Recent Highlights in Peripheral Nerve

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Warning

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Outline

• Advances in Peripheral Neuropathy
  o “CIDP” variants
  o CANVAS, CMT, ATTRv Amyloid

• Treatment Trials for Peripheral Neuropathies
  o ATTRv Amyloid
  o GBS
  o CIDP
Advances in “CIDP” ...
Clinical Phenotypes of CIDP

Bonschoten C et al, Lancet Neurology 18:2019
The node of Ranvier

IgG4 Antibodies to Nodal and Paranodal proteins

• CIDP-like disease with a different pathogenesis
  o IgG4 antibodies have a low capacity to bind to FcγIIb-receptors, cannot activate complement, and are considered anti-inflammatory

• Occur in about 10% of CIDP with atypical phenotypes and impaired response to standard treatments

• Paranodal: NF155, Contactin1, CASPR1 (contactin associated protein-1)

• Nodal: NF140 and 186

• Patients with IgG4 antibodies may not respond sufficiently to standard CIDP treatment but can show remarkable improvement with rituximab

• ? IgM antibodies to NF155 and NF186

Bonschoten C et al, Lancet Neurology 18:2019
# Antibodies to Neurofascin

## Neurofascin 155
- Subacute severe onset
- Motor > sensory
- Sensory ataxia
- Young age of onset
- Tremor
- Distal predominant
- CNS (ataxia/nystagmus/demyelination)
- High CSF protein/papilledema
- Poor response to IVIG
- Partial response to corticosteroids
- Good response to PLEX or rituximab

## Neurofascin 140/186
- Subacute severe onset
- Motor and sensory
- Sensory ataxia
- Nephrotic syndrome/retroperitoneal fibrosis
- Cranial neuropathies can occur
- Respiratory involvement
- Conduction blocks
- Partial response to IVIG
- Partial response to corticosteroids
- Good response to rituximab

Bonschoten C et al, Lancet Neurology 18:2019
Delmont et al, Brain 18:2019
Comparison of IgG$_4$ 140/186 vs 155

Table 2: Comparison of clinical features of patients with anti-Nfasc140/186 IgG or anti-Nfasc155 and of seronegative CIDP patients

<table>
<thead>
<tr>
<th></th>
<th>Anti-Nfasc140/186 IgG</th>
<th>Anti-Nfasc155 IgG$_4^*$</th>
<th>Seronegative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>5</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>Age in years, median (range)</td>
<td>61 (2-70)</td>
<td>29 (10-76)</td>
<td>58 (22-82)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>3 (60)</td>
<td>48 (69)</td>
<td>30 (39)</td>
</tr>
<tr>
<td>Subacute onset, n (%)</td>
<td>4 (80)$^a$</td>
<td>13/55 (24)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Sensory ataxia, n (%)</td>
<td>4 (80)</td>
<td>45/70 (64)$^a$</td>
<td>29 (38)</td>
</tr>
<tr>
<td>Tremor, n (%)</td>
<td>0</td>
<td>31/70 (44)$^a$</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Cranial nerve involvement, n (%)</td>
<td>2 (40)</td>
<td>7/32 (22)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>CNS demyelination, n (%)</td>
<td>0</td>
<td>7/70 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Modified Rankin scale, median (range)</td>
<td>4 (4-5)$^a$</td>
<td>3 (1-5)</td>
<td>2 (0-5)</td>
</tr>
<tr>
<td>Good response, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIG</td>
<td>3/4 (75)</td>
<td>16/70 (23)$^a$</td>
<td>48/60 (80)</td>
</tr>
<tr>
<td>Steroids</td>
<td>3/4 (75)</td>
<td>34/70 (49)</td>
<td>19/27 (70)</td>
</tr>
</tbody>
</table>

$^a$Taken from Ng et al, 2012; Querol et al, 2014; Ogata et al, 2015b; Devaux et al, 2016; Kadoya et al, 2016.

