PolyNeuro exchange

Dosing schedules for IVIG: The use of *an* algorithm as a suggestion for personalized dosing

Disclosure

- The presentation contains information outside the labelled indication for intravenous immunoglobulin (IVIG)

Personalized medicine

"Personalized medicine is health care that tailors interventions to individual variation in risk and treatment response."[1]

- Maximize effectiveness and reduce disability
- Reduce risk
- Minimize dose (reduce dose or increase frequency)
- Maximize 'convenience'

1. Conti R et al. Med Decis Making 2010;30:328-40

‘2g/kg over 5 days’: Where did it start?

BLOOD *The Journal of Hematology*

JULY, 1960 VOL. XVI, NO. 1

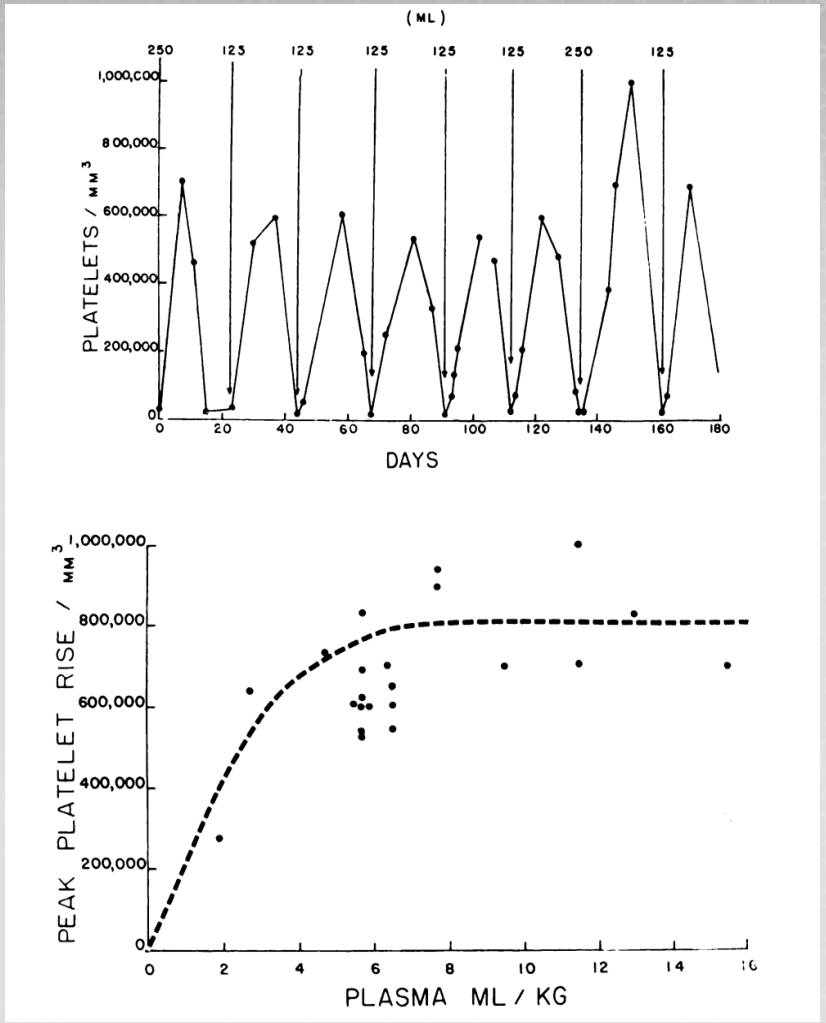
Studies on Thrombopoiesis. I. A Factor in Normal Human Plasma Required for Platelet Production; Chronic Thrombocytopenia Due to its Deficiency

By Irving Schulman, Mila Pierce, Abby Lukens and Zinet Currimbhoy

Schulman I et al Blood 1960;16:943-57

During the acute phase of ITP transfusions of platelets or freshly drawn blood are of value in controlling hemorrhage, but we have found such measures necessary infrequently. The use of plasma transfusions to stimulate thrombopoiesis[5, 6] is of interest and is being explored further. At present, however, this must be considered experimental.

Schulman I et al. Pediatrics 1964;33:979-80



Schulman I et al. Blood 1960;16:943-57

‘2g/kg over 5 days’: Where did it start?

Gugler E. Die kindlichen Thrombopenien[2]

- 1st description of a favorable response in a child with chronic ITP who received 3 doses of IVIG
  - 2 ml day 1
  - 5 or 10 ml on day 2 or 3
  - Platelet count rose to 300 900*10^9/l

HIGH-DOSE INTRAVENOUS GAMMAGLOBULIN FOR IDIOPATHIC THROMBOCYTOPENIC PURPURA IN CHILDHOOD[1]

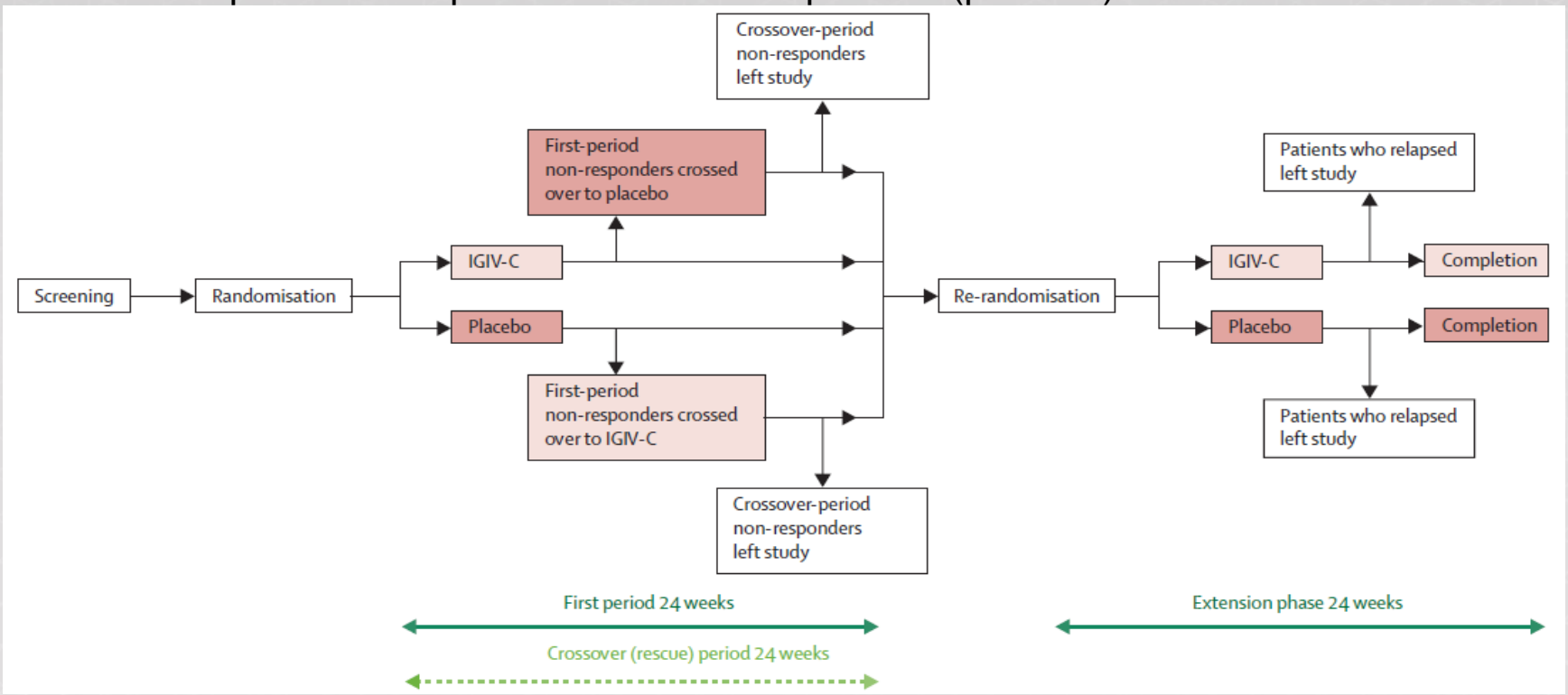
P. IMBACH, S. BARANDUN, V. d’APUZZO, C. BAUMGARTNER, A. HIRT, A. MORELL, E. ROSSI, M. SCHÖNI, M. VEST, H. P. WAGNER

