The Use of IVIG and SCIG in Neurology Patients

Vera Bril, MD
ORBCoN Spring Symposium
April 24, 2015
<table>
<thead>
<tr>
<th>Neurological Condition</th>
<th>Recommendation</th>
<th>Dose/Frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)</td>
<td><strong>Acute CIDP:</strong> IVIG is recommended for short-term management of new-onset CIDP or CIDP relapses. <strong>Chronic CIDP:</strong> IVIG may be considered in combination with other immunosuppressive therapy for the long-term management of CIDP.</td>
<td><em>Initial treatment:</em> Total dose of 2 g/kg divided over 2 to 5 days. <em>Maintenance therapy:</em> a systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. Maximum dose per treatment course should not exceed 2g/kg.</td>
</tr>
<tr>
<td>Guillain-Barré Syndrome (GBS) including Miller-Fisher syndrome and other variants</td>
<td>IVIG is recommended for symptoms of grade 3 severity (able to walk with aid) or greater; or symptoms less than grade 3 severity that are progressing. Treatment should be given within 2 weeks of symptom onset.</td>
<td>Adult: Total dose of 2 g/kg divided over 2 to 5 days. Pediatric: Total dose of 2 g/kg divided over 2 days.</td>
</tr>
<tr>
<td>Multifocal motor neuropathy (MMN)</td>
<td>IVIG is recommended as first-line treatment of for MMN.</td>
<td><em>Initial treatment:</em> Total dose of 2 g/kg divided over 2 to 5 days. <em>Maintenance therapy:</em> tailor to the lowest dose that maintains clinical efficacy, usually 1 g/kg or less per treatment course.</td>
</tr>
<tr>
<td>Myasthenia gravis (MG)</td>
<td>IVIG recommended for severe exacerbations of myasthenia gravis or myasthenic crises. IVIG is not recommended for patients with chronic MG.</td>
<td>Total dose of 2 g/kg divided over 2 to 5 days. If additional therapy is required, the dose should be adjusted depending upon response and titrated to the minimum effective dose.</td>
</tr>
<tr>
<td>Neurological Condition</td>
<td>Recommendation</td>
<td>Dose/Frequency of Administration</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis2,4 (ADEM)</td>
<td>IVIG is an option for monophasic ADEM when first-line therapy with high-dose corticosteroids fails or when there are contraindications to steroid use, and for treatment of relapsing ADEM to eliminate steroid dependency or for those patients who fail to respond, or have contraindications, to steroids.</td>
<td>Adults: Total dose of 2 g/kg divided over 2 to 5 days. Pediatric: Total dose of 2 g/kg divided over 2 days.</td>
</tr>
<tr>
<td>Lambert-Eaton Myasthenic Syndrome2,4 (LEMS)</td>
<td>IVIG is an option for treatment of LEMS. Objective evidence of clinical improvement is needed for sustained use of IVIG.</td>
<td>Initial treatment: Total dose of 2 g/kg divided over 2 to 5 days. Maintenance therapy: a systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. The maximum dose of IVIG per treatment course should be 2 g/kg.</td>
</tr>
<tr>
<td>Multiple sclerosis2,3 (MS)</td>
<td>IVIG is an option for treatment of patients with relapsing-remitting MS who fail, decline, or are not able to take standard immunomodulatory drug therapies.</td>
<td>1 g/kg monthly with or without a 5 day induction of 0.4 g/kg daily.</td>
</tr>
<tr>
<td>Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections2,4 (PANDAS)</td>
<td>IVIG is an option for treatment of patients with PANDAS. Diagnosis of PANDAS requires expert consultation.</td>
<td>Total dose of 2 g/kg divided over 2 days is recommended as a reasonable option.</td>
</tr>
<tr>
<td>Neurological Condition</td>
<td>Recommendation</td>
<td>Dose/Frequency of Administration</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Polymyositis2</td>
<td>IVIG may be considered as an option for patients with polymyositis who fail to respond to first-line therapies (e.g., steroids).</td>
<td><strong>Initial treatment:</strong> Total dose of 2 g/kg divided over 2 to 5 days. <strong>Maintenance therapy:</strong> A systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. Maximum dose of IVIG per treatment course should be 2 g/kg.</td>
</tr>
<tr>
<td>Rasmussen’s encephalitis(^{2,4})</td>
<td>IVIG is an option as a short-term, temporizing measure for patients with Rasmussen’s encephalitis. Not recommended for long-term therapy.</td>
<td><strong>Adults:</strong> Total dose of 2 g/kg divided over 2 to 5 days. <strong>Pediatric:</strong> Total dose of 2 g/kg divided over 2 days.</td>
</tr>
<tr>
<td>Stiff Person’s syndrome(^{2,4})</td>
<td>IVIG is an option for treatment of Stiff Person syndrome if gabaergic medications fail or for patients who have contraindications to gabaergic medications.</td>
<td><strong>Initial treatment:</strong> Adults: Total dose of 2 g/kg divided over 2 to 5 days. <strong>Pediatric:</strong> Total dose of 2 g/kg divided over 2 days. <strong>Maintenance therapy:</strong> A systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. Maximum dose of IVIG per treatment course should be 2 g/kg.</td>
</tr>
</tbody>
</table>
Lack of Evidence

