Neuropathy GROUP
EURO-NMD

Mary Reilly (London) chair

Davide Pareyson (Milan) deputy chair and lead for inherited neuropathies

Pieter van Doorn (Rotterdam) lead for inflammatory neuropathies
David Adams (Paris) lead for TTR- Familial Amyloid Polyneuropathy
Jana Heberlova (Prague) lead for paediatric neuropathies

PAGs’ representative: Jean-Philippe Plançon
(Daniel Tanesse & Françoise Pelcot deputy representatives)
Report

- Mapping of centres and activities: Questionnaire went out to all centres to collect members with interest in neuropathy – inherited – inflammatory – paediatrics
- Guidelines registry being developed – gap analysis
- Interactions with PNS (Mary Reilly, Pieter van Doorn), CMTR (Davide Pareyson) - EAN (Peter van Den Bergh, Davide Pareyson, Antonio Toscano)
- Planning meeting took place during the PNS Board Meeting in Baltimore 24th Oct 2017 (Reilly, Pareyson, van Doorn) & in Paris 3rd Nov 2017 (Reilly, Pareyson, Adams, van Den Bergh)
- Updates on recent developments in the neuropathy field
- Subgroups and interactions with other ERNs: hTTR-amyloidosis
- Interactions with PAGs
- Proposal for a Neuropathy Day
Map of Neuropathy centres/groups

- 42/62 answered (20 still missing)
- 42 centres see neuropathy patients
- 39 see adults and 37 see children
- 42 see inherited and 41 see inflammatory neuropathy patients
List of Guidelines, Consensus conferences, Recommendations for Neuropathies

POLYNEUROPATHY IN GENERAL


GBS

1) EFNS/PNS guidelines: in preparation (van Doorn PA, van den Bergh PYK, Hadden R et al)


CIDP


MMN

List of Guidelines, Consensus conferences, Recommendations for Neuropathies

PARAPROTEINEMIC NEUROPATHY

VASCULITIC NEUROPATHY

IVIg

PLASMAPHERESIS

OUTCOME MEASUREMENTS

NEUROPATHOLOGY (SKIN AND SURAL NERVE BIOPSY)
List of Guidelines, Consensus conferences, Recommendations for Neuropathies

MOLECULAR DIAGNOSIS AND GENETIC TESTING IN GENERAL


ATTR-RELATED NEUROPATHY


3) Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet Journal of Rare Diseases 2013, 8:31. Ando Y et al.

CHARCOT-MARIE-TOOTH AND RELATED NEUROPATHIES (dHMN, HNPP, HNA)


PORPHYRIA

Action for guidelines

• Collection and collation of Guidelines, Consensus conferences, Recommendations = TO BE COMPLETED

• Analysis of existing guidelines = TO BE DONE

• GAP ANALYSIS = ONGOING

• Planned Guidelines
  – PNS/EAN: Guillain-Barrè Syndrome, CIDP
  – TTR-related Amyloidosis ?