Institute for Clinical and Experimental Cancer Research, University of Bern; Department of Paediatrics, University Hospitals, Bern; Children’s Hospital, Kantonsspital Bruderholz; and Section of Paediatrics, District Hospital Mendrisio, Switzerland

1. Imbach P et al. Lancet 1981;1:1228-31
2. Gugler E. Die kindlichen Thrombopenien in: Rossi E, ed. Pädiatrischer Fortbildungskurs – Blutkrankheiten im Kindesalter. Basel: Karger 1964;11-12

IVIG in CIDP Efficacy Study (ICE)

- Results of the ICE Study 2008:[1]
  - First period: Patients in the IVIG group had a significant improvement compared with placebo
  - Extension phase: No significant differences in efficacy outcome measures vs baseline values. Participants who continued to receive IVIG had a longer time to relapse than did patients treated with placebo (p=0.011)



CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy

1. Hughes RAC et al. Lancet Neurol 2008;7:136-44

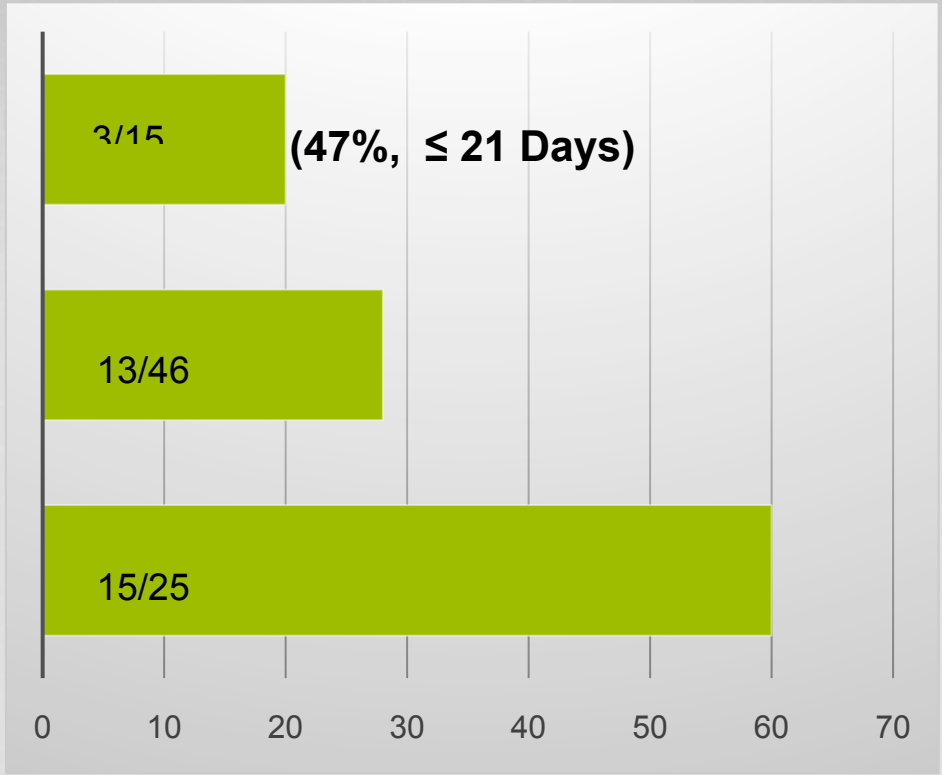
British Peripheral Nerve Society IVIG usage in CIDP survey 2014[1]

- 48 peripheral nerve neurologists participated in a live survey of CIDP management
- Simple typical CIDP history
  - 80% IVIG first-line treatment
  - 71% wait for deterioration/routine follow-up before 2nd dose
  - 86% would eventually give a 2nd dose with no improvement but without a scheduled plan
  - 97% respondents would reassess the requirement for further dosing or the dose needed, before continuing
  - 63% increase the dose interval to establish continued immunoglobulin (Ig) responsiveness in patients with stable disease

1. Lunn M et al. J Peripher Nerv Syst 2015. *In press*

Individually optimized therapy frequently requires dosing more often than monthly

- Conclusion drawn from data obtained in several studies



1. Rajabally YA et al. J Neurol 2013;260:2052-6
2. Broyles R et al. Postgrad Med 2013;125:65-72
3. Kuitwaard K et al. J Neurol Neurosurg Psychiatry 2013;84:859-61

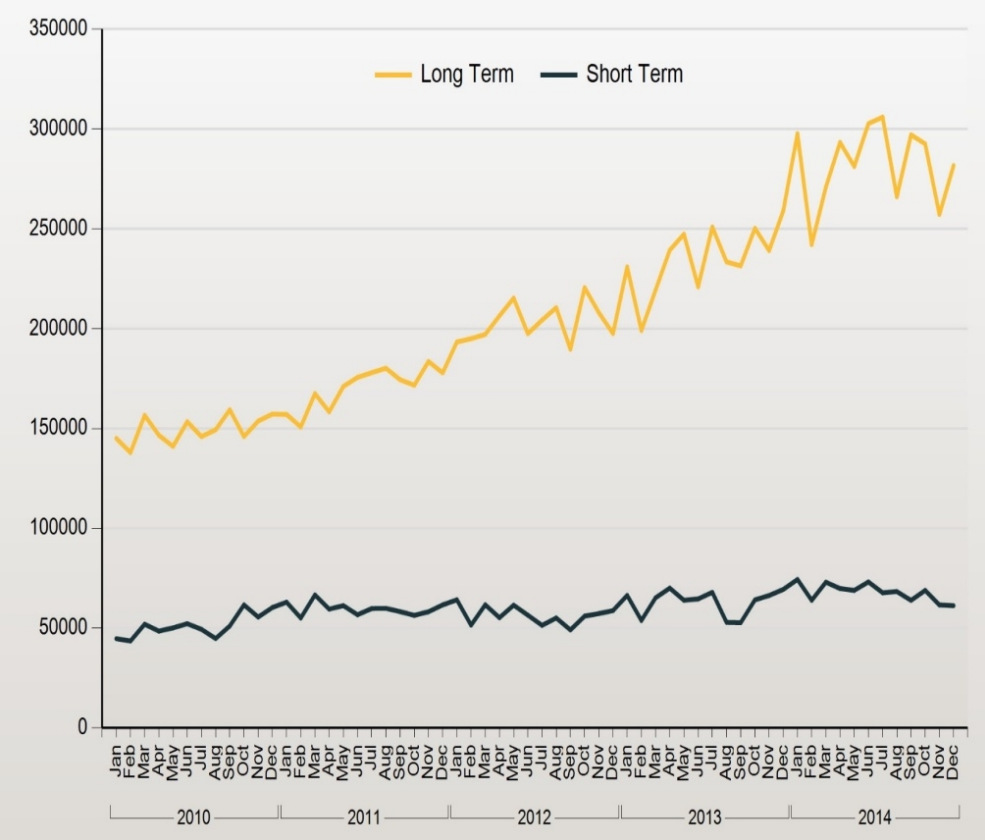
How much IVIG are the UK using?[1]