- IgM paraprotein-associated PNP
- IBM
- Post-polio syndrome
- Diabetic radiculoplexus neuropathy
- Polymyositis

Negative Trials

- Alzheimer’s disease
- Inclusion Body Myositis
- Multiple Sclerosis
  - Chronic progressive
  - Remitting - relapsing
Challenges In MG Research

• Rare disease
  (Prevalence estimates approx 15/100,000 although increasing with time)
• Patients eligible for trials is reduced=
  Inclusion/exclusion criteria
• Heterogeneous (AchRAb, Anti MUsk, Purely Ocular, etc)
• Outcome Measures
Study of IVIG in MG

- Randomized, controlled, masked study of placebo or IVIG in patients with worsening weakness due to MG

- First Level 1 evidence for IVIG

- Patients with moderate-severe MG and worsening weakness improved with IVIG therapy: QMG Score of -4.10 points at day 14

Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. Neurology 68:837-841, 2007
RCT of IVIG vs Placebo

• Rationale:
  
  No strong previous evidence of for IVIG tx

• 51 patients randomized to IVIG or placebo

• Evaluator masked study.

• Primary outcome was the QMG score at day 14

RCT of IVIG vs PLEX

Rationale:

No strong previous evidence of superiority of either treatment, although some beliefs that PLEX is superior

84 patients randomized to IVIG or PLEX

Evaluator masked study.

Primary outcome was the QMG score at day 14

Barth D, Nabavi M, Ng E, New P, Bril V. Neurology 2011;76:217-223
## Change in QMGS

<table>
<thead>
<tr>
<th></th>
<th>IVIG</th>
<th>PLEX</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B/L QMGS</td>
<td>14.2 ± 4.0</td>
<td>14.4 ± 3.8</td>
<td>0.83</td>
</tr>
<tr>
<td>Δ Day 0-14</td>
<td>3.2 ± 4.1</td>
<td>4.7 ± 4.9</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Barth D, Nabavi M, Ng E, New P, Bril V. Neurology 2011;76:217-223*
Duration of Treatment Effect

Time to worsening

Patients who had worsening (%)

Time (days)

IVIG
PLEX
Patient Status

- 18 patients needed additional tx (after 14D)
  - 10 IVIG and 8 PLEX
- 15 patients withdrew prior to day 60
  - 10 on IVIG and 9 on PLEX ($X^2 = 0.79$)
  - IVIG: 8 worsening, 2 withdrew consent
  - PLEX: 7 worsening, 2 withdrew consent
Conclusions

- IVIG is comparable to PLEX in the treatment of moderate-severe MG
- Duration of treatment effect is similar
- Tolerability of both treatments similar
Myasthenia Gravis

- IVIG vs placebo: effective
- IVIG vs PLEX: comparable
- Both class I studies that provide best evidence for IVIG in MG
- Planned MG studies: Grifols those with MG crises, open IVIG treatment; another IVIG or placebo at 14 days - similar to #1. CSL planning on maintenance treatment in those with uncontrolled MG/unacceptable side-effects. Baxter also considering MG studies. Efficacy of SCIG in MG underway.
IVIG vs. PLEX Changes in QOL

Table 2  Changes in MG-QOL in patients receiving IVIG and PLEX

<table>
<thead>
<tr>
<th></th>
<th>IVIG (n=32)</th>
<th>PLEX (n=30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔMG-QOL-60, day 1–14</td>
<td>−13±17</td>
<td>−19±22</td>
<td>0.4</td>
</tr>
<tr>
<td>ΔMG-QOL-60, day 1–21</td>
<td>−11±29</td>
<td>−18±27</td>
<td>0.3</td>
</tr>
<tr>
<td>ΔMG-QOL-60, day 1–28</td>
<td>−23±32</td>
<td>−17±23</td>
<td>0.4</td>
</tr>
<tr>
<td>ΔMG-QOL-15, day 1–14</td>
<td>−6±9</td>
<td>−7±8</td>
<td>0.5</td>
</tr>
<tr>
<td>ΔMG-QOL-15, day 1–21</td>
<td>−7±10</td>
<td>−8±9</td>
<td>0.8</td>
</tr>
<tr>
<td>ΔMG-QOL-15, day 1–28</td>
<td>−9±11</td>
<td>−5±5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

There was no significant difference in the change in MG-QOL-60 and MG-QOL-15 in patients treated with IVIG and PLEX at days 14, 21 and 28 after treatment. IVIG, intravenous immunoglobulin; MG-QOL, myasthenia gravis-quality of life; PLEX, plasma exchange.

