PolyNeuro exchange

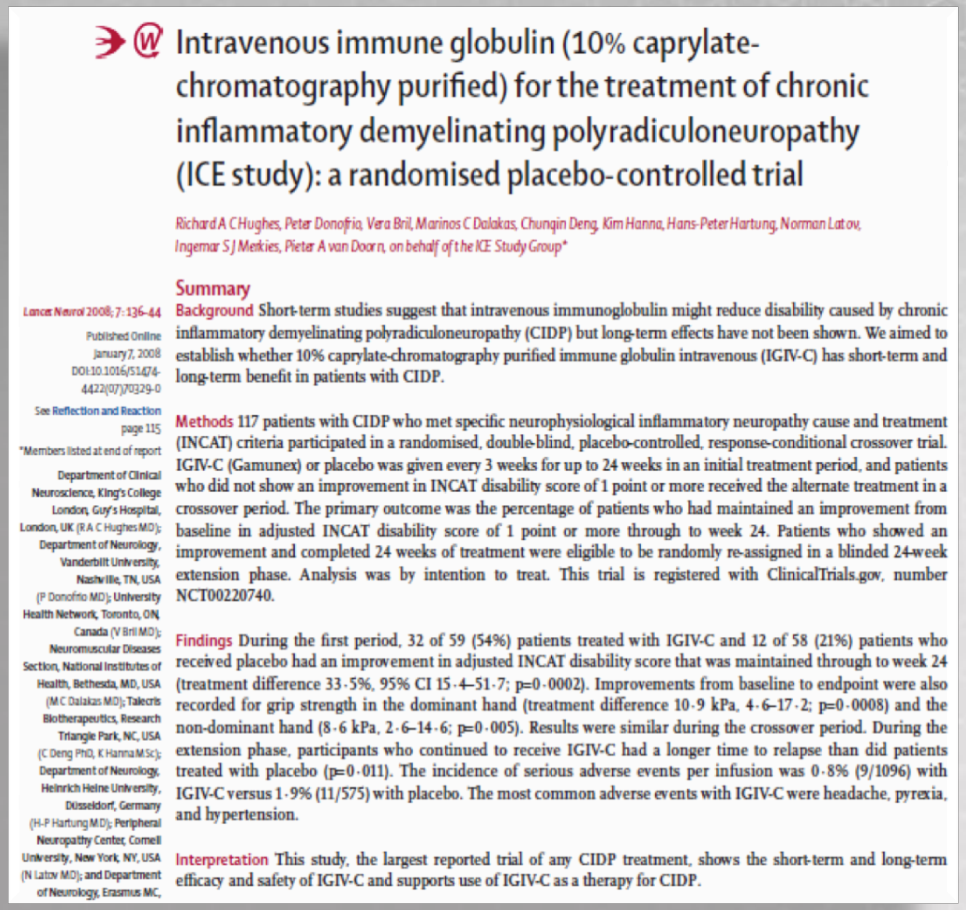
Optimizing IgG Therapy in Chronic Autoimmune Neuropathies

Treatment of inflammatory neuropathy with IVIG

- IVIG therapy is FDA-approved for CIDP and MMN[1]

ICE study[2]

- Loading dose: 2 g/kg bw
- Maintenance: 1 g/kg bw every 3 weeks
- 54% of IVIG group improved vs 21% of placebo group through week 24 (statistically significant)



Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial

Richard A C Hughes, Peter Donofrio, Vera Bril, Marinos C Dalakas, Chunqin Deng, Kim Hanna, Hans-Peter Hartung, Norman Latov, Ingemar S J Merkies, Pieter A van Doorn, on behalf of the ICE Study Group*

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See Reflection and Reaction page 115

*Members listed at end of report
Department of Clinical Neuroscience, King's College London, Guy's Hospital, London, UK (R A C Hughes MD); Department of Neurology, Vanderbilt University, Nashville, TN, USA (P Donofrio MD); University Health Network, Toronto, ON, Canada (V Bril MD); Neuromuscular Diseases Section, National Institutes of Health, Bethesda, MD, USA (M C Dalakas MD); Talecris Biotherapeutics, Research Triangle Park, NC, USA (C Deng PhD, K Hanna M Sc); Department of Neurology, Heinrich Heine University, Düsseldorf, Germany (H-P Hartung M D); Peripheral Neuropathy Center, Cornell University, New York, NY, USA (N Latov MD); and Department of Neurology, Erasmus MC,

Summary

Background Short-term studies suggest that intravenous immunoglobulin might reduce disability caused by chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) but long-term effects have not been shown. We aimed to establish whether 10% caprylate-chromatography purified immune globulin intravenous (IGIV-C) has short-term and long-term benefit in patients with CIDP.