- Recorded grams of immunoglobulin/year

Year	Recorded grams
2010	2,410,367
2011	2,767,505
2012	3,128,858
2013	3,593,652
2014	4,230,904

£150.2m in 2014
~0.15% NHS annual budget

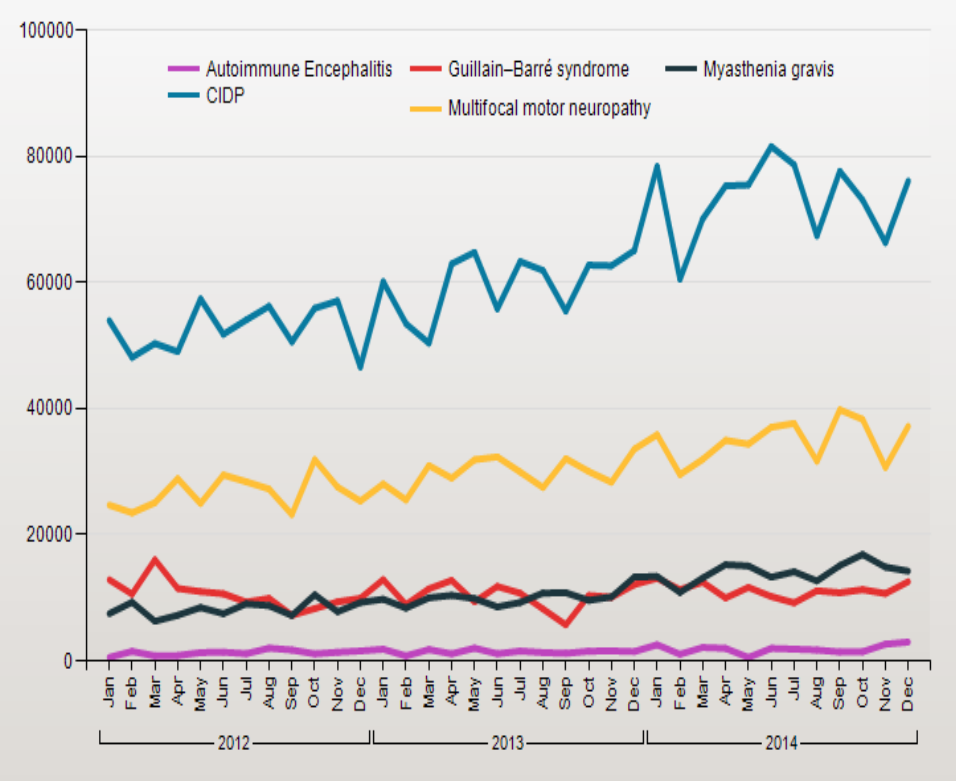
- Monthly immunoglobulin usage by regime



1. Data extracted from the National Immunoglobulin Database (UK). Available at: http://www.ivig.nhs.uk/ Accessed July 2015

Usage and diagnosis: IVIG in the UK[1]

- Monthly usage by diagnosis

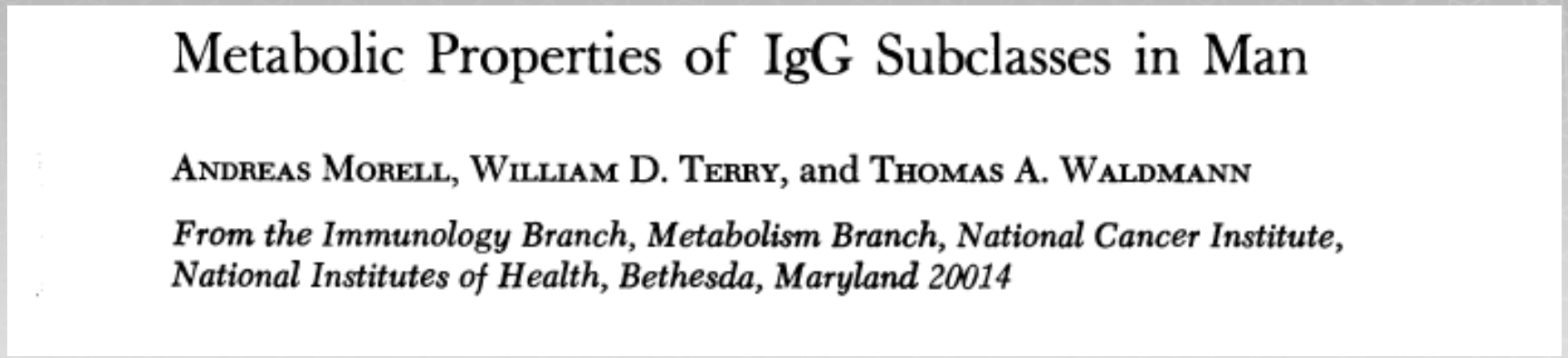


- Number of patients treated by year

Diagnosis	2011	2012	2013	2014
CIDP	914	1048	1175	1270
Guillain–Barré syndrome	700	789	815	819
Multifocal motor neuropathy	405	432	476	531
Myasthenia gravis	392	419	499	569
Autoimmune encephalitis	50	90	122	145

1. Data extracted from the National Immunoglobulin Database (UK). Available at: http://www.ivig.nhs.uk/ Accessed July 2015

Towards rational personalized dosing?