$^b$P < 0.001 as compared to seronegative CIDP patients.
Antibodies to Contactin/CASPR1

Contactin 1
- Subacute severe onset
- Young age of onset
- Motor > sensory (GBS)
- Sensory ataxia
- Tremor
- Proximal and distal
- High CSF protein
- Conduction blocks
- Poor response to IVIG
- Partial response to corticosteroids
- Good response to PLEX or rituximab

CASPR1
- Subacute severe onset
- Motor > sensory (GBS)
- Neuropathic pain
- Distal > proximal
- Poor response to IVIG
- Good response to rituximab

Bonschoten C et al, Lancet Neurology 18:2019
Doppler K et al, Brain 139:2016.
Advances in Hereditary Neuropathies
Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia

- CANVAS - cerebellar ataxia, neuropathy, vestibular areflexia syndrome
  - RFC1 – recessive AAGGG repeat expansion in intron 2, cause of familial CANVAS in 23 pts
  - Also screened 150 patients with late-onset ataxia and found 33 sporadic cases
    - 63% positive if late-onset cerebellar ataxia and sensory neuronopathy
    - 92% if full syndrome (with vestibular areflexia)
<table>
<thead>
<tr>
<th></th>
<th>Familial cases ($n = 23$)</th>
<th>Sporadic cases ($n = 33$)</th>
<th>All cases ($n = 56$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>12 (52%)</td>
<td>15 (45%)</td>
<td>27 (48%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age at onset</td>
<td>53 ± 8</td>
<td>54 ± 10</td>
<td>54 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration at exam</td>
<td>13 ± 9</td>
<td>10 ± 6</td>
<td>11 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>23 (100%)</td>
<td>33 (100%)</td>
<td>56 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cerebellar syndrome</td>
<td>18 (78%)</td>
<td>27 (82%)</td>
<td>45 (80%)</td>
<td>NS</td>
</tr>
<tr>
<td>Bilateral vestibular impairment</td>
<td>17 (74%)</td>
<td>13 (39%)</td>
<td>30 (53%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>4 (17%)</td>
<td>9 (27%)</td>
<td>13 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (30%)</td>
<td>14 (42%)</td>
<td>21 (37%)</td>
<td>NS</td>
</tr>
<tr>
<td>SAP upper limbs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced</td>
<td>6/21 (29%)</td>
<td>4/31 (13%)</td>
<td>10/52 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Absent</td>
<td>15/21 (71%)</td>
<td>27/31 (87%)</td>
<td>42/52 (81%)</td>
<td>NS</td>
</tr>
<tr>
<td>SAP lower limbs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced</td>
<td>2/21 (10%)</td>
<td>1/31 (3%)</td>
<td>3/52 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Absent</td>
<td>19/21 (90%)</td>
<td>30/31 (97%)</td>
<td>49/52 (94%)</td>
<td>NS</td>
</tr>
<tr>
<td>Normal motor conduction</td>
<td>19/21 (90%)</td>
<td>26/31 (84%)</td>
<td>45/52 (87%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cerebellar atrophy at CT/MRI scan</td>
<td>14/17 (82%)</td>
<td>21/25 (84%)</td>
<td>35/42 (83%)</td>
<td>NS</td>
</tr>
<tr>
<td>Full-blown CANVAS syndrome</td>
<td>15 (65%)</td>
<td>11 (33%)</td>
<td>26 (46%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

NS, not significant; SAP, sensory action potential.
ATP1A1 encodes alpha1 subunit of Na, K ATPase and missense mutations associated in loss of function defect

- 7 families from 4 continents
- Distal leg and arm weakness with normal proximal strength
- Reduced vibratory sensation in the legs and some hands
- Age of onset varied from childhood to adult even within the same family
- Pes cavus
• Recessive mutation in mitochondrial copper – binding protein SCO2 (COX assembly protein) → fatal infantile cardioencephalomyopathy with COX deficiency
• Compound heterozygotes in SCO2 → axonal polyneuropathy (CMT4)
• Motor neuropathy – prox/distal, cranial
• Not yet developed cardiomyopathy
• Lived past infancy
**ATTRv Amyloidosis**

