Altogether, specific mutations in the small heat shock proteins affect the axonal transport via induced hyperphosphorylation of neurofilaments and stabilization of the microtubule network. Both pathomechanisms can be targeted by drugs in experimental models and may open possibilities for future treatment strategies.
I report NO DISCLOSURE

Update in the management of chronic immune-mediated neuropathies
Jean-Marc Leger, MD, FAAN, National Referral Center for Neuromuscular Diseases, University Hospital Pitié-Salpêtrière and University Paris VI , Paris, France

The so-called immune-mediated neuropathies encompass an acute form, Guillain-Barré syndrome (GBS) and chronic forms, mainly chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy with persistent conduction block (MMN), and polyneuropathy associated with IgM monoclonal gammopathy of unknown significance (MGUS) binding to myelin-associated-glycoprotein (IgM anti-MAG-MGUS polyneuropathy).
These neuropathies have common features, which are clinical and electrophysiological signs indicative of a demyelinating process, raised protein in CSF, the presence in some of them of serum auto-antibodies binding to recognized antigens of the peripheral nerve myelin, and signs of demyelination/remyelination in nerve biopsies.
Chronic forms need to be distinguished on strictly defined criteria, as the response to treatment may differ according to the type of the neuropathy. For example, MMN and IgM anti-MAG-MGUS polyneuropathy do not respond to corticosteroids, while CIDP may respond either to corticosteroids, plasma exchanges or intravenous immunoglobulin. In 2010, 3 Guidelines firstly edited in 2006, have been revised by a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society, on management of respectively CIDP, MMN and paraproteinemic demyelinating neuropathies.
This review will give an update on the management of these immune-mediated neuropathies, mainly the choice of the best type and the regimen of their immunomodulatory treatment.

Clinical trials and biomarkers in CMT.
Shahram Attarian

Abstract missing

Symposium- Young Investigators Symposium
• *Justine Marsolier (France)* • *Marie Thérèse Daher (France)* • *Muriel Sebastien (France)* • *Pierre Klein (France)*

Plenary Session- SMA and Therapeutics
• *Richard Finkel (USA)* • *Jerry Mendell (USA)* • *Olivier BIONDI (FRANCE)*

SMA Therapeutics: opportunities, challenges and promising new treatments
Richard S. Finkel, MD

Multiple treatment strategies for spinal muscular atrophy have entered clinical trials in recent years. This talk will review the theory, pre-clinical evidence, and human clinical trial experience of these treatments. Standards of care have altered the natural history of SMA. Infants with type 1 may live longer with nutritional and ventilatory support. The advent of growing rods for correction of scoliosis has changed orthopedic management for children with type 2. Outcome measures have been developed and are still being refined for SMA type 1 (CHOP-INTEND and HINE scales, motor nerve CMAP), type 2 (versions of the Hammersmith scale and upper limb module) and type 3 (Hammersmith expanded scale, 6 minute walk test). Regulatory authorities favor motor function scales that are clinically meaningful.
Initial drug trials in SMA examined repurposed use of existing drugs: HDAC inhibitors to increase gene transcription (valproic acid, phenylbutyrate), modulators of exon 7 inclusion in *SMN2* (valproic acid, hydroxyurea, quinazolone), inhibition of excitotoxicity (glutaminergic: riluzole; GABAergic: gabapentin) or muscle mitochondrial enhancement (l-carnitine). None of these, unfortunately, demonstrated meaningful benefit. Oral albuterol/salbutamol has shown some benefit in type 2 and 3 patients and is often used as off-label treatment in the clinic.

Current drug therapy efforts are in three areas:
1. Promotion of exon 7 inclusion in *SMN2*:
    a. Anti-sense oligonucleotides: Ionis/Biogen, “nusinersen” by intrathecal administration, now in phase 2/3 studies in infants (symptomatic type 1 and presymptomatic) and children (type 2). The earlier phase 2 open-label studies have shown promising responses in motor function, and survival (type 1).
    b. Small-molecule drugs
        i. Roche, “RO6885247”: phase 1 RCT, currently on clinical hold, in types 1, 2, 3; infant-age 55; “RO7034067”: is in early phase 1 testing.
        ii. Novartis, “LMI070”, phase 1/2 open label in infants with type 1, to study MTD, PK, PD, motor and respiratory function.

2. Neuroprotective/mitochondrial enhancer: Trophos/Roche, "olesoxime", completed phase 2/3 RCT; benefit was seen over 96 weeks in non-ambulant types 2-3, ages 3-25 years.
3. Muscle enhancement: Cytokinetics,"CK-2127107", phase 2 RCT in types 2 and 3, age 12+ years, evaluating motor function, strength, PFTs and PK in 2 dosing cohorts vs. placebo.

Gene transfer therapy – a phase 1 study with intravenous administration of scAAV9-SMN in infants will be reported by Dr. J Mendell, Nationwide Children's Hospital.

Summary: Both AAV-mediated gene therapy and downstream disease modifying drug therapy strategies are currently in clinical trials for treatment of SMA. Several show promise with hope for infants, children and adults suffering from this progressive motor neuron disorder. Combined treatment may eventually offer a rational multidimensional approach to optimizing therapeutic benefit. How early to treat and how much of the phenotype can be rescued remains a question.