Metabolic Properties of IgG Subclasses in Man

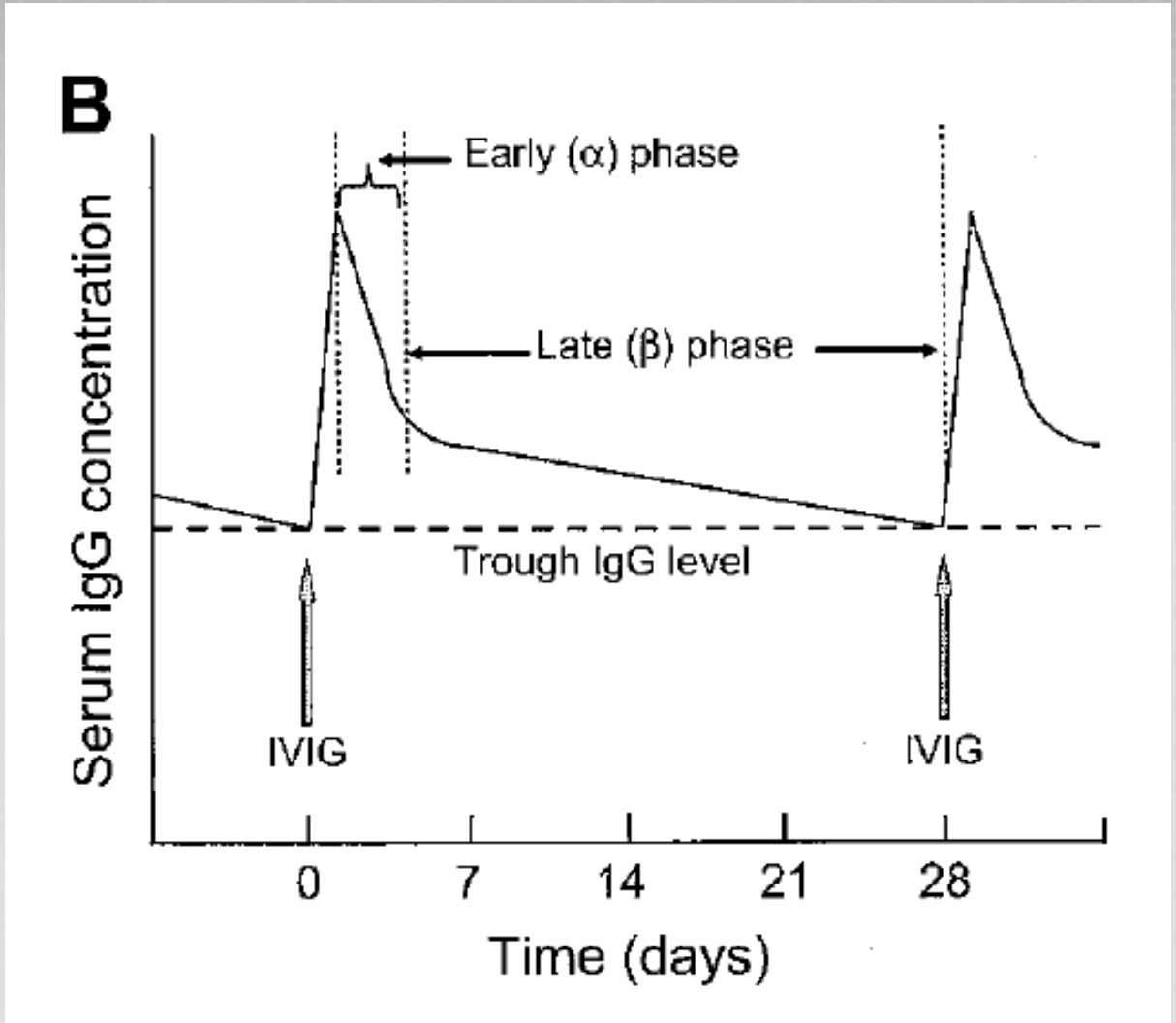
ANDREAS MORELL, WILLIAM D. TERRY, and THOMAS A. WALDMANN

From the Immunology Branch, Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

- Half-life of IgG varies from person to person and across subclasses[1]
  - IgG_1, IgG_2 and IgG_4: average biological half-life of 21 days
  - IgG_3: average biological half-life 7.1 days
- Half-life of IgM is much shorter
- Rational dosing period is within 6 to 9 weeks

1. Morell A et al. J Clin Invest 1970;49:673-80

Typical pharmacokinetic curve of IVIG[1]



1. Bonilla F. Immunol Allergy Clin North Am 2008;28:803-19

Adipose tissue also plays a role[1]

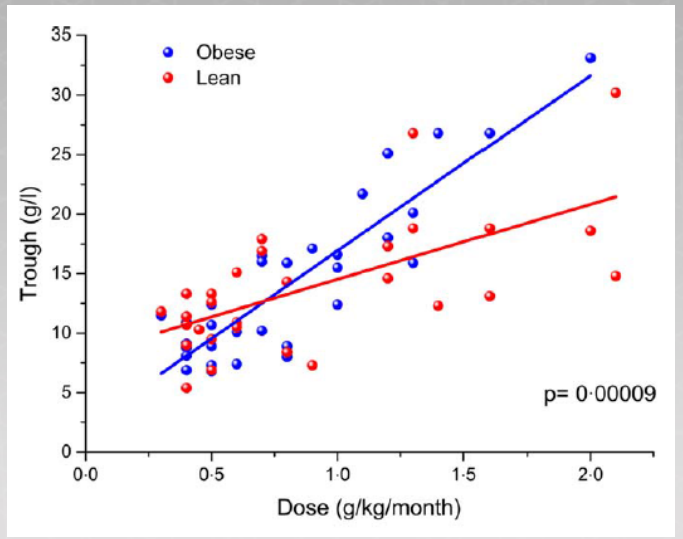
- IgG is a relatively polar molecule with a small volume of distribution (V_D)
- Adipose tissue is poorly perfused
  - Blood volume 2/3 per kg body weight (50 vs 75 ml/kg)
- FcRn expression may be lower in adipose tissue
- 31 obese-lean pairs were analyzed
  - Disease, age and sex matched
  - Lean BMI <30 kg/m^2: Obese BMI >30 kg/m^2
- Data were collected on patients who received Ig for:
  - PID (replacement therapy)
  - Autoimmune neurological conditions (immunomodulation)
- IgG trough, increment and efficiency were compared between patient subgroups as follows:
  - Lean/obese
  - Replacement/immunomodulation

BMI: Body mass index
PID: Primary immunodeficiencies

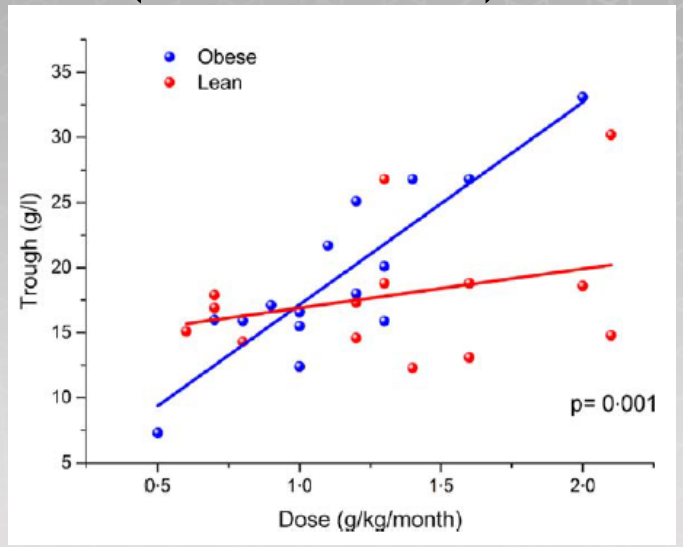
1. Hodkinson JP et al. Clin Exp Immunol 2015;181:179-87

Adipose tissue also plays a role (continued)[1]