Methods 117 patients with CIDP who met specific neurophysiological inflammatory neuropathy cause and treatment (INCAT) criteria participated in a randomised, double-blind, placebo-controlled, response-conditional crossover trial. IGIV-C (Gamunex) or placebo was given every 3 weeks for up to 24 weeks in an initial treatment period, and patients who did not show an improvement in INCAT disability score of 1 point or more received the alternate treatment in a crossover period. The primary outcome was the percentage of patients who had maintained an improvement from baseline in adjusted INCAT disability score of 1 point or more through to week 24. Patients who showed an improvement and completed 24 weeks of treatment were eligible to be randomly re-assigned in a blinded 24-week extension phase. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00220740.

Findings During the first period, 32 of 59 (54%) patients treated with IGIV-C and 12 of 58 (21%) patients who received placebo had an improvement in adjusted INCAT disability score that was maintained through to week 24 (treatment difference 33·5%, 95% CI 15·4–51·7; p=0·0002). Improvements from baseline to endpoint were also recorded for grip strength in the dominant hand (treatment difference 10·9 kPa, 4·6–17·2; p=0·0008) and the non-dominant hand (8·6 kPa, 2·6–14·6; p=0·005). Results were similar during the crossover period. During the extension phase, participants who continued to receive IGIV-C had a longer time to relapse than did patients treated with placebo (p=0·011). The incidence of serious adverse events per infusion was 0·8% (9/1096) with IGIV-C versus 1·9% (11/575) with placebo. The most common adverse events with IGIV-C were headache, pyrexia, and hypertension.

Interpretation This study, the largest reported trial of any CIDP treatment, shows the short-term and long-term efficacy and safety of IGIV-C and supports use of IGIV-C as a therapy for CIDP.

bw: bodyweight, CIDP: chronic inflammatory demyelinating polyneuropathy, FDA: Food and Drug Administration, IVIG: intravenous immunoglobulin, MMN: multifocal motor neuropathy

1. FDA Immune Globulin Intravenous Indications. Available at: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/ LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm. Accessed Mar 2016.
2. Hughes RAC *et al.* Lancet Neurol. 2008;7(2):136–144.

IVIG: How should we give it?