### Changes in MG-QOL for Responders Compared to Non Responders

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔMG-QOL 60</td>
<td>-22 ± 26 *</td>
<td>-7 ± 20 *</td>
</tr>
<tr>
<td></td>
<td>95% CI: (-31, -14)</td>
<td>95% CI: (-15, 2)</td>
</tr>
<tr>
<td>ΔMG-QOL 15</td>
<td>-9 ± 8 #</td>
<td>-2 ± 7 #</td>
</tr>
<tr>
<td></td>
<td>95% CI: (-12, -6)</td>
<td>95% CI: (-5, 1)</td>
</tr>
</tbody>
</table>

* The mean decrease (improvement) in QOL 60 was greater in responders than in non-responders (t-test: mean difference: -15; t= -2.49; CI: [-28, -3], p=0.015)

# The mean decrease (improvement) in QOL 15 was greater in responders than in non-responders (t test: mean difference: -7; t= -3.44; CI: [-11, -3], p=0.001)
The table below shows the changes in QOL for patients treated with IVIG or PLEX for MG.

<table>
<thead>
<tr>
<th>Scale item</th>
<th>Δ score responders</th>
<th>Δ score non-responders</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>'I am frustrated by my MG'</td>
<td>-1.2±1.4</td>
<td>-0.2±1.3</td>
<td>0.006</td>
</tr>
<tr>
<td>'I have trouble eating because of MG'</td>
<td>-1.2±1.3</td>
<td>-0.5±1.8</td>
<td>0.04</td>
</tr>
<tr>
<td>'I have to make plans around my MG'</td>
<td>-0.5±1.1</td>
<td>0.2±1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>'I have difficulty speaking due to MG'</td>
<td>-1.1±1.2</td>
<td>-0.1±0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>'I feel overwhelmed by my MG'</td>
<td>-0.7±1.13</td>
<td>0.25±1.2</td>
<td>0.005</td>
</tr>
</tbody>
</table>

The mean change in items 1, 3, 7, 9 and 11 was greater in responders than in non-responders to treatment; p values are for t test. MG-QOL, myasthenia gravis-quality of life.

Predictors of Response to Immunomodulation

- Are there any clinical factors that are correlated with response to IVIG and PLEX?
- Are there any genetic factors associated with response to IVIG?
- Can these help us decide how to treat a given patient?
Clinical Predictors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-responder (n = 47)</th>
<th>Responder (n = 58)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (% women)</td>
<td>61</td>
<td>49</td>
<td>0.22</td>
</tr>
<tr>
<td>Age</td>
<td>55.1</td>
<td>59.9</td>
<td>0.12</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>72.6</td>
<td>57.1</td>
<td>0.32</td>
</tr>
<tr>
<td>Baseline clinical status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QMGS (baseline)</td>
<td>12.6</td>
<td>14.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Previous thymectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymus status</td>
<td>32.6</td>
<td>38.2</td>
<td>0.84</td>
</tr>
<tr>
<td>Thymoma (%)</td>
<td>25</td>
<td>25.4</td>
<td>0.55</td>
</tr>
<tr>
<td>Previous treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous Ig (%)</td>
<td>13.6</td>
<td>14.5</td>
<td>0.90</td>
</tr>
<tr>
<td>Previous PLEX (%)</td>
<td>18.2</td>
<td>10.9</td>
<td>0.30</td>
</tr>
<tr>
<td>Current immunosuppressive treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently on prednisone (%)</td>
<td>45.5</td>
<td>36.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Currently on azathioprine (%)</td>
<td>29.6</td>
<td>14.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Currently on mycophenolate mofetil (%)</td>
<td>11.4</td>
<td>1.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Electrophysiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repetitive nerve stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline decrement (%)</td>
<td>12.0</td>
<td>18.3</td>
<td>0.10</td>
</tr>
<tr>
<td>Immediately post-exercise (%)</td>
<td>13.7</td>
<td>16.7</td>
<td>0.12</td>
</tr>
<tr>
<td>Decrement 1 minute post-exercise (%)</td>
<td>13.4</td>
<td>19.2</td>
<td>0.13</td>
</tr>
<tr>
<td>Single-fiber EMG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jitter (μs)</td>
<td>86.6</td>
<td>122.5</td>
<td>0.0005</td>
</tr>
<tr>
<td>Abnormal pairs (%)</td>
<td>59.3</td>
<td>76.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Blocking pairs (%)</td>
<td>9.6</td>
<td>18.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Antibody status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AChRAb-positive (%)</td>
<td>55.0</td>
<td>84.9</td>
<td>0.001</td>
</tr>
<tr>
<td>AChRAb titers (μmol/L)</td>
<td>166.2</td>
<td>209.1</td>
<td>0.18</td>
</tr>
<tr>
<td>MuSK-positive (%)</td>
<td>7.5</td>
<td>5.6</td>
<td>0.72</td>
</tr>
<tr>
<td>Seronegative patients (AChRAb~ MuSK~) (%)</td>
<td>37.5</td>
<td>7.7</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Clinical Predictors

Multivariable Logistic Regression Analysis showed that only Baseline severity (QMGS) was associated with response.