- **Autosomal Dominant**
  - Most affected are heterozygous
- **>130 different mutations – most single nucleotide substitution**
- **Variant TTR is in blood at birth**
  - Doesn’t form amyloid until adulthood
- **Most common mutation Val30Met**
  - Accounts for 50% of TTR-FAP mutations
  - Portugal, Sweden, Italy, Cyprus, Majorca

![Diagram showing various factors affecting Phenotypic Variability in ATTRv Amyloidosis](https://via.placeholder.com/150)
# Familial amyloid polyneuropathy

<table>
<thead>
<tr>
<th>Endemic</th>
<th>Nonendemic and Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset &lt; 40 years</td>
<td>Onset &gt; 50 years</td>
</tr>
<tr>
<td>LD small fiber sensory motor neuropathy</td>
<td>Neuropathy affects all fibers and may mimic CIDP</td>
</tr>
<tr>
<td>Life-threatening autonomic dysfunction</td>
<td>Mild autonomic symptoms</td>
</tr>
<tr>
<td>Cachexia and death within 10.8 years</td>
<td>Late onset has more severe course</td>
</tr>
<tr>
<td>Cardiac, renal and ocular involvement</td>
<td>More variability due to genetic heterogeneity</td>
</tr>
</tbody>
</table>
Improvement in diagnosis of ATTRv cardiac amyloid – Radionuclide bone scintigraphy

- Radionuclide bone scintigraphy with technetium-labeled bisphosphonates (DPD, PYP, HMDP) localize to cardiac amyloid deposits
- Graded by degree of uptake
  - Grade 1 = mild uptake less than bone
  - Grade 2 = moderate uptake equal to bone
  - Grade 3 = high uptake greater than bone

Gillmore et al, Circulation 2016
## Sensitivity and Specificity of Radionuclide ‘Bone’ Scintigraphy Compared with EMB Histology

<table>
<thead>
<tr>
<th></th>
<th>Positive Scan (Grade 1, 2, or 3), n</th>
<th>Negative Scan (Grade 0), n</th>
<th>Sensitivity and Specificity (CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac amyloid deposits</strong></td>
<td>289</td>
<td>38</td>
<td>88 (84-92) sensitive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No cardiac amyloid deposits</strong></td>
<td>6</td>
<td>41</td>
<td>87 (73-95) specific</td>
</tr>
<tr>
<td><strong>Cardiac ATTR amyloid deposits</strong></td>
<td>259</td>
<td>2</td>
<td>&gt;99 (97-100) sensitive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No cardiac ATTR amyloid deposits</strong></td>
<td>36</td>
<td>77</td>
<td>68 (59-77) specific</td>
</tr>
</tbody>
</table>

When combining grade 2 or 3 cardiac uptake and absence of monoclonal protein, specificity increased to 100% for cardiac ATTR amyloid

Gillmore et al, Circulation 2016
Utility of Skin Biopsy for ATTRv Diagnosis

- 72 patients
- 30 with genetically confirmed ATTRv
  - 20/32 had TTR-FAP
  - 10/32 normal exams
- 20 with healthy controls
- 20 diabetic PN
- 2 with MM/AL amyloid

- 70% of TTR-FAP patients showed positive amyloid deposits
- 2 AL patients were positive
- 2/10 TTR-noPN were positive

Clinical Trials in Peripheral Neuropathy

ATTRv Amyloid
New Treatments for ATTRv FAP

Elimination of source of TTR variants:
- Liver transplantation
- Gene silencing
  - Antisense oligonucleotides - Inotersen
  - Small interfering RNA - Patisiran