• Dissemination and application = ONGOING
<table>
<thead>
<tr>
<th>CMT type</th>
<th>Compound</th>
<th>Rationale</th>
<th>Preclinical studies</th>
<th>Translatability to patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT1A</td>
<td>Progesterone antagonists/modulators: onapristone, lonaprisone, ulipristal acetate</td>
<td>Down-regulation of PMP22 overexpression</td>
<td>Onapristone effective in CMT1A rats</td>
<td>Onapristone toxic, onapristone has hormonal action, need to reduce side effects; trial with ulipristal acetate ongoing (NCT02600286, EzdaraCT2015-001716-36)</td>
</tr>
<tr>
<td>CMT1A</td>
<td>Soluble neuregulin 1</td>
<td>Balancing PI3K-Akt and Mek-Erk signaling pathways</td>
<td>Effective in CMT1A rats</td>
<td>Already used in other diseases, but risk of side effects</td>
</tr>
<tr>
<td>CMT1A</td>
<td>PXT3003 (combination of low-dose baclofen, naltrexone, D-sorbitol)</td>
<td>Down-regulation of PMP22 overexpression</td>
<td>Encouraging results in cellular models and in CMT1A rats</td>
<td>Phase II concluded; phase III trial ongoing (NCT03023540)</td>
</tr>
<tr>
<td>CMT1A</td>
<td>P2X7 purinoreceptor inhibitors</td>
<td>Reduce abnormal calcium influx into Schwann cells, mediated by P2X7 overexpression</td>
<td>Improvement of limb strength, distal motor latency and myelinated fibre number in CMT1A rats</td>
<td>To be considered for clinical trials in CMT1A</td>
</tr>
<tr>
<td>CMT1A</td>
<td>GABA-B receptor modulators</td>
<td>Down-regulation of PMP22 overexpression</td>
<td>Tested in CMT1A rats</td>
<td>Baclofen contained in PXT3003 (see above)</td>
</tr>
<tr>
<td>CMT1A</td>
<td>Neurotrophin 3 (NT3)</td>
<td>Adeno-associated virus delivery of NT3, neurotrophic action</td>
<td>Encouraging results in Trembler J mice</td>
<td>Subcutaneous NT3 already tested in a pilot trial</td>
</tr>
<tr>
<td>CMT1A-CMT1E</td>
<td>Gene silencing (ASO, siRNA, shRNA)</td>
<td>Partial silencing of overexpressed CMT1A or mutated CMT1E PMP22 gene</td>
<td>Allele specific L16P pmp22 siRNA effective in Trembler J mice</td>
<td>To be considered</td>
</tr>
<tr>
<td>CMT1A</td>
<td>Starvation, rapamycin</td>
<td>Action on endoplasmic reticulum stress and/or autophagy</td>
<td>Effective in Trembler J mice</td>
<td>Rapamycin too toxic</td>
</tr>
<tr>
<td>CMT1A-CMT1B</td>
<td>Sephin 1</td>
<td>UPR inhibition, GADD34 phosphatase inhibitor</td>
<td>Effective in CMT1B models</td>
<td>Possible</td>
</tr>
<tr>
<td>CMT1B</td>
<td>Curcumin</td>
<td>UPR inhibition</td>
<td>Effective in mouse models of CMT1B and CMT1E</td>
<td>Possible</td>
</tr>
<tr>
<td>CMT1B</td>
<td>Leothin and other lipids</td>
<td>Improve impaired lipid biogenesis in Schwann cells</td>
<td>Studies on CMT1A rats ongoing</td>
<td>Possible</td>
</tr>
<tr>
<td>CMT1B</td>
<td>Selective Nax-1.8 blockers (C31, others)</td>
<td>Detrimental ectopic Nax1.8 expression in motor nerves in CMT1B models</td>
<td>Acute treatment with C31 effective in Mrp2 +/- and +/- mice</td>
<td>Possible</td>
</tr>
<tr>
<td>Hypermyelinating CMT (CMT4B, CMT4J, HNPP)</td>
<td>Niacin/Niaspan</td>
<td>Activation of TACE, secretase of neuregulin 1–III</td>
<td>Effective in mouse models of CMT4B1 and HNPP</td>
<td>Possible for hypermyelinating neuropathies (i.e. CMT4B1-2, HNPP)</td>
</tr>
<tr>
<td>CMT4B, CMT4J</td>
<td>Apilimod</td>
<td>Inhibition of PIKfyve, enzyme in phosphoinositide metabolism where MTM2 and FIG4 are active</td>
<td>Under investigation</td>
<td>Already used in phase II clinical trials for Crohn disease and rheumatoid arthritis</td>
</tr>
<tr>
<td>CMTX1</td>
<td>Gene therapy, lentiviral-GJB1 intrathecal delivery</td>
<td>Gene delivery substituting lacking GJB1</td>
<td>Effective in Cx32 KO mice by intrathecal administration</td>
<td>To be assessed</td>
</tr>
<tr>
<td>CMT1A - CMTX1 (all CMT)</td>
<td>ACE-083</td>
<td>Locally acting myostatin inhibitor</td>
<td>Dose dependent increase in muscle mass and strength in various animal models</td>
<td>A Phase I trial concluded; phase II trial in preparation on CMT1A and CMTX1, NCT03124459</td>
</tr>
<tr>
<td>CMT2 - dHMN (all CMT2-dHMN8)</td>
<td>HDCA6 (Histone deacetylase) inhibitors</td>
<td>Acetylation of α-tubulins improving axonal transport</td>
<td>Effective in mutant HSPT1 mice and iPSCs from HSPT1 patients</td>
<td>Possible</td>
</tr>
<tr>
<td>CMT2D</td>
<td>VEGF (vascular endothelial growth factor)</td>
<td>Antagonised aberrant interaction of mutated Gαs to Neurotphin 1 receptor</td>
<td>Enhanced expression of VEGF improved motor function in CMT2D mice</td>
<td>To be assessed</td>
</tr>
<tr>
<td>HSAN1</td>
<td>Lserine supplementation</td>
<td>Overcome SPTC1-2 defect</td>
<td>Improved measures of motor and sensory performance and decrease of deoxysphingolipids levels in transgenic HSAN1 mice</td>
<td>Pilot study performed with decrease of deoxysphingolipids levels; further trials in preparation, NCT01733407</td>
</tr>
</tbody>
</table>
Therapeutical approaches for Transthyretin-related Amyloidosis