- The ICE study used 2 g/kg bw loading with 1 g/kg bw every 3 weeks maintenance

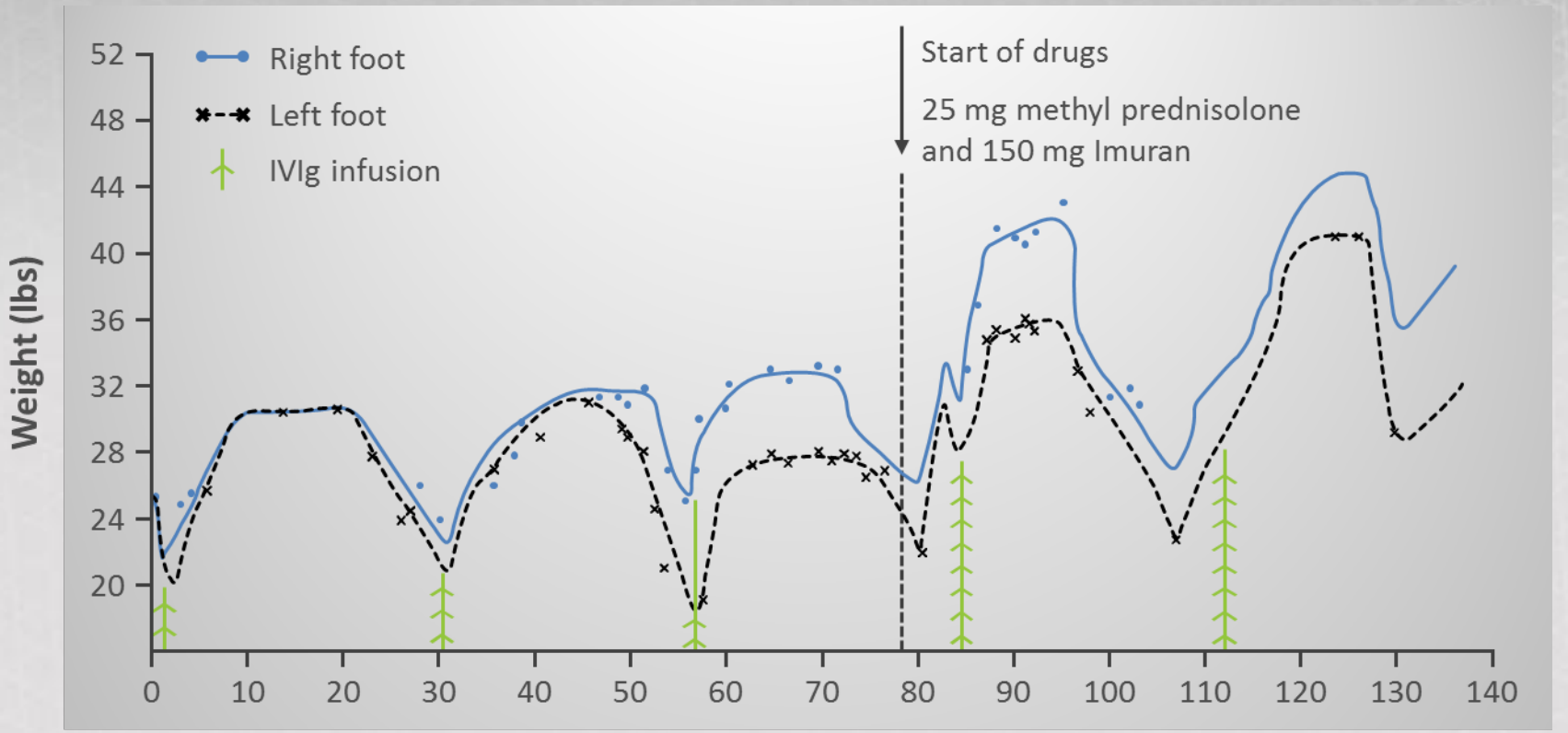
But…

- Prescribing patterns vary widely
- Efficacy of non-ICE trial regimens is unknown

Currently no IVIG dose trials
• Best loading dose? • Best maintenance dose? • Best dosing interval?

Patients are different
• IVIG pharmacokinetic variability • CIDP pathophysiology variability • Disease activity variability

IVIG treatment-related fluctuations: Wear-off[1]

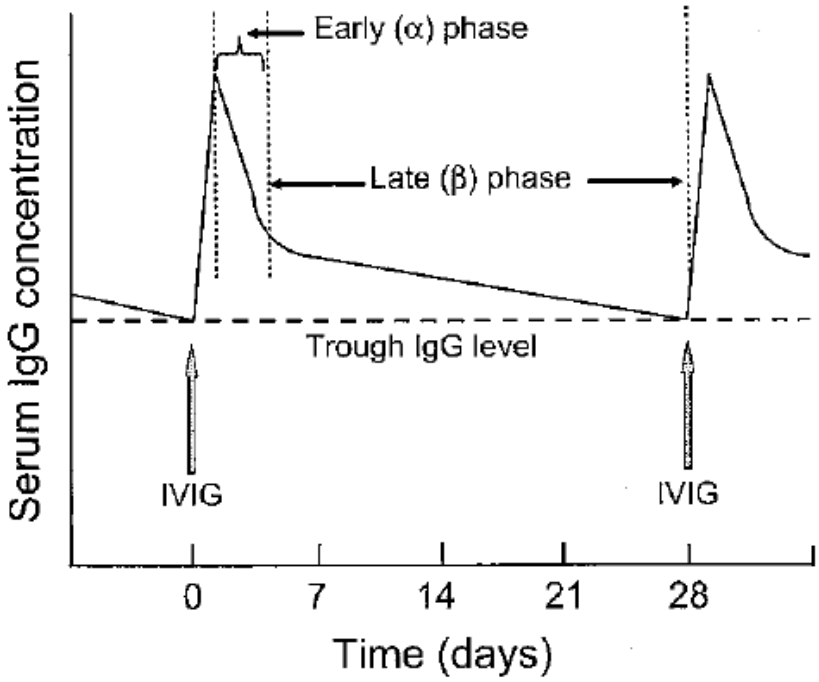


1. Pollard JD, Armati PJ. J Peripher Nerv Syst. 2011;16(1):15–23.

Pharmacokinetics of IVIG

- Infusion of 2 g/kg bw IVIG increases serum IgG level >4 fold[1]
  - Pretreatment means of 700–1,060 mg/dL to peaks of >3,000 mg/dL[1,2]
- Serum IgG level drops by approx. 50% over 48–72 hours[2,3]
  - IgG is distributed into total extracellular fluid volume,[4,5] which is about double the intravascular volume[2]
- After rapid equilibration, IgG is catabolized with first-order kinetics and a half-life of 21–30 days[2,5]