Tetramer stabilization:
- Diflunisal
- Tafamidis

Reduction of TTR deposits in tissue:
- Doxycycline
- TUDCA

Enhanced clearance of amyloid deposits:
- Anti-SAP mAb

TTR monomers → Misfolding → Aggregation → TTR amyloid

Liver production and secretion into the blood

Stabilized TTR tetramer
Assessment of Neuropathy in TTR FAP: Comparison of Neuropathy Impairment Scores

NIS (244 points)
- Sensation (32)
- Reflexes (20)

NIS-LL (88 points)
- Sensation (16)
- Reflexes (8)
- Motor strength/weakness (192)

NIS+7 (270 points)
- Sensation (32)
- Reflexes (20)
- Motor strength/weakness (192)

mNIS+7Alyxiam (304 points)
- Motor strength/weakness (192)

mNIS+7lonis (346.3 points)
- Motor strength/weakness (192)

BP, blood pressure; VDT, vibration detection threshold
Inotersen

- Once weekly 300 mg SQ
- Treatment of Stage 1 (ambulatory) or 2 (amb w/ assistance) FAP
- Phase 3 randomized 2:1, 172 pts
- NIS 10-130, TTR mutation, path evidence of amyloid
- Exclude NYHA class III or higher
- Approved in US, Europe, Canada, Japan
Inotersen

- Improvement in modified NIS+7 (mNIS+7) and Norfolk Quality of Life – Diabetic Neuropathy questionnaire total score

- Effect as early as 8 months and sustained at 15 months
Inotersen

• Safety concerns
  - Thrombocytopenia
  - Glomerulonephritis

• REMS program for enhanced monitoring of platelets, renal function and liver function

• Open label extension (104 wk)
  - Improvement in NIS+7 and QOL
  - No new safety concerns

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=60)</th>
<th>Inotersen (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>60 (100)</td>
<td>111 (99)</td>
</tr>
<tr>
<td>Event related to trial regimen†</td>
<td>23 (38)</td>
<td>87 (78)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>13 (22)</td>
<td>36 (32)</td>
</tr>
<tr>
<td>Event related to trial regimen†</td>
<td>1 (2)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>0</td>
<td>3 (3)‡</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>1 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0</td>
<td>1 (&lt;1)§</td>
</tr>
<tr>
<td>Tubulointerstitial nephritis</td>
<td>0</td>
<td>1 (&lt;1)¶</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Embolic stroke</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>5 (4)</td>
</tr>
</tbody>
</table>

Patisiran

- 0.3 mg/kg IV q 3 weeks
- Treatment of Stage 1 or 2 FAP
- Phase 3 randomized 2:1, 225 pts
- NIS 5-130, PND ≤ IIIb, TTR mutation
- Exclude NYHA class III or higher
- Approved in US and Europe

Adams D et al; NEJM, 2018
Pinto MV et al; Arq Neuropsiquiatr, 2018
Patisiran

- Improvement in modified NIS+7 (mNIS+7) and Norfolk Quality of Life – Diabetic Neuropathy questionnaire total score

- Effect as early as 9 months for NIS

- Secondary endpoint showed improvement including 10-meter mBMI, Composite Autonomic Symptom Score 31

Patisiran

Well tolerated with infusion related reactions that rarely interrupted treatment

<table>
<thead>
<tr>
<th>Safety and Side Effects</th>
<th>Placebo (n=77) no. of patients (%)</th>
<th>Patisiran (n=148) no. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>75 (97)</td>
<td>143 (97)</td>
</tr>
<tr>
<td>Adverse events occurring in ≥105 of patients in either group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29 (38)</td>
<td>55 (37)</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>17 (22)</td>
<td>44 (30)</td>
</tr>
<tr>
<td>Fall</td>
<td>22 (29)</td>
<td>25 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (21)</td>
<td>22 (15)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>7 (9)</td>
<td>28 (19)</td>
</tr>
<tr>
<td>Constipation</td>
<td>13 (17)</td>
<td>22 (15)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>14 (18)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (14)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (10)</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (12)</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (12)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (10)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (12)</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (9)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (8)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>8 (10)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>11 (14)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (10)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Syncope</td>
<td>8 (10)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation of the trial regimen</td>
<td>11 (14)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Adverse event leading to withdrawal from the trial</td>
<td>9 (12)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (8)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>31 (40)</td>
<td>54 (36)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>28 (36)</td>
<td>42 (28)</td>
</tr>
</tbody>
</table>
Clinical Trials in Peripheral Neuropathy