Spinal Muscular Atrophy Type 1 responds to gene replacement therapy

Jerry R Mendell, Samiah Al-Zaidy, Richard Shell, W Dave Arnold, Louise Rodino-Klapac, John T Kissel, Thomas W Prior, Carlos Miranda, Linda Lowes, Lindsay Alfano, Katherine Berry, Christopher Petek, Kathleen Church, Lyndsey Braun, Sarah Corcoran, Kathrin Meyer, Shibi Likhite, Arthur HM Burghes, Kevin D Foust, Brian K Kaspar

Spinal muscular atrophy (SMA) is the most common genetic cause of infant death with mutations of survival motor neuron 1 gene (SMN1) on chromosome 5q13 affecting 1 in 10,000 live births. Presently, there is no treatment. We have seen promising results in our ongoing gene therapy (GT) trial. Ten SMA infants have been enrolled in this trial. Criteria included: onset of symptoms before 6 months, homozygous loss of the *SMN1* gene, 2 copies of SMN2, and no c.859G>C exon 7 mutation gene modifier.

This was a dose escalation study with intravenous delivery of the SMN in self complementary adeno-associated virus (scAAV9.CB.SMN): Group 1 (n=3) $6.7x10^{13}$ vg/kg and Group 2 (n=7) $2.0x10^{14}$ vg/kg. The lower dose cohort was 6.3±0.57 months (m) at enrollment and had a CHOP INTEND (CI) 16.33±10.50. These patients still survive at 22.3±1.52m with their current CHOP INTEND at 23.6±11.9. The higher dose cohort was grouped by age at gene transfer: Group 2A (Pts 6 and 10) treated at earliest time points in the study, 2 and 1 month of age respectively, had a baseline CHOP INTEND of 47 and 50. Both achieved a normal post treatment score of 64 at 11.5 and 5 months age respectively; Group 2B (Pts 4, 5, 7, 9) with mean treatment age of 4±0.8m, baseline CHOP INTEND of 29.25±3.68 and a current age of 13.25±3.3 months reached a post treatment score of 53.0±2.0; and group 2C (Pt 8), the oldest treated infant at 8 months had baseline CHOP INTEND 12 and showed no improvement at 15 months old.

SAEs in this trial were limited to transient liver enzyme elevation without clinical manifestations and correlated with high level IFN-g ELISpot assays to AAV9 capsid. This transaminasemia responded well to short term oral prednisolone treatment

In summary, SMN gene therapy for SMA1 is neuroprotective allowing motor development to continue. At a mid-level CHOP INTEND score with enrollment at age 4.0 ± 0.8m, improvement for group 2B is highly significant with functional development to an SMA type 2 phenotypic-equivalent. An older age at enrollment (8 months) with low CHOP INTEND showed no efficacy despite higher dose. This GT trial strongly supports this mode of treatment for SMA1, far exceeding the decline on CHOP INTEND (-1.27 units per year) demonstrated by natural history. These results have been reached without a single death, paving the path for future gene transfer for SMA1 and frame a therapeutic dose and CHOP INTEND score at enrollment that has potential to completely reverse the natural history of the disease.

Why physical exercise could be proposed for SMA patient care?

Olivier Biondi, Frederic Charbonnier

Spinal Muscular Atrophy (SMA) is a group of autosomal recessive neurodegenerative diseases characterized by the specific loss of spinal motor neurons, caused by insufficient level of SMN protein expression. Three main types of SMA are commonly distinguished according to the age of onset and the severity of motor capacity impairments (Harding & Thomas, 1980), *i.e.* the severe form type 1 SMA (Werdnig-Hoffman disease), the intermediate form type 2 SMA, and the mild form type 3 SMA (Kugelberg-Wellander disease). No cure is presently available for SMA and patient care is usually provided through supportive ventilation, feeding assistance and passive limbs- and thoracic-physiotherapy (Bladen *et al.*, 2014). Since our first report, a decade ago, showing that a 5-day training program was sufficient to promote SMN expression in the spinal cord of severe type SMA-like mice, active physical exercise appeared as a promising approach for alleviating SMA symptoms. However, the lack of data dealing with the effects of different exercise types and intensities on diseased motor units still precludes the use of active physiotherapy in SMA patients. Indeed, physical exercise consists in different practices involving various motor, metabolic and physiological solicitations, including concentric *vs* eccentric contractions, anaerobic *vs* oxidative pathways, voluntary *vs* forced exercises and long-term *vs* acute training exercise programs. We investigated the effects of two different exercises types in adult type 3 SMA-like mice (Tsai et al., 2006) over 10 consecutive months, either submitted to a high intensity and amplitude swimming-based training or to a low intensity and amplitude running-based training (Grondard et al., 2008). We reported compelling evidence of specific exercise-induced benefits for SMA adult motor units, both at the structural and functional levels leading to the maintenance of neuromuscular junctions and skeletal muscle phenotypes. If both exercise types significantly enhanced motor neuron survival, independently of SMN expression, all the exercise-induced benefits were quantitatively and qualitatively dependent of the specific characteristics of each exercise, suggesting that the related neuroprotection is strongly dependent on the specific activation of some motor neuron subpopulations. Therefore, our studies have reinforce the idea that a better understanding of the effects of "well controlled" physical exercise on motor units could provide several clues for designing rehabilitation programs for SMA patients. Our findings have been used to design an innovative clinical trial for SMA patients, which is currently ongoing in France. The main objectives of this trial are to design and validate a new motor function scale for neurodegenerative disorders and to evaluate the exercise-induced benefits for type 2 and 3 SMA patients.