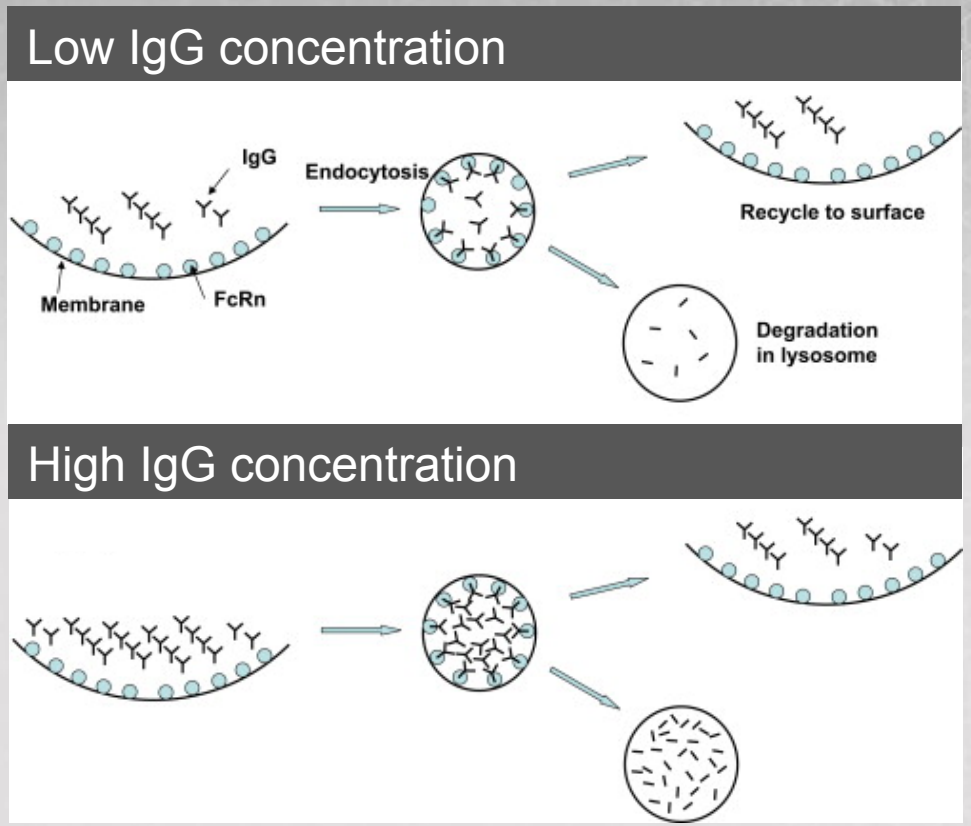
Typical pharmacokinetic curve of IVIG[5]



1. Reinhart WH, Berchtold PE. Lancet. 1992;339(8794):662–664.
2. Berger M, Allen JA. Muscle Nerve. 2015;51(3):315–326.
3. Pirofsky B. Am J Med. 1984;30,76(3A):53–60.
4. Waldmann TA, Strober W. Prog Allergy. 1969;13:1–110.
5. Bonilla FA. Immunol Allergy Clin North Am. 2008;28(4):803–819.

Pharmacokinetics of IVIG

- IgG catabolism is slow[1]
  - Saturable endothelial cell receptor, FcRn, protects IgG from lysosomal degradation[2]
- FcRn receptor saturation with exogenous IVIG keeps endogenous pathologic IgG from recycling and increases its degradation[1,3]



This is likely to be an important concentration-dependent mechanism by which IVIG can compete with autoantibodies without affecting their production

FcRn: neonatal Fc (Fragment crystallizable) receptor

1. Bonilla FA. Immunol Allergy Clin North Am. 2008;28(4):803–819.
2. Yu Z, Lennon VA. N Engl J Med. 1999;340(3):227–228.
3. Roopenian DC, Akilesh S. Nat Rev Immunol. 2007;7(9):715–725.