Guillain-Barre Syndrome
• Rationale: Despite IVIG and PLEX improving prognosis and reducing disability, ~20% of treated patients still have some disability at 6 months

• Eculizumab targets the complement pathway (monoclonal Ab to C5)
  o Prior studies suggest pivotal in nerve damage especially when associated with GM1 or GD1a antibodies (30-40% of GBS patients)
  o Animal models shown to be protective against neuropathy

Misawa et al., Lancet Neurology 17:2018
Nobile-Orazio, Lancet Neurology 17:2018
Eculizumab in GBS

- 24 week multicenter, double-blind, placebo-controlled phase II trial in Japan

- 2:1 IVIG plus eculizumab or placebo
  - 1/wk for 4 weeks (before or during IVIG)

- Primary outcomes
  - Efficacy (proportion of patients with restored ability to walk independently (functional grade ≤ 2)
  - Safety
Eculizumab in GBS

- 61% in Eculizumab and 45% in placebo reached functional grade ≤ 2 at week 4 (didn’t meet the 50% threshold – 42%)
- 3 SAE
  - Eculizumab – anaphylaxis
  - Eculizumab – ICH and brain abscess (HTN, direct oral anticoagulant)
  - Placebo - depression

Limitations: small number and no direct comparison to placebo
Historical control group was less severe
Dose finding, endpoints, time to assess effect (longer outcome)

Misawa et al, Lancet Neurology 17:2018
Nobile-Orazio, Lancet Neurology 17:2018
Clinical Trials in Peripheral Neuropathy

CIDP
• Rationale: Because of side-effects, expense and limited effectiveness of first line CIDP treatments, alternative immunomodulatory agents are often used despite the lack of formal evidence of efficacy

• Fingolimod, a sphingosine-1-phosphate receptor agonist, retaining T-lymphocytes in secondary lymphoid organs → depleting circulating T cells

• Approved for RRMS
Fingolimid for CIDP

- Double-blind, international, randomized, placebo-controlled, parallel-group, event driven study

- 1:1 fingolimod versus placebo
  - IVIG stopped day before fingolimod or placebo
  - Corticosteroids tapered off over 8 weeks prior

- Primary endpoint: time to first confirmed worsening (≥ 1 point on the INCAT disability scale)

Hughes et al, Lancet Neurology 17:2018
Fingolimid for CIDP

- 54 fingolimid (41 IVIG, 13 corticosteroids),
- 52 placebo (41 IVIG, 11 corticosteroids)
- 44 worsening events – stopped for futility
  - Survival estimate of proportion free from worsening 42% in fingolimid and 43% placebo
- 40% of participants in placebo were able to stop treatment without relapse
- SAE 9 (17%) fingolimid vs 4 (8%) placebo
  - Headache, HTN, extremity pain

Limitations: 60% in both groups had no worsening in 6 months before trial
IVIG was abruptly stopped, corticosteroids were tapered - ? effect
Dose finding, endpoints, time to assess effect (longer outcome)
Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial

Ivo N van Schaik, Vera Bril, Nan van Geloven, Hans-Peter Hartung, Richard A Lewis, Gem Sobue, John-Philip Lawo, Michaela Praus, Orel Mielke, Billie L Deum, David R Cornblath, Inqenar SJ Merkies, on behalf of the PATH study group*

• Rationale: No evidence for SCIg showing efficacy in balancing immune dysregulation in autoimmune diseases