Table 3. Independent predictors of response to immunomodulation generated from multivariate logistic regression modeling.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline QMGS</td>
<td></td>
</tr>
<tr>
<td>&lt;11 (reference)</td>
<td>1.0</td>
</tr>
<tr>
<td>11–16*</td>
<td>13.0 (1.02–381.5)</td>
</tr>
<tr>
<td>&gt;16*</td>
<td>15.3 (1.34–414.3)</td>
</tr>
</tbody>
</table>

The following variables were included: baseline QMGS (modeled in three categories); jitter; previous immunomodulation; and current immunosuppressive medication use (prednisone, azathioprine, mycophenolate mofetil). Factors that did not show significance after being run through the model are not shown.

*P < 0.05.

Clinical Predictors

However, other evidence of relationship with severity. (SFEMG)

Magnitude of QMGS change was significant (MCID)

Clinical Predictors

AchRAb were correlated on bivariate analyses with response to treatment.

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-Responders</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>AchRAb positive</td>
<td>43 (66%)</td>
<td>22 (34%)</td>
<td>65</td>
</tr>
<tr>
<td>AchRAb negative</td>
<td>7 (24%)</td>
<td>22 (76%)</td>
<td>29</td>
</tr>
</tbody>
</table>

$X^2: 14.218 \ p=0.0001$

No correlation with AchRAb titres
Polymorphisms of Fc receptor associated with different diseases and response to certain treatments.

Other Predictors

IVIG action mediated in part by interaction with Fc receptors.

Genotype frequencies for Fcγ receptor polymorphisms and baseline QMGS values.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>QMGS baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FcγR2A-131H/R (rs1801274)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/H n=25 (40%)</td>
<td>14 ± 5</td>
<td></td>
</tr>
<tr>
<td>H/R n=31 (49%)</td>
<td>12 ± 3</td>
<td></td>
</tr>
<tr>
<td>R/R n=7 (11%)</td>
<td>15 ± 5</td>
<td></td>
</tr>
<tr>
<td>FcγR2B 232 I/T (rs1050501)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>I/I n=54 (86%)</td>
<td>10 ± 2</td>
<td></td>
</tr>
<tr>
<td>I/T n=9 (14%)</td>
<td>14 ± 5</td>
<td></td>
</tr>
<tr>
<td>FcγR3A 158 F/V (rs396991)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V/V n=15 (24%)</td>
<td>14 ± 4</td>
<td></td>
</tr>
<tr>
<td>V/F n=48 (76%)</td>
<td>14 ± 6</td>
<td></td>
</tr>
<tr>
<td>FcγR3B NA1/NA2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA1/NA1 n= 17 (27%)</td>
<td>16 ± 6</td>
<td></td>
</tr>
<tr>
<td>NA1/NA2 n=27 (43%)</td>
<td>13 ± 4</td>
<td></td>
</tr>
<tr>
<td>NA2/NA2 n=19 (30%)</td>
<td>13 ± 3</td>
<td></td>
</tr>
</tbody>
</table>

No significant difference with healthy controls

IVIG and PLEX Conclusions

- Both treatments produce improvement in function (QMGS) and in Quality of Life.
- There is no difference in the magnitude of improvement between treatments.
- Patients with higher severity likely to benefit the most.
- AchRAb negative patients also benefit from treatment.
- Fc receptor polymorphisms do not correlate to response to IVIG

Novel Scale for MG

- QMGS has redundant items and is time-consuming
- Derivation of items mostly by expert opinion
- Does not incorporate concept of fatigue that is a main concern of patients
- Development of a novel scale to assess MG in clinics and in clinical trials underway
Immune mediated polyneuropathy

- Chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome and multifocal motor neuropathy are all forms of peripheral neuropathy.

- If treated early, disease progression may be slowed; however, if treatment is not started until late in the course of the disease, permanent damage may have already occurred.