Other dosing considerations

- Pharmacodynamic variability[1]
  - FcRn receptor expression
  - IVIG treatment naïve
  - Chronic Ig exposure
- CIDP immunopathology variability[2]
  - Myelin vs axon vs nodal dysfunction
- Disease activity (severity) variability[3]

The optimal IVIG dose and treatment interval required to achieve and maintain maximum benefit is unknown but is likely variable between individuals… and perhaps in a single individual at different disease stages

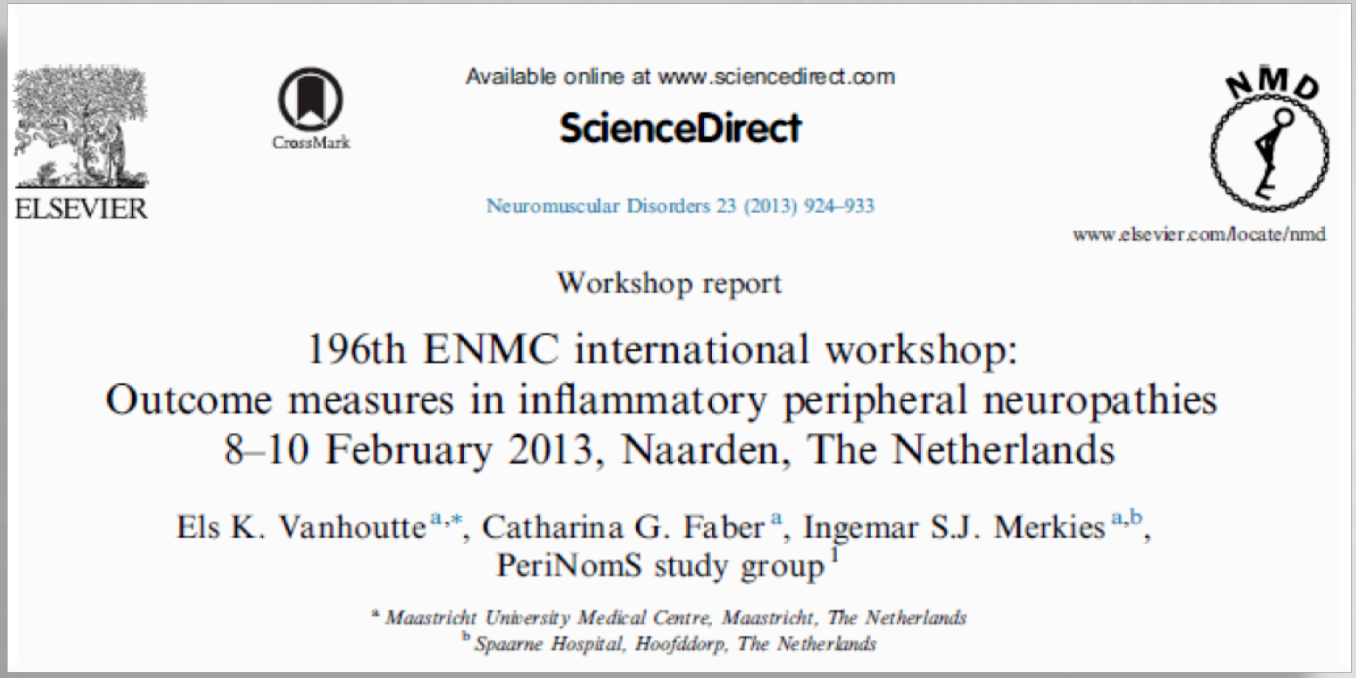
1. Kuitwaard K *et al.* J Neurol Neurosurg Psychiatry. 2013;84(8):859–861.
2. Dalakas MC. Biochim Biophys Acta. 2014;1852(4):658[illegible]66.
3. Kuitwaard K *et al.* Ann Neurol. 2009;66(5):597–603.

How do we individualize treatment?

How do we individualize treatment?

- The following needs to be assessed:
  - Is our treatment working?
  - Is our treatment working because the neuropathy is better?