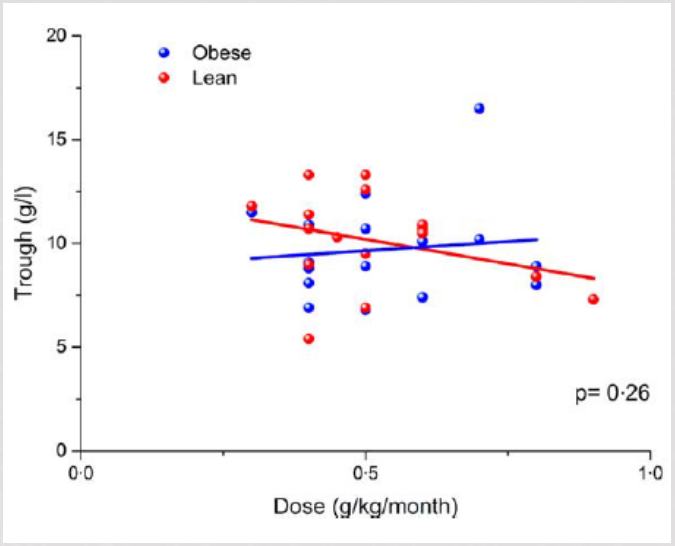
Replacement and immunomodulation



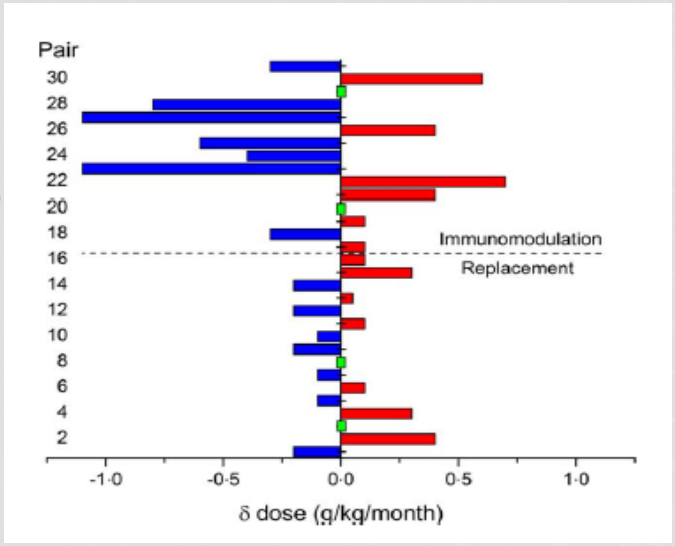
Immunomodulation



Replacement

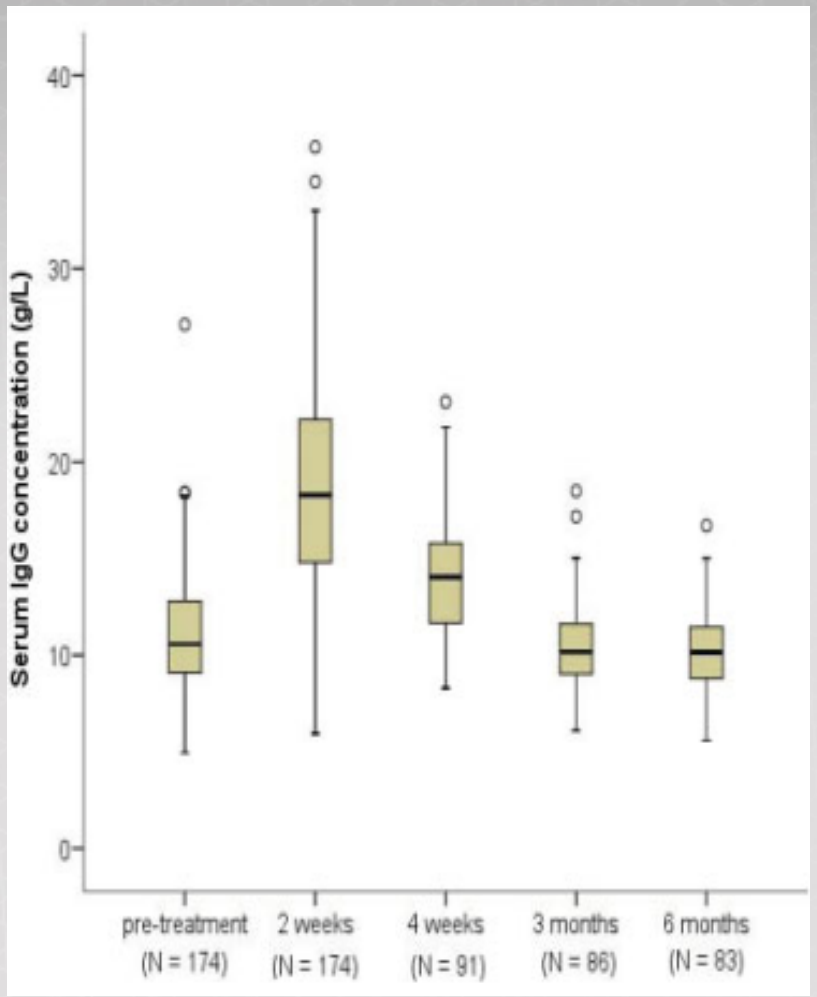


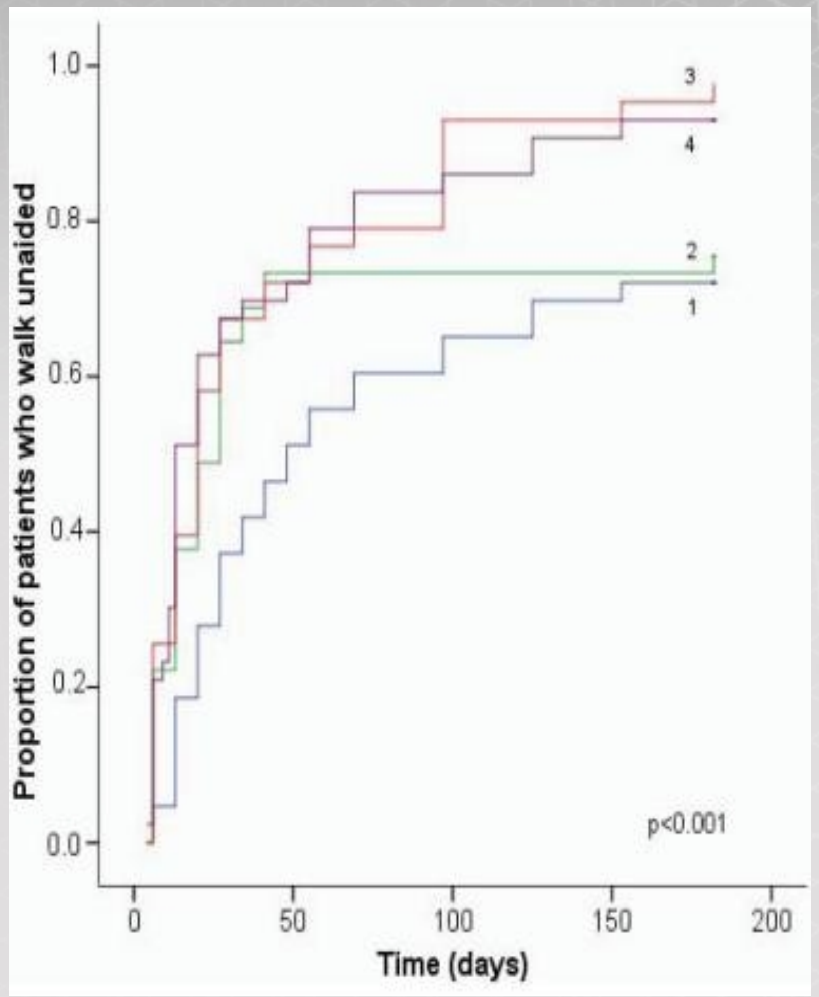
Ig dose required to achieve the desired clinical outcome in matched pairs