- The following slides discuss current thoughts on pathogenesis and individual aspects of the three peripheral neuropathies.
Pathogenic processes significant to inflammatory neuropathies

- There are common pathogenic processes involved in acute and chronic inflammatory immune neuropathies:

  - **Axonal dysfunction**
    - Axonal dysfunction causes alterations in impulse propagation at the Nodes of Ranvier which slows / blocks conduction
    - Changes in conduction results in transient weakness which can be reversible with treatment; however, may lead to axonal degeneration

  - **Demyelination**
    - Leads to dysfunction at inter- / para- nodes affecting conduction
    - Transient weakness can be reversible with treatment; may lead to permanent axonal damage

  - **Axonal structural damage**
    - If axonal degeneration occurs, it is less amenable to treatment and is more likely to cause permanent disability

CIDP: chronic inflammatory demyelinating polyneuropathy, GBS: Guillain-Barré Syndrome
Temporal evolution of disease: The GBS to CIDP continuum

- It is currently unclear what causes acute or chronic forms of disease

CIDP: chronic inflammatory demyelinating polyneuropathy, GBS: Guillain-Barré Syndrome
CIDP Variants

Healthy

Classical CIDP

DADS

MADSAM

Pure Sensory

Pure Motor

Focal

Motor Deficits

Sensory Deficits

Hughes et al. Eur J Neurol 2006;13:326-332,
Current understanding of GBS pathogenesis

At least 2 GBS variants have a complement-mediated stage where a membrane-attack complex (MAC) is formed

Acute inflammatory demyelinating polyneuropathy (AIDP)
Auto-antibodies bind to unidentified myelin antigens and activate complement. MAC forms on outer surface of Schwann cells and initiates vesicular degeneration. Macrophages later scavenge myelin debris.

Acute motor axonal neuropathy (AMAN)
IgG anti-GM1 / GD1a auto-antibodies bind to membrane antigens leading to MAC formation
- Sodium channel clusters are disrupted or disappear at lengthened nodes in addition to the disruption of paranodal junctions
- This disruption may result in myelin detachment leading to nerve-conduction failure, muscle weakness, and possibly axonal degeneration. Macrophages subsequently invade and scavenge injured axons.

Current understanding of CIDP pathogenesis

- May be caused by abnormal immune response mediated by lymphocytes and macrophages, in addition to auto-antibodies and complement.

- In CIDP patients:
  - Pro-inflammatory and regulatory cytokines - elevated in the CSF
  - Serum TNF-α levels are raised - correlate with disease activity
  - Activated T-cells, mainly CD4+ - increased in the circulation
  - Antigen-driven, major histocompatibility complex class I restricted, CD8+ T-cell-mediated attack.²

- T-cells may activate residing macrophages, leading to:
  - Enhanced phagocytosis
  - Production of pro-inflammatory molecules, e.g.:
    - Reactive oxygen species
    - Proteases
    - Pro-inflammatory cytokines.

- Auto-antibodies may contribute to disease process by complement activation or antibody-dependent cellular toxicity.

Current understanding of MMN pathogenesis

- In up to 60% of MMN patients, antibodies against gangliosides including GM1 are present.¹

- Antibodies may bind to GM1 and cause disruption of ion channel clusters, which leads to conduction block;² a defining physiologic feature of this disease.

- The resultant progressive axonal damage may lead to progressive axonal loss and permanent disability.²

GBS

- Corticosteroids ineffective
  
  *Hughes and van Doorn. Cochrane Database Syst Rev 2012;8:CD001446*

- Corticosteroids don’t add to IVIG
  
  *van Koningsveld et al. Lancet 2004;363:192-196*

- PLEX = IVIG; both work
  
  *Bril, Ilse, Pearce, Dhanani, Kong, Sutton. Neurology 1996;46:100-103. IVIG and PLEX
Guillain-Barré Syndrome Trial Group. Lancet 1997;349:225-230*

- IVIG does not add to PLEX
  
  *Guillain-Barré Syndrome Trial Group. Lancet 1997;349:225-230*

- Mycophenolate mofetil + IVIG + steroid no better than IVIG alone
  
  *Garssen et al. J Neurol Neurosurg Psychiatry 2007;78:1012-1013*
CIDP and Steroids

Steroids are better than no treatment


Improvement at 6 weeks: IVIG = Prednisolone


Pulsed steroids seem to be favorable (remission, side effects)


ICE Trial Results
Primary Outcome Measure

- Improvement in adjusted INCAT disability score

≥ 1-point improvement from baseline in adjusted INCAT through week 24

Response to treatment

<table>
<thead>
<tr>
<th></th>
<th>IVIG-C</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=58)</td>
<td>54.2</td>
<td>20.7</td>
</tr>
<tr>
<td>p=0.0002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Table 2: Lancet Neurol 2008;7:136-144.

ICE Trial Results
Time to relapse (extension phase)

- A significant improvement in adjusted INCAT disability score
- Improvement in secondary measures of impairment
- Protection against relapse during the treatment period

87% of IVIG-C group remained relapse-free during the 24 week treatment period

ICE Trial second phase

Results
Change from baseline in conduction block for all extremity motor nerves

Adapted from Table 5: Bril V, Katzberg, et al. Muscle Nerve 2009;39::448-455.
ICE Trial Results

INCAT responders by 1st or 2nd dose

- 1st Dose: n=14
- 2nd Dose: n=30

*statistical significance not reported

Adapted from Latov N. Deng C. et al. Arch Neurol 2010; 67(7):E1-E6
CIDP: First-line therapy