Assessment of neurological outcomes



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Neuromuscular Disorders 23 (2013) 924–933

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Workshop report

196th ENMC international workshop: Outcome measures in inflammatory peripheral neuropathies 8–10 February 2013, Naarden, The Netherlands

Els K. Vanhoutte[a,*], Catharina G. Faber[a], Ingemar S.J. Merkies[a,b], PeriNomS study group[1]

[a] *Maastricht University Medical Centre, Maastricht, The Netherlands*
[b] *Spaarne Hospital, Hoofddorp, The Netherlands*

Table 1
Overview of the minimum core set, recommendations, and future needs.

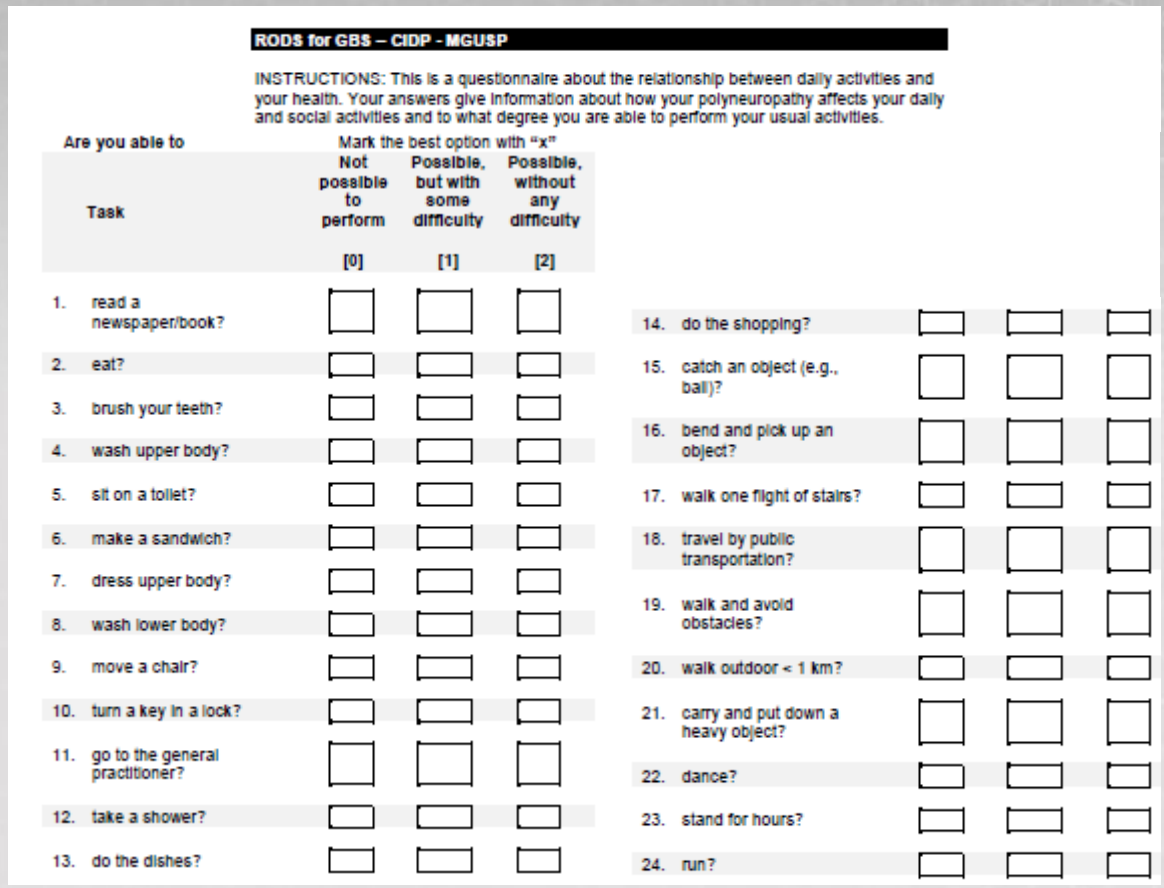
	GBS	CIDP	MMN	MGUSP
Minimal core set				
Impairment level	Martin Vigorimeter RT-mISS Being ventilated (Y/N) Duration of ventilation	Martin Vigorimeter RT-mISS 'Manual muscle testing'	Martin Vigorimeter Patient-specific muscle testing RT-MRC scores	Not yet defined; further study required
Activity and participation level	R-ODS GBS disability scale	R-ODS Original INCAT disability score	R-ODS MMN	See above
Quality of life level	–	5-PGIC SF-36	RT-QoL scale	See above
Recommendations				
Impairment level	RT-MRCss Original MRCss RT-FSS	11-PI-NRS RT-FSS	–	RT-mISS
Activity and participation level		–	–	R-ODS Original INCAT 10-point
Quality of life level		–	–	PGIC SF36 or Euro-QoL
Future needs				
Impairment level	Pain Muscle dynamometer/RT-MRCss	RT-MRCss Pain Walking test	–	Define core set Pain Ataxia Tremor 9-hole PEG test
Activity and participation level	Cross-cultural R-ODS	Cross-cultural R-ODS	Expanding the R-ODS	Define core set
Quality of life level	RT-QoL scale	RT-QoL scale	RT-QoL scale	RT-QoL scale

