing-off** before the next dose is due.
- Recent studies of the electrophysiology and immunology of these diseases suggest that **antibody-induced reversible dysfunction of nodes of Ranvier (conduction blocks, disability) which responds to immunotherapy more rapidly** than would be expected for demyelination or axonal damage/repair per se.
- Frequent strength evaluation and disability measurements, performed by the patient at home, can be used to assess the extent and duration of responses to IgG doses.

Individualization of IgG treatment regimens may optimise efficacy, minimise disability, and identify non responders / remissions

M BERGER, J A ALLEN. Muscle Nerve 51: 315–326, 2015

BEL-HIZ-0015



A,B: Serum IgG levels in a patient with X-linked (Bruton's) aggamaglobulinemia.
A: IVIG at 406 mg/kg (30 grams total) every 22 days. The solid line represents the calculated mean IgG level over the entire interval.
B: SCIG at 12 grams/week (36 grams total), a 20% increment in dose. The IgG remains at a near steady state with a mean of 850 mg/dL.
(Berger Clin Immunol 2004;112:1–7)

C: Cyclic response to IVIG from CIDP patient superimposed on typical pharmacokinetic curve of IVIG (on a logarithmic scale) – Increase in muscle strength accompanying the rapid rise in serum IgG level following each monthly dose, but then the decrease in strength shortly after the IgG level falls.

(Bonilla Immunol Allergy Clin North Am 2008;28:803–819)

BEL-HIZ-0015

EXCLUSION CRITERIA – PATH STUDY

- Cardiomyopathy, significant cardiac arrhythmia requiring treatment, unstable or advanced ischemic heart disease, congestive heart failure
- Severe hypertension
- Chronic kidney disease stage IV and V
- Known hyperprolinemia
- Bleeding disorders
- Severe skin disease at the planned injection sites
- History of thrombotic episodes within the 2 years before enrollment:
  - pulmonary embolism
  - deep vein thrombosis
  - myocardial infarction
  - thromboembolic stroke
  - known hypercoagulable state.

Ivo N van Schaik et al, Lancet Neurol 2018; 17: 35–46

BEL-HIZ-0015

EXCLUSION CRITERIA

- Known allergic or other severe reactions to blood products:
  - intolerance to previous IVIG
  - history of hemolysis after IVIG infusion
  - aseptic meningitis
  - recurrent severe headache
  - hypersensitivity or severe generalized skin reaction
- Patients with the following laboratory results:
  - serum IgA level less than 5% of the lower limit of normal.
  - abnormal laboratory parameters:
    creatinine greater than 1·5 times the upper limit of normal (ULN)
    blood urea nitrogen >3 times the ULN if the increase is related to potential kidney disease
    haemoglobin less than 10 g/dL

Ivo N van Schaik et al, Lancet Neurol 2018; 17: 35–46

BEL-HIZ-0015

SCIG VERSUS IVIG: ADVERSE EFFECTS, HEALTH ECONOMICS AND QUALITY OF LIFE

- Substantial evidence from the immunological literature of less adverse events with SCIG compared with IVIG.
- A systematic review and meta-analysis of nearly 1500 patients with primary antibody deficiencies from 47 publications demonstrates this (OR favoring SCIG vs IVIG 0.09; range 0.07–0.11; p<0.001).
- The risk of serious adverse effects such as thromboembolism or anaphylactic shock is documented with IVIG in inflammatory neuropathy. This risk has been generally considered lower with SCIG.
- However a worldwide study of four IVIG products and two SCIG products demonstrated a thromboembolic reporting rate with subcutaneous therapy, which was equal for the two brands studied and, importantly, higher than that with three of four IVIG products considered. These data cast some doubt about definite relative safety of SCIG versus IVIG in relation to thromboembolic risk.