1. Hodkinson JP et al. Clin Exp Immunol 2015;181:179-87

Serum IgG levels and response in GBS[1]

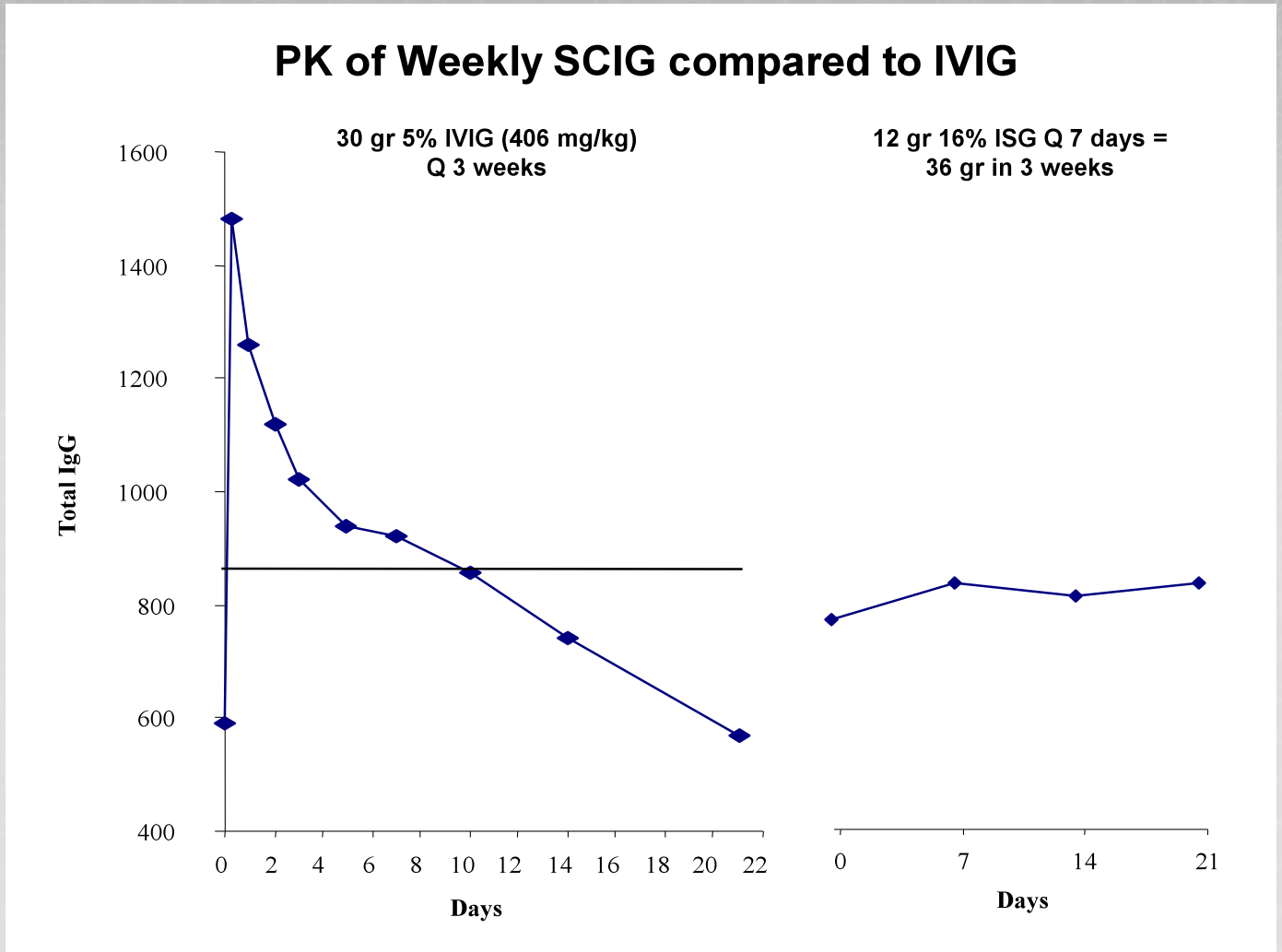




GBS: Guillain–Barré syndrome

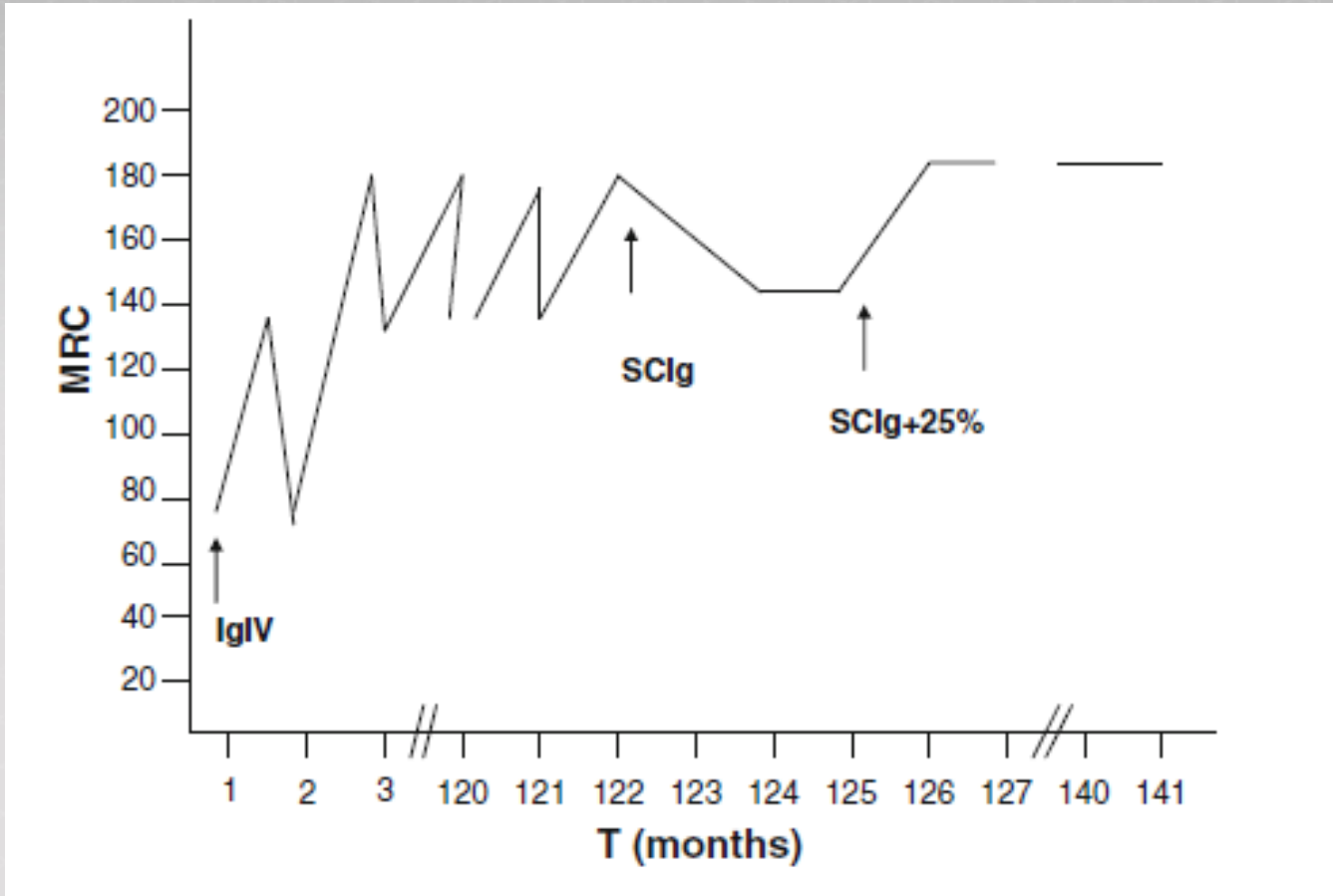
1. Kuitwaard K et al. Ann Neurol 2009;66:597-603

