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)

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

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

<table>
<thead>
<tr>
<th>Currently no IVIG dose trials</th>
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<tbody>
<tr>
<td>• Best loading dose?</td>
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<td>• Best maintenance dose?</td>
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<td>• Best dosing interval?</td>
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<th>Patients are different</th>
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<tr>
<td>• IVIG pharmacokinetic variability</td>
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<tr>
<td>• CIDP pathophysiology variability</td>
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<td>• Disease activity variability</td>
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IVIG treatment-related fluctuations: Wear-off

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\(^2,5\)

Pharmacokinetics of IVIG

- IgG catabolism is slow\textsuperscript{1}  
  - Saturable endothelial cell receptor, FcRn, protects IgG from lysosomal degradation\textsuperscript{2}

- FcRn receptor saturation with exogenous IVIG keeps endogenous pathologic IgG from recycling and increases its degradation\textsuperscript{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

Other dosing considerations

- Pharmacodynamic variability¹
  - FcRn receptor expression
  - IVIG treatment naïve
  - Chronic Ig exposure
- CIDP immunopathology variability²
  - Myelin vs axon vs nodal dysfunction
- Disease activity (severity) variability³

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

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

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

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<th>Table 1</th>
<th>Overview of the minimum core set, recommendations, and future needs.</th>
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<td>GBS</td>
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<td><strong>Minimal core set</strong></td>
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<td>Impairment level</td>
<td>Martin Vigorimeter</td>
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<td>RT-mISS</td>
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<td>Being ventilated (Y/N)</td>
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<td>Duration of ventilation</td>
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<td>R-ODS</td>
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<td>GBS disability scale</td>
<td>Original INCAT disability score</td>
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<td>Quality of life level</td>
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<td><strong>Recommendations</strong></td>
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<td>RT-MRCss</td>
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<td><strong>Future needs</strong></td>
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<td>Muscle dynamometer/RT-MRCss</td>
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<td>Walking test</td>
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<td>Activity and participation level</td>
<td>Cross-cultural R-ODS</td>
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<td>Quality of life level</td>
<td>RT-QoL scale</td>
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</table>

RT, Rasch transformed; mISS, modified INCAT sensory sum score; 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.
RODS disability score\textsuperscript{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

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

Grip strength measurements

- 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

### A pathway to dose optimization

<table>
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<tr>
<th>ICE study</th>
<th>Factors influencing treatment</th>
<th>Re-directing course</th>
</tr>
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</table>
| • 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

Maintenance IVIG: 1 g/kg over 1–2 days every 3 weeks

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
- 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

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\(^3\)

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Optimization limitations

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