- In the acute treatment of CIDP, the effects of IVIG (2 g/kg), plasmapheresis and glucocorticosteroids are probably not different during a treatment period of 6 weeks, but statistical equivalence has not been proven (Eftimov et al. 2009)

- About 60% of all patients respond to one of these therapies (Mehndiratta and Hughes 2002)

- Positive response to the initial immunotherapy in 69% of patients (64% with steroids, 78% after IVIG and 56% after plasmapheresis) (Cocito et al. 2010)

- Response in 82% of patients treated with IVIG (Tackenberg et al. 2007)

SCIG in CIDP

PATH : Multicenter Study

CIDP according to EFNS/PNS
Repeated tx with IVIG
IVIG tx during last 8 weeks prior
No PNP of other causes

CIDP relapse during IVIG withdrawal period

CIDP improvement during IVIG re-stabilization
Stable INCAT score

SCIG for 24 weeks

Outcome:
SCIG is efficacious in treating CIDP
SCIG is safe and tolerable

Screening
IVIG Withdrawal
IVIG Loading
IVIG Re-stabilization
SCIG Initiation
SCIG Treatment
CIDP: More dropouts but more remissions with steroids compared to IVIG

Does Preparation of IVIG Matter?

- Likely not
- Kuitwaard performed RCT with freeze-dried and liquid forms of IVIG in CIDP with comparable outcomes
- (Kuitwaard, JNNP, 2010)
<table>
<thead>
<tr>
<th>Table 3. Immunosuppressant and immunomodulatory drugs that have been reported to be beneficial in chronic inflammatory demyelinating polyradiculoneuropathy (Class IV evidence [Hughes et al., 2004; Kuitwaard and van Doorn, 2009]).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>Azathioprine</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Ciclosporin</td>
</tr>
<tr>
<td>Etanercept</td>
</tr>
<tr>
<td>Interferon-α</td>
</tr>
<tr>
<td>Interferon-β 1a</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td>Stem cell transplantation (haematopoietic)</td>
</tr>
</tbody>
</table>
**Table 1** Analysis of response to treatment with immunosuppressive and immunomodulatory agents: on 110 patients who used 158 different procedures

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>R</th>
<th>% R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA</td>
<td>77</td>
<td>21</td>
<td>27</td>
<td>0.86</td>
</tr>
<tr>
<td>RTX</td>
<td>18</td>
<td>6</td>
<td>33</td>
<td>0.89</td>
</tr>
<tr>
<td>CsA</td>
<td>12</td>
<td>3</td>
<td>25</td>
<td>0.99</td>
</tr>
<tr>
<td>CYP</td>
<td>13</td>
<td>5</td>
<td>38</td>
<td>0.54</td>
</tr>
<tr>
<td>MTX</td>
<td>12</td>
<td>2</td>
<td>17</td>
<td>0.67</td>
</tr>
<tr>
<td>MFM</td>
<td>12</td>
<td>3</td>
<td>25</td>
<td>0.99</td>
</tr>
<tr>
<td>IFNβ</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0.78</td>
</tr>
<tr>
<td>IFNα</td>
<td>11</td>
<td>4</td>
<td>36</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*N*, number of therapeutic procedures; *R*, number of patients who responded to the treatment; % *R*, percentages of responding patients; *P*, Fisher’s test; AZA, azathioprine; RTX, rituximab; CsA, cyclosporine A; CYP, cyclophosphamide; MTX, methotrexate; MFM, mycophenolate mofetil; IFNβ, beta-interferon; IFNα, alpha-interferon.
Methotrexate trial in CIDP negative

- NSD in MTX or placebo in reducing dose of prednisone or IVIG by 20%
- ?trial design

RMC trial group Lancet Neurol 2009;8:158-64
CIDP Studies

- Hematopoietic stem cell transplant in CIDP, Northwestern University, Richard Burt, recruiting
- Phase III NPB-01 Maintenance therapy, recruiting
- Privigen: completed: positive
- Lipoic acid study: completed 2013, ?results
- *SCIG, Path, recruiting
- SCIG, Extension, to follow Path
CIDP Studies

- IVIG compared with prednisone, 6m, France, ?recruiting or completed
- *Fingolimod 0.5 mg/d or placebo, Novartis, recruiting
- Exercise: recruiting, Aarhus
- Avonex: completed
- Alemtuzumab, Genzyme
- MRI and US monitoring in CIDP, MMN, Aarhus
MMN

- IVIG works
  - Katzberg study on SCIG in Toronto
  - Some other reports positive

- Steroids do not work and may worsen the condition
  - Reports from 1990-1997
Case Presentation : NCS
## Case Presentation: NCS