Y A Rajabally, J Neurol Neurosurg Psychiatry 2014;85:631–637
H Abolhassani et al. J Clin Immunol 2012;32:1180–92
V I Leussink et al. Ther Adv Neurol Disord, 2016, 9: 336–343
M B Funk et al. Vox Sanguinis (2013) 105, 54–64

BEL-HIZ-0015

CONTRAINDICATIONS TO SCIG

- Anaphylactic or severe systemic reactions to human immune globulin or components of the individual products.
- The prescribing data also state that it is contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity. ***(controversial)***
  - Patients with IgA deficiency, an undetectable level of IgA on laboratory assay, may have undetectable IgA but do not necessarily have anti-IgA antibodies.
  - A review of the literature to determine the role of anti-IgA antibodies in causing adverse reactions to Ig.: data supported no specific conclusion.
  - Authors noted that IgA-deficient patients who experienced reactions to intravenous infusions were able to tolerate subcutaneous infusions. They recommended a switch to SCIG in IgA-deficient patients who have adverse reactions to IVIG.
  - Studies noted that patients with undetectable levels of IgA were able to tolerate SCIG.

Rachid R , Bonilla FA . The role of anti-IgA antibodies in causing adverse reactions to gamma globulin infusion in immunodeficient patients: a comprehensive review of the literature . J Allergy Clin Immunol . 2012 ; 129 (3): 628-634 .

Horn J , Thon V , Bartonkova D , et al. Anti-IgA antibodies in common variable immunodeficiency (CVID): diagnostic workup and therapeutic strategy . Clin Immunol . 2007 ; 122 (2): 156-162 .

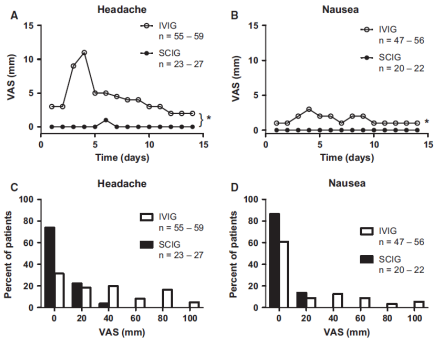
Shapiro R . Administration of immunoglobulin replacement via rapid subcutaneous push is well tolerated in IgA-deficient patients [abstract] . Ann Allergy Asthma Immunol. 2009 ; 103 (5 suppl 3): A115 .

M.E M. Younger et al Journal of Infusion Nursing. 2015, 38, 1: 70 - 79

IVIGs: contra indicated in patients with anti-IgA antibodies
SCIG: use with caution

BEL-HIZ-0015

HEADACHE AND NAUSEA AFTER TREATMENT WITH HIGH-DOSE SUBCUTANEOUS VERSUS INTRAVENOUS IMMUNOGLOBULIN

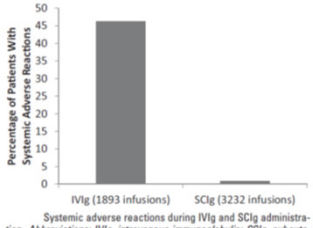


All IVIG-treated patients (n = 59) received PRIVIGEN

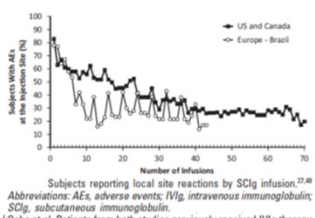
L H Markvardsen et al. Basic & Clinical Pharmacology & Toxicology, 2015, 117, 409–412

BEL-HIZ-0015

ADVERSE EVENTS



Systemic adverse reactions during IVIg and SCIg administration. *Abbreviations: IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.* (Data from Gardulf et al.[19])



Subjects reporting local site reactions by SCIg infusion.[27,48] *Abbreviations: AEs, adverse events; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.* (Ochs et al. Patients from both studies previously received IVIg therapy before initiating treatment with SCIg.)

Gardulf A , Hammarstrom L , Smith CI . Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. Lancet . 1991 ; 338 (8760): 162-166 .

Ochs HD et al. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases . J Clin Immunol. 2006 ; 26 (3): 265-273

BEL-HIZ-0015

Compared with intravenous immunoglobulin treatment, subcutaneous immunoglobulin:

Can more easily be self-administered at home,

Has a lower incidence of adverse effects relating to peak immunoglobulin levels,

Equal efficacy at the adequate dosage

BEL-HIZ-0015

Hôpital Erasme ULB

QUESTIONS?