Philippe Kerschen, MD¹
Violaine Plante-Bordeneuve, MD, PhD²,³,*

Curr Treat Options Neurol (2016) 18: 53

<table>
<thead>
<tr>
<th>TTR suppressors</th>
<th>TTR stabilizers</th>
<th>TTR scavengers</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Liver transplanted*</td>
<td>- Diflunisal*</td>
<td>- Doxycycline/TUDCA ***</td>
</tr>
<tr>
<td>- Gene silencing ‡‡ (ASOs,sirNAs)</td>
<td>- Tafamidis*</td>
<td>- CPHPC/anti-SAP antibodies ***</td>
</tr>
</tbody>
</table>

- Liver
- Eyes
- CNS (choroid plexus)

Unstable TTR tetrarners → Monomers and soluble oligomers → Tissue amyloid deposits

* Available treatment ‡‡ Phase 3 studies completed, results pending *** Phase 1/2 studies completed
Report on two trials with gene silencing in hATTR-neuropathy

To cite this article: Philip N. Hawkins, Yukio Ando, Angela Dispensieri, Alejandra Gonzalez-Duarte, David Adams & Ole B. Suhr (2015) Evolving landscape in the management of transthyretin amyloidosis, Annals of Medicine, 47:8, 625-638, DOI: 10.3109/07853890.2015.1068949
<table>
<thead>
<tr>
<th>Compound - Study</th>
<th>Inoserten – Neuro-TTR (Ionis)</th>
<th>Patisiran – Apollo (Alnylam)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-Sense Oligonucleotides</td>
<td>RNAi lipid nanoparticles</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Bind to wild type and mutated TTR mRNA</td>
<td></td>
</tr>
<tr>
<td><strong>TTR reduction</strong></td>
<td>75-79%</td>
<td>84%; 87.8% mean max serum reduction</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Subcutaneously - once a week</td>
<td>Intravenously - every 3 weeks</td>
</tr>
<tr>
<td><strong>Study Phase</strong></td>
<td>Phase 3 completed, OLE ongoing</td>
<td>Phase 3 completed, OLE ongoing</td>
</tr>
<tr>
<td><strong>Ratio treated:placebo</strong></td>
<td>2:1</td>
<td>2:1</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>15 months</td>
<td>18 months</td>
</tr>
<tr>
<td><strong>Primary Endpoints</strong></td>
<td>Norfolk QoL, mNIS+7</td>
<td>mNIS+7</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>172 randomised, 150 completed</td>
<td>225 randomised, 193 completed</td>
</tr>
<tr>
<td></td>
<td>17 treated dropped out</td>
<td>29 placebo dropped out</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Norfolk = 12 points difference at 15 months; 50% improved</td>
<td>Norfolk = 21.1 points difference at 18 months; 51.6% improved</td>
</tr>
<tr>
<td></td>
<td>mNIS+7 = 20 points difference at 15 months; 47% stabilised or improved</td>
<td>mNIS+7 = 33.99 point difference at 18 months; 56% improved</td>
</tr>
<tr>
<td></td>
<td>Independent from disease stage, presence of cardiopathy, type of mutation</td>
<td>Independent from disease stage, presence of cardiopathy, type of mutation</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Thrombocytopenia (4 cases, 1 death); 6 renal problems</td>
<td>Infusion related reactions, peripheral edema</td>
</tr>
</tbody>
</table>
Recent and ongoing RCT’s in GBS and CIDP

CIDP:
Path-trial Lancet Neurology Nov 2017

GBS:
Second dose IVIg. SID-GBS (large RCT in NL, almost finished)
ICA-GBS (Willison), n=8 Glasgow JPNS 2017
JET-GBS (Kuwabara) n= 30? Japan, not published yet. Phase 2 trial with Eculizumab, monoclonal antibody that by binding to C5 inhibits complement activation. At 24 weeks, marked improvement in motor function was observed in patients treated with eculizumab
Building subgroups: the example of amyloidosis

• EURO-NMD
  – Neuropathy (Muscle); Pathology; Genetics; Neurophysiology; Imaging

• Other ERNs: rare cardiac diseases (cardiomyopathy); blood disorders; autoinflammatory diseases

• PAGs

• Interactions with Institutions – Health Ministry for novel drug access
Neuropathy day

• ONE day dedicated to Peripheral Neuropathies
• All Europe, all centres
• Open wards and laboratories
• Workshops, presentations, meetings with patients