### Motor Summary Table

<table>
<thead>
<tr>
<th>Site</th>
<th>NR</th>
<th>Onset (ms)</th>
<th>O-P Amp (mV)</th>
<th>P-T Amp (mV)</th>
<th>Full Dur (ms)</th>
<th>Full Area (mV·ms)</th>
<th>Site1</th>
<th>Site2</th>
<th>Dist (cm)</th>
<th>Vel (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right Median Motor (Abd Poll Brev)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>4.8</td>
<td>8.1</td>
<td></td>
<td>12.6</td>
<td>9.38</td>
<td>36.66</td>
<td>Elbow</td>
<td>Wrist</td>
<td>28.0</td>
<td>50</td>
</tr>
<tr>
<td>Elbow</td>
<td>10.4</td>
<td>7.8</td>
<td></td>
<td>12.1</td>
<td>10.23</td>
<td>44.29</td>
<td>Axilla</td>
<td>Elbow</td>
<td>10.0</td>
<td>53</td>
</tr>
<tr>
<td>Axilla</td>
<td>12.3</td>
<td>7.3</td>
<td></td>
<td>11.2</td>
<td>10.63</td>
<td>46.37</td>
<td>Erbs</td>
<td>Axilla</td>
<td>37.0</td>
<td>65</td>
</tr>
<tr>
<td>Erbs</td>
<td>18.0</td>
<td>5.2</td>
<td></td>
<td>7.4</td>
<td>10.39</td>
<td>30.48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Right Peroneal Motor (Ext Dig Brev)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>6.8</td>
<td>2.9</td>
<td></td>
<td>4.0</td>
<td>6.95</td>
<td>9.82</td>
<td>B Fib</td>
<td>Ankle</td>
<td>35.0</td>
<td>41</td>
</tr>
<tr>
<td>B Fib</td>
<td>15.3</td>
<td>2.7</td>
<td></td>
<td>3.8</td>
<td>8.05</td>
<td>11.03</td>
<td>Poplt</td>
<td>B Fib</td>
<td>8.0</td>
<td>44</td>
</tr>
<tr>
<td>Poplt</td>
<td>17.1</td>
<td>2.7</td>
<td></td>
<td>3.7</td>
<td>7.89</td>
<td>10.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Right Tibial Motor (Abd Hall Brev)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>5.8</td>
<td>0.5</td>
<td></td>
<td>0.9</td>
<td>10.47</td>
<td>2.18</td>
<td>Knee</td>
<td>Ankle</td>
<td>44.0</td>
<td>39</td>
</tr>
<tr>
<td>Knee</td>
<td>17.0</td>
<td>0.5</td>
<td></td>
<td>0.9</td>
<td>13.13</td>
<td>3.34</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Right Ulnar Motor (Abd Dig Minimi)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>5.2</td>
<td>5.7</td>
<td></td>
<td>10.1</td>
<td>8.52</td>
<td>25.06</td>
<td>B Elbow</td>
<td>Wrist</td>
<td>27.0</td>
<td>45</td>
</tr>
<tr>
<td>B Elbow</td>
<td>11.2</td>
<td>4.3</td>
<td></td>
<td>7.3</td>
<td>9.77</td>
<td>20.87</td>
<td>A Elbow</td>
<td>B Elbow</td>
<td>12.0</td>
<td>40</td>
</tr>
<tr>
<td>A Elbow</td>
<td>14.2</td>
<td>3.8</td>
<td></td>
<td>6.3</td>
<td>10.63</td>
<td>22.01</td>
<td>Axilla</td>
<td>A Elbow</td>
<td>8.0</td>
<td>50</td>
</tr>
<tr>
<td>Axilla</td>
<td>15.8</td>
<td>3.6</td>
<td></td>
<td>5.5</td>
<td>10.47</td>
<td>21.39</td>
<td>Erb's</td>
<td>Axilla</td>
<td>37.0</td>
<td>62</td>
</tr>
<tr>
<td>Erb's</td>
<td>21.8</td>
<td>2.3</td>
<td></td>
<td>3.6</td>
<td>12.42</td>
<td>17.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**IVIG in MMN**

- 44 patients with MMN, x-over design tx with IVIG or placebo for 12 weeks with 3 stabilization phases

- Stabilization or improvement in grip strength, MRC score, disability scales & less x-overs in IVIG group compared to deterioration in placebo group

- 59 patients on maintenance home IVIG for MMN since 1994 in Holland

- Benefits: travel costs, convencience and reduced time off work. Safety profile equivalent when infusion procedures followed

Hahn et al. JPNS Dec 2013.