Weekly SCIG results in steady-state IgG: Levels out peak and trough of IVIG (case report)[1]



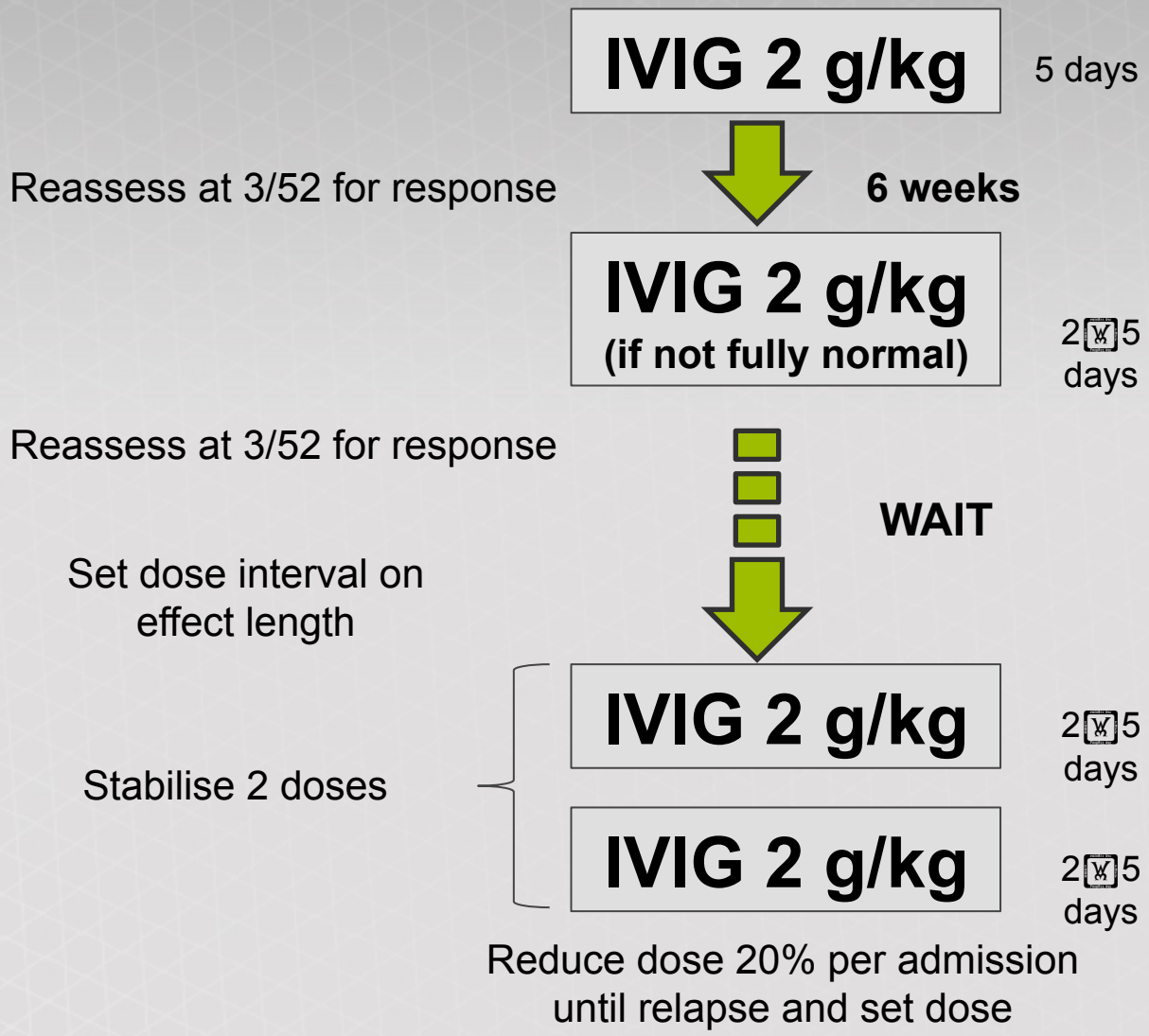
1. Berger M and Allen JA. Muscle Nerve 2015; 51:315-26

Response to IVIG and SCIG in MMN (case report)[1]



1. Dacci P et al. Neurol Sci 2010;31:829-31

Personal practice[1]



Initiate with education

Use the lowest dose possible

Reassess dose at least annually with withdrawal if necessary

IgG dependency?

1. Lunn M et al. J Peripher Nerv Syst 2015. *In press*

Dose modification: Factors for changing[1]

Factors	Modification
Age >60 and risk factors	Infusion duration
MMNCB vs CIDP	Interval modification
Headache ‘aseptic meningitis’	Dose and interval modification
Allergy	Piriton, hydrocortisone, alternative
Pompholyx	Usually nothing
Patient needs/request/convenience	

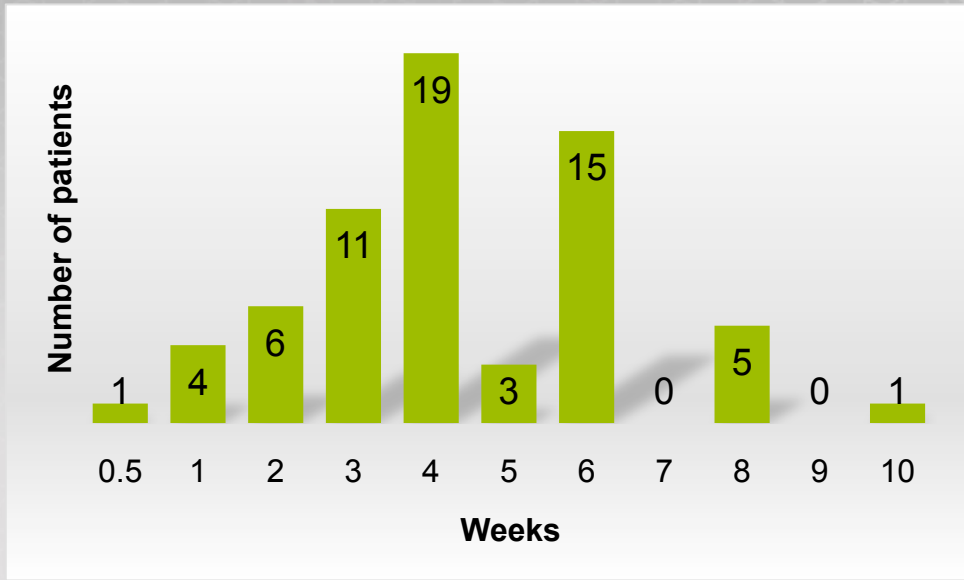
MMNCB: Multifocal motor neuropathy with persistent conduction blocks
CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy

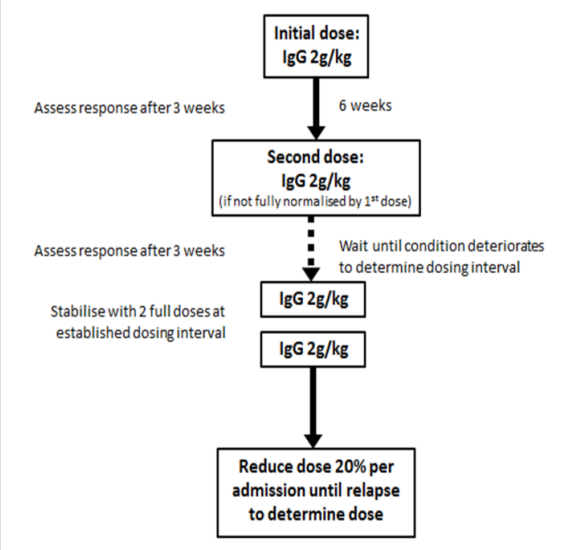
1. Lunn M et al. J Peripher Nerv Syst 2015. *In press*

Optimized dosing NHNN over 5 years[1]

Characteristic	Patients (n=71)
Gender	
Male	48 (67.6%)
Female	23 (32.4%)
Age (years)	56.9 ± 13.9
Weight (kg)	77.8 ± 16.6
Condition	
CIDP	39 (54.9%)
MMN	24 (33.8%)
Sensory ganglionopathy	3 (4.2%)
Chronic immune sensory polyradiculopathy	2 (2.8%)
Demyelinating neuropathy and IgM paraproteinaemic neuropathy	3 (4.2%)

NHNN: National Hospital for Neurology and Neurosurgery





1. Lunn M et al. J Peripher Nerv Syst 2015. *In press*

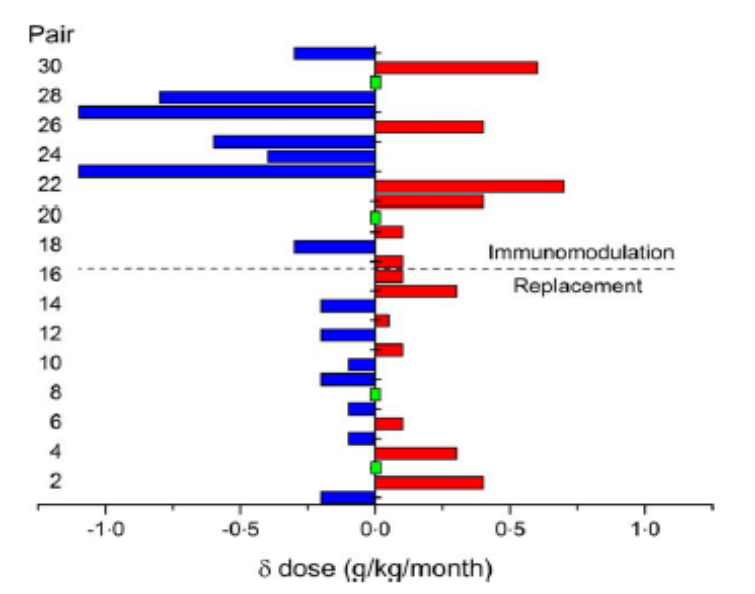
What does this translate to?[1]

- 9 brands of immunoglobulin were used in 71 patients
- At the date of data collection 63/71 patients were still receiving treatment
  - 8 patients eventually stopped
- 16.9% of the patients required *or received* IVIG at intervals of ≤2 weeks

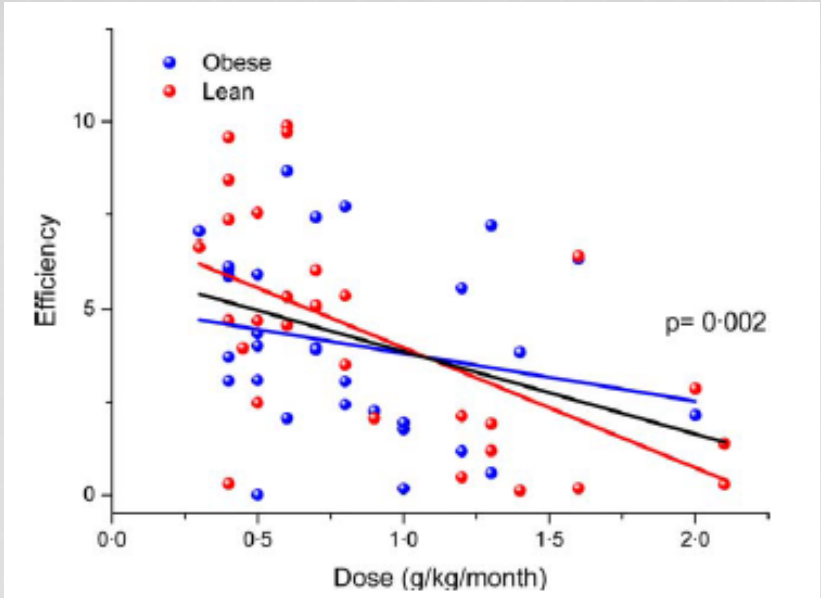
1. Lunn M et al. J Peripher Nerv Syst 2015. *In press*

Long-term IVIG treatment

- On stable long-term treatment, patients received 1.37 ± 0.56 g/kg per IVIG course[1]
- Mean dosing interval was 4.3 weeks (range 0.5–10 weeks)[1]
- Each treatment was administered over a median of 2 days (range 1–5 days) with a mean ± SD dose of 0.67 ± 0.32 g/kg/day[1]



- Obese patients more commonly receive a lower dose than non-obese patients, in an immunomodulation setting[2]



- Higher doses are less efficient in achieving Ig increments[2]
- Reduce and fractionate?

1. Lunn M et al. J Peripher Nerv Syst 2015. *In press*
2. Hodkinson JP et al. Clin Exp Immunol 2015;181:179-87

Cost comparison[1]

- Comparison with IVIG 2 g/kg every 6 weeks
  - IVIG cost reduced at NHNN from £3.40 million to £2.92 million per annum
  - Day case bed (chair) days drops from 3,074 to 2,325, (£768,500 to £581,000)
  - Best scenario optimization of doses maximally saves £661,415 per annum

1. Lunn M et al. J Peripher Nerv Syst 2015. *In press*

Summary

- IVIG pharmacokinetics are highly variable and dependent on a number of factors
- Rationale for dosing
- *An* (not the) algorithm that might be useful to patients, caregivers and policymakers