• SCIg has shown efficacy in primary immunodeficiency syndromes

Van Schaik et al, Lancet Neurology 17:2018
SClG for CIDP maintenance

• International, randomized, double-blind, placebo-controlled study
• 1:1:1 0.2 g/kg, 0.4 g/kg SClG weekly versus placebo for maintenance treatment for 24 weeks I
• CIDP patients responding to IVIG
• Primary endpoint: proportion of patients with a CIDP relapse or withdrew for any other reason
SQIg for CIDP maintenance

- 172 patients (58 high dose, 57 low dose, 57 placebo)
- 62 (36%) had a CIDP relapse
  - 32 (56%) in placebo
  - 19 (33%) in low-dose
  - 11 (19%) in high-dose

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low-dose SQIg</th>
<th>High-dose SQIg</th>
<th>Overall p-value*</th>
<th>Low-dose SQIg vs placebo</th>
<th>High-dose SQIg vs placebo</th>
<th>High-dose SQIg vs low-dose SQIg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td>63.2%</td>
<td>39.0%</td>
<td>33.7%</td>
<td>0.0002</td>
<td>0.49 (0.29–0.84)</td>
<td>0.38 (0.22–0.67)</td>
<td>0.80 (0.43–1.49)</td>
</tr>
<tr>
<td></td>
<td>(50.9–75.4)</td>
<td>(27.7–53.1)</td>
<td>(22.8–47.8)</td>
<td></td>
<td>0.007</td>
<td>0.005</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>58.8%</td>
<td>35.0%</td>
<td>22.4%</td>
<td>&lt;0.0001</td>
<td>0.48 (0.27–0.85)</td>
<td>0.25 (0.12–0.49)</td>
<td>0.53 (0.25–1.12)</td>
</tr>
<tr>
<td></td>
<td>(46.1–72.0)</td>
<td>(23.9–49.3)</td>
<td>(12.9–37.2)</td>
<td></td>
<td>0.009</td>
<td>&lt;0.0001</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Data in parentheses are 95% CIs. Data are Kaplan-Meier estimates. All tests are one-sided, with significance defined at a p value of less than 0.025. SQIg = subcutaneous immunoglobulin. *Log-rank test for trend. †Regular log-rank test.

Table 3: Probability of primary outcome or relapse at 24 weeks.
ARR was 25% in low dose vs placebo, 30% in high dose vs placebo and 6% in high dose vs low dose.

Probability of remaining relapse free was 77.6% in high-dose, 65% in low-dose, 41.2% in placebo.

NNT 2.7 HD, 4.4 LD.
SQIg for CIDP Maintenance

- SAE 11 (6 patients) – 5 (8%) SCIg vs 1 (2%) placebo
  - 20-30% had mild to moderate infusion related reactions
- 62 (90%) were treated with rescue SCIg
  - 33 (59%) required more than one induction dose (up to 4 maintenance doses)
  - 23/30 (70%) recovered – return to baseline INCAT

Limitations:
Despite the dependency test, 37% of patients on placebo did not relapse
A considerable number of patients had missing data for exploratory outcomes (preference)
No follow-up on some rescued patients

- Patients with CIDP who have stabilized with IVIg can be switched to SCIg
- 26% might relapse
- Several might withdraw due to discomfort with tubes, pumps or infusion site reactions
- Some prefer SCIg because of independence and convenience
- Good if poor venous access, cardiovascular risks or systemic IVIg-related side-effects

Van Schaik et al, Lancet Neurology 17:2018
Summary

• Many important discoveries and clinical trials in peripheral neuropathy in the last year have advanced our knowledge and treatment

• Improved our understanding of why some “CIDP” patients do not respond to standard treatment

• Gene discovery for CANVAS patients and late-onset ataxia

• Less invasive methods to diagnosis ATTRv and major advances in treatment with gene silencing

• SC Ig is an alternative maintenance therapy for CIDP patients
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