RT, Rasch transformed; mISS, modified INCAT sensory sumscore; R-ODS, Rasch-built overall disability scale; MRCss, Medical Research Council sum score; FSS, fatigue severity scale; 5-PGIC, 5-points patient global impression of change; 11-PI-NRS, 11-point pain-intensity numerical rating scale; QoL, quality of life.

Vanhoutte EK *et al.* Neuromuscul Disord. 2013;23(11):924–933.

RODS disability score[1–3]

- Developed for patients with inflammatory neuropathies
- Captures clinically meaningful changes over time
- May be a good way to define a patient as a treatment responder
- Completed in 2–3 minutes



RODS for GBS – CIDP - MGUSP

INSTRUCTIONS: This is a questionnaire about the relationship between daily activities and your health. Your answers give information about how your polyneuropathy affects your daily and social activities and to what degree you are able to perform your usual activities.

Are you able to — Mark the best option with "x"

Task	Not possible to perform [0]	Possible, but with some difficulty [1]	Possible, without any difficulty [2]
1. read a newspaper/book?	☐	☐	☐
2. eat?	☐	☐	☐
3. brush your teeth?	☐	☐	☐
4. wash upper body?	☐	☐	☐
5. sit on a toilet?	☐	☐	☐
6. make a sandwich?	☐	☐	☐
7. dress upper body?	☐	☐	☐
8. wash lower body?	☐	☐	☐
9. move a chair?	☐	☐	☐
10. turn a key in a lock?	☐	☐	☐
11. go to the general practitioner?	☐	☐	☐
12. take a shower?	☐	☐	☐
13. do the dishes?	☐	☐	☐
14. do the shopping?	☐	☐	☐
15. catch an object (e.g., ball)?	☐	☐	☐
16. bend and pick up an object?	☐	☐	☐
17. walk one flight of stairs?	☐	☐	☐
18. travel by public transportation?	☐	☐	☐
19. walk and avoid obstacles?	☐	☐	☐
20. walk outdoor < 1 km?	☐	☐	☐
21. carry and put down a heavy object?	☐	☐	☐
22. dance?	☐	☐	☐
23. stand for hours?	☐	☐	☐
24. run?	☐	☐	☐

GBS: Guillain-Barré syndrome, RODS: Rasch-built Overall Disability Scale, MGSUP: monoclonal gammopathy of undetermined significance related polyneuropathy

1. Draak TH *et al.* Neurology. 2014;2;83(23):2124–2132.
2. van Nes SI *et al.* Neurology. 2011;25;76(4):337–345.
3. RODS for GBS-CIDP. Available at: http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/peripheral_nerve/patient_info/RODS%20for%20GBS-CIDP%202.pdf. Accessed Mar 2016.

Grip strength measurements[1–3]

Martin Vigorimeter[1]

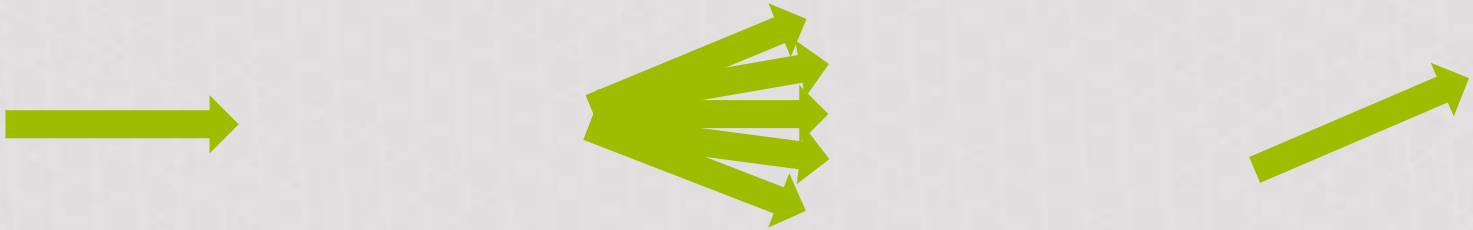
Jamar Dynamometer[2]