Cats et al. JPNS Feb 2011.
SCIG for MMN

Efimov 2009 (n=10, 10% SCIG)
- 50% IVIG maintenance: 5/10 patients deteriorated or withdrew
- 100% IVIG maintenance: 4/5 maintained improvement

Harbo 2010 (n=6, 16% SCIG)


SCIG for MMN

Study : High Dose SCIG (20% Hizentra) for Maintenance Treatment of MMN

• **Aim**: To evaluate if IgPRO20 (Hizentra 20%) SCIG is a safe and effective alternative to maintenance IVIG for treatment of MMN

• Patients with a confirmed diagnosis of MMN with or without CB who were clinically active on regular dose of IVIG included

• 15-patient, open-label study transitioning patients IVIG to SCIG in 1 : 1.5 dosing ratio, maximum 2 g / kg / month immunoglobulin dose
Study Design: Smooth Transition Protocol

Week 1: Screening & Baseline
Week 2: Infusion & Training
Week 3: Infusion & Training (as necessary)
Month 3: Follow-up Visit
Month 6: End-of-study Visit

25% increase allowed (up to 2g/kg)

25% increase allowed (up to 2g/kg)

Monthly IVIG (g)
Weekly SCIG dose (g) = \frac{\text{MAXIMUM DOSE} = 2 \text{ g/kg/month}}{\# \text{ weeks between IVIG doses}}

25% Dose
50% Dose
100% Dose

I V I G
Self-administration
Infusion details

- All 15 patients recruited to date:
  - 11 men/4 women, ages 31-82, duration of symptoms 2-41 years, IVIG ranging from 0.3-2 g / kg / month

- Two to three clinic visits were required for training, ranging from 2-3 hours each

- Five of thirteen patients had family members or caregivers present for the training sessions; only 3 required caregivers to administer SCIG at home
Infusion Details

- Number of sites for infusion ranged from 2 to 4 with a maximum volume of 20 ml/site was infused initially, increased to 40 ml/site per week as tolerated.

- Total infusion volume average 150 mL (range 50-305 mL/week) and average total infusion time per week was 1.6 hours (range 1 to 2.5 hours) per session.

- Eleven out of 15 patients chose to infuse in the abdomen, of which 4 patients also chose to rotate sites to the thighs and lower back. The remaining 4 patients infused primarily in the thighs.
Benefits of SCIG
Vilija Rasutis

- Studied solely as a maintenance therapy in pts. already on IVIG
- Subcutaneous weekly infusions keep IgG levels at a steady state - consistent
- No pre-meds required
- Side effects are mainly - localized*
- Autonomy and independence a plus
- Less costly
- **NO VENOUS ACCESS**

Berger M. Subcutaneous administration of IgG. Immunol Allergy Clin North Am. 2008;28 (4): 779-
Equipment for SC infusion with Hizentra
Side Effects re. to SCIG therapy

Localized: redness, swelling, itching, and /or bruising at the site

leakage

Others and not as common:

- Headache/migraine
- Nausea and/or vomiting and fatigue
- Pain
- Diarrhea
- Cough
- Rash
- Fever, chills, SOB, dizziness

INTERVENTIONS and MANAGEMENT OF SITE REACTIONS:

- Rate control
- Needle Placement and rotation of sites
- Cool compresses
Infusion Aspects in NMD with Hizentra

- Patient education
- Dose/Volume
- Site selection
- Needle type
- Infusion Pump/rate
- Ongoing support/education
Main Results

11 out of 15 (73% of patients) completed 6 months of infusion

- Maintenance MRC score, Jamar grip strength, Health Utility Index QOL, Guy’s disability score
- One patient missed final visit by 2 weeks and on f/u maintained grip strength, dec MRC

- 3 out of 15 (20%) patients on 2 g/kg experienced drop in IgG levels and intolerable deterioration in upper extremity strength → IVIG rescue

- Mean patient satisfaction scores 17.8-19.9 (/20)
Adverse Events

- **Common:** itching, burning, mild redness (erythema), and/or swelling.
- **Resolution ~ 12-24 hours,** intensity may be related to time needed for body to adjust to Hizentra.  
- **Mild-moderate erythema,** swelling managed with site rotation, change in needle length / infusion rates (n=15)
- **One patient responding to SCIG developed intolerable skin erythema,** swelling and elevated liver enzymes, one patient exiting study developed mild hemolysis and pancytopenia (n=2)
MMN
IVIG + Mycophenolate Ineffective

MMN
IVIG + Rituximab ineffective

MMN - Cyclophosphamide

- Case series point to effect in some patients
  - Brannagan: 50mg/kg x 4 days

- High rate of serious side effects

- Moderate effect possible in combination with IVIG

- IV cyclophosphamide is effective in more than 70% of MMN patients (0.5 to 1.0 gm/m² for 6 months) (Pestronk)

- Brannagan, Muscle Nerve 2006;34:246-250.
MMN - Negative Reports

- Interferon beta
- Cyclosporine
- Azathrioprine
- Methotrexate
- Rituximab
- Infliximab
- Eculizumab

An Immunologists’ Rating for IVIG

- Immunologists rate CIDP as CCC
- Evidence supports use
- Participate and urge patient activism
Considerations

- How to ensure access for NM patients
- Concern about the cost of the treatment
- Is the dosing the same for different NM disorders
- Do changes in Ig levels matter
- What route of administration should be used
- There is a great need for targeted immune therapies and better understanding of the pathophysiology of NM disorders