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 is health care that tailors interventions to individual variation in risk and treatment response.”

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

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\textsuperscript{5,6} is of interest and is being explored further. At present, however, this must be considered experimental.


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

Gugler E. Die kindlichen Thrombopenien²

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 \( \times \) 10^9/l

HIGH-DOSE INTRAVENOUS GAMMAGLOBULIN FOR IDIOPATHIC THROMBOCYTOPENIC PURPURA IN CHILDHOOD¹

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IVIG in CIDP Efficacy Study (ICE)

- Results of the ICE Study 2008:
  - 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

British Peripheral Nerve Society
IVIG usage in CIDP survey 2014¹

• 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

Individually optimized therapy frequently requires dosing more often than monthly

- Conclusion drawn from data obtained in several studies

- Rajabally\(^1\)
  - Interval increase and dose reduction
  - 3/15 (47%, \(\leq\) 21 Days)

- Broyles\(^2\)
  - Pharmacy records
  - Unclear/heterogeneous method
  - 13/46

- Kuitwaard\(^3\)
  - Dose increase and interval reduction
  - 15/25

Percent of patients receiving IVIG at interval \(\leq 15\) days

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1. Rajabally YA et al. J Neurol 2013;260:2052-6
How much IVIG are the UK using?¹

- Recorded grams of immunoglobulin/year

<table>
<thead>
<tr>
<th>Year</th>
<th>Recorded grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>2,410,367</td>
</tr>
<tr>
<td>2011</td>
<td>2,767,505</td>
</tr>
<tr>
<td>2012</td>
<td>3,128,858</td>
</tr>
<tr>
<td>2013</td>
<td>3,593,652</td>
</tr>
<tr>
<td>2014</td>
<td>4,230,904</td>
</tr>
</tbody>
</table>

- Monthly immunoglobulin usage by regime

£150.2m in 2014
~0.15% NHS annual budget

Usage and diagnosis: IVIG in the UK

- Monthly usage by diagnosis
- Number of patients treated by year

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

Towards rational personalized dosing?

- Half-life of IgG varies from person to person and across subclasses:
  - IgG₁, IgG₂ and IgG₄: average biological half-life of 21 days
  - IgG₃: average biological half-life 7.1 days

- Half-life of IgM is much shorter
- Rational dosing period is within 6 to 9 weeks

Typical pharmacokinetic curve of IVIG\textsuperscript{1}

Adipose tissue also plays a role

- 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

Adipose tissue also plays a role (continued)\(^1\)

Serum IgG levels and response in GBS

GBS: Guillain-Barré syndrome

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

PK of Weekly SCIG compared to IVIG

- 30 gr 5% IVIG (406 mg/kg) Q 3 weeks
- 12 gr 16% ISG Q 7 days = 36 gr in 3 weeks

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

### Dose modification: Factors for changing

<table>
<thead>
<tr>
<th>Factors</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 and risk factors</td>
<td>Infusion duration</td>
</tr>
<tr>
<td>MMNCB vs CIDP</td>
<td>Interval modification</td>
</tr>
<tr>
<td>Headache ‘aseptic meningitis’</td>
<td>Dose and interval modification</td>
</tr>
<tr>
<td>Allergy</td>
<td>Piriton, hydrocortisone, alternative</td>
</tr>
<tr>
<td>Pompholyx</td>
<td>Usually nothing</td>
</tr>
<tr>
<td>Patient needs/request/convenience</td>
<td></td>
</tr>
</tbody>
</table>

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

Optimized dosing NHNN over 5 years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (67.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (32.4%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>56.9 ± 13.9</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>77.8 ± 16.6</td>
</tr>
<tr>
<td><strong>Condition</strong></td>
<td></td>
</tr>
<tr>
<td>CIDP</td>
<td>39 (54.9%)</td>
</tr>
<tr>
<td>MMN</td>
<td>24 (33.8%)</td>
</tr>
<tr>
<td>Sensory ganglionopathy</td>
<td>3 (4.2%)</td>
</tr>
<tr>
<td>Chronic immune sensory</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Polyradiculopathy</td>
<td></td>
</tr>
<tr>
<td>Demyelinating</td>
<td>3 (4.2%)</td>
</tr>
<tr>
<td>Neuropathy and IgM</td>
<td></td>
</tr>
<tr>
<td>Paraproteinaemic neuropathy</td>
<td></td>
</tr>
</tbody>
</table>

NHNN: National Hospital for Neurology and Neurosurgery

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

Long-term IVIG treatment

- On stable long-term treatment, patients received $1.37 \pm 0.56$ 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 $0.67 \pm 0.32$ 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?

Cost comparison

• 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

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