- Grip strength is a sensitive tool for assessing clinically relevant changes in patients with CIDP
- Reliable measure of global strength in CIDP, not limited to upper limb or exclusively motor function
- It is not a time consuming procedure

1. Vanhoutte EK *et al.* Eur J Neurol. 2013;20(5):748–755.
2. Draak TH *et al.* Neurology. 2014;2;83(23):2124–2132.
3. Rajabally YA, Narasimhan M. J Neurol Sci. 2013;325(1-2):36–38.

A pathway to dose optimization

ICE study	Factors influencing treatment	Re-directing course
• Loading dose: 2 g/kg bw • Maintenance dose: 1 g/kg every 3 weeks	• Pharmacodynamics • Immunopathology • Disease activity	• RODS • Grip strength
At this dose 54% of patients improved	**Optimal dose to achieve and maintain maximum benefit is likely variable**	**Disease specific outcome measures to document treatment response or non-response**



An evidence based place to start	Understand the factors influencing treatment	Treatment guided by patient-specific measures of benefit

An approach to optimize IVIG during the treatment of CIDP

Collect baseline RODS and grip strength measurements along with assessments typical of the neurologic examination

Discuss the objective of treatment with patients

Load IVIG: 2 g/kg bw over 2–5 consecutive days[1]
Maintenance IVIG: 1 g/kg over 1–2 days every 3 weeks[1]

Reassess neurologic examination, RODS, and grip strength at 1 and 3 months

- If no objective improvement by 3 months, stop IVIG
  - Patients that respond to IVIG usually do so by the third infusion
  - If no improvement, refer to neuromuscular specialist for reconsideration of diagnosis and treatment
- If clear sustained improvement at 3 months, begin IVIG taper once improvement plateaus
  - 13–30% of patients require only a single course of IVIG[2,3]
- If there is improvement but it is not sustained through the infusion cycle (wear-off), shorten the infusion interval
  - 20%–60% of patients might benefit with dosing intervals <15 days[4,5]

1. Hughes RAC *et al.* Lancet Neurol. 2008(2);7:136–144.
2. Van den Bergh PY *et al.* Eur J Neurol. 2010;17(3):356–363.
3. Rajabally YA. Muscle Nerve. 2015;51(5):657–661.
4. Rajabally YA *et al.* J Neurol. 2013;260(8):2052–2056.
5. Kuitwaard K *et al.* J Neurol Neurosurg Psychiatry. 2013;84(8):859–861.

An approach to optimize IVIG during the treatment of CIDP

During IVIG taper, periodically reassess examination, RODS, grip strength

- Spread infusion interval to 4 weeks, then 5 weeks, then 6 weeks over several months
- Decrease dose by 20% each month over several months
  - If objective decline or if clinically relevant wear-off emerges then hold dose at lowest effective dose

During IVIG escalation, periodically reassess exam, RODS, grip strength

- Shorten infusion interval to 2 weeks or even 1 week
- Increase dose by 20% each month over several months
  - If objective stabilization or if clinically relevant wear off resolves then hold dose at lowest effective dose

During stable maintenance IVIG escalation, periodically reassess

- Repeat dose reduction or dose escalation trials at 6 month intervals to continually assess the need for ongoing treatment and individualized dosing optimization

If frequent high dose or long-term IVIG is required, then subspecialty neuromuscular consultation for consideration of other treatment approaches should be considered

- Corticosteroid and plasma exchange efficacy is documented[1,2]
- Efficacy of all other immunosuppressant agents is not documented[3]

1. Mehndiratta MM *et al*. Cochrane Database Syst Rev. 2015;8:CD003906.
2. Dyck PJ *et al.* Ann Neurol. 1982;11(2):136–141.
3. Mahdi-Rogers M *et al.* Cochrane Database Syst Rev. 2013;6:CD003280.

Optimization limitations

- No “best” way to optimize
- No IVIG dosing trials
- Does not account for the role of corticosteroids as first-line treatment