Updates on Neuromuscular Disorders 2016

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Who is This Guy? Why is he Keeping me Awake?

• Neurologist
• Fellowship in neuromuscular medicine at Case Western Reserve
• Certified in neuromuscular medicine by the ABPN

• Certified in electrodiagnostic medicine by the ABEM
• Member of the Medical/Scientific advisory board for the Myasthenia Gravis Foundation of America

Disclosures

• Physician at MDA clinic
• No other financial disclosures
• Some off-label uses will be discussed
• Some slides in this presentation were provided by the companies who developed the drugs being discussed
Learning Objectives

At the conclusion of this activity, participants will be able to...

1. Explain the pathophysiology of neuromuscular diseases for which new possible treatments are being investigated.
2. Describe some of the recent and ongoing clinical trials investigating possible treatments for neuromuscular diseases.
3. Recognize how exon-skipping therapies may benefit patients with Duchenne muscular dystrophy.

What We’re Going to Cover Today

• What do you mean, “neuromuscular disorders?”
• Myasthenia Gravis and Thymectomy
• Duchenne Muscular Dystrophy and Eteplirsen
• SMA and nusinersen
• CMT 1-A and PXT3003
Nervous System

- Brain
- Spinal cord
- Anterior horn cells
- Roots
- Plexuses
- Nerves
- NMJ
- Muscle

Medical Speak

- Brain  ------------------------ Encephalopathy
- Spinal cord  -------------- Myelopathy
- Anterior horn cells  -------- Motor neuron disease
- Roots  ---------------------- Radiculopathy
- Plexuses  ----------------- Plexopathy
- Nerves  --------------------- Neuropathy
- NMJ  ----------------------- NMJ disorder
- Muscle  --------------------- Myopathy
Central Nervous System

- Brain  ------------- CNS
- Spinal cord  ----- CNS
- Anterior horn cells
- Roots
- Plexuses
- Nerves
- NMJ
- Muscle

Peripheral Nervous System

- Brain  ------------- CNS
- Spinal cord  ----- CNS
- Anterior horn cells
- Roots
- Plexuses
- Nerves
- NMJ
- Muscle

Neuromuscular Disorders

- Anterior horn cells  ------------- Motor neuron disease
- Roots  ------------------------ Radiculopathy
- Plexuses  ------------------ Plexopathy
- Nerves  --------------------- Neuropathy
- NMJ  ------------------------ NMJ disorder
- Muscle  --------------------- Myopathy
Today's Topics

- Anterior horn cells ------- Spinal Muscular Atrophy
- Nerves ------------------- CMT 1-A
- NMJ --------------------- Myasthenia Gravis
- Muscle ------------------ DMD

Myasthenia Gravis and Thymectomy

What is Myasthenia Gravis?
Neuromuscular Disorders

- Anterior horn cells ------------ Motor neuron disease
- Roots ------------------ Radiculopathy
- Plexuses ------------- Plexopathy
- Nerves ------------- Neuropathy
- NMJ -------------------- NMJ disorder
- Muscle ------------- Myopathy

A Brief History of Myasthenia

- Term coined in 1895 by Friedrich Jolly
- Earlier cases were described
- Thomas Willis in *De Anima Brutorum* 1672

Source:

Typical History

- Weakness, ptosis, diplopia, blurred vision, dysphagia, or dyspnea
- Fluctuating course
- Better in the morning, worse at night
- Worse after exercise, or other fatigue
- Gradual or rapid onset
- Perhaps precipitated by new medication
- No sensory symptoms
- Painless
Physical Exam Findings

- Weakness, ptosis, dysconjugate gaze
- Strength or ptosis worsens with continued effort
- Ptosis may improve with ice pack
- Otherwise normal neurological exam

Image Source: Pakistan Myasthenic Welfare Organization
http://www.pmwo.org.pk/mg.html
Overall Incidence

- 2.1 to 5.0 per million people per year
- This has not changed much over the years

Sources:

Prevalence

- Prevalence rate has increased since the 1950s
- Declining mortality rate
- Estimated to be about 20 per 100,000

Sources:

MG in Hawai‘i

- Expected Incidence: 5 new cases per year
- Expected Prevalence: 284 people
Hospital Admissions


MG in Hawai‘i


Clinical Course

- Not progressive
- Fluctuating symptoms
- Risk of worsening
- Risk of MG Crisis
- Very variable from patient to patient
Ocular Myasthenia Gravis

• 35% of MG patients present with purely ocular symptoms
• 50-80% will progress to generalized disease
• Believed to be most likely in first 2 years

Sources:

Myasthenia Gravis Crisis

• MG exacerbation that leads to respiratory failure
• Weakness of respiratory muscles
• Weakness of bulbar muscles
• Most severe complication of MG
• Requires critical care

Source:

Mortality

• Appx. 30% in the mid-1950s
• Closer to 3% in the late 1990s

Sources:
3 Main Treatments

- Cholinesterase inhibitors (pyridostigmine)
- Corticosteroids
- “Steroid-sparing” agents

Pyridostigmine Bromide

- aka Mestinon
- 60mg tabs
- 30 – 60 mg to start
- Can go higher
- > 180mg rarely effective
- Q 3 – 6 hours
- Sustained-release available


Corticosteroids

- No agreement as to optimal dose
- High doses often recommended (80-100mg/day)
- Alternate-day treatment also suggested
- Slow taper down
- Up to 20% of patients need prednisone for life

Steroid-Sparing Agents

- Allow patients to be on lower doses of prednisone, or even to get off prednisone
- Take months for effect to be seen
- Azathioprine
- Mycophenolate Mofetil
- Cyclosporine

AAN Guidelines

- “...the benefit of thymectomy in nonthymomatous autoimmune MG has not been established conclusively.”
- “For patients with nonthymomatous autoimmune MG, thymectomy is recommended as an option to increase the probability of remission or improvement (Class II).”


Myasthenia Gravis and Thymectomy

What is Thymectomy?
Why would anyone think of this?

• 1939, Blalock et al. removed a cystic thymic tumor from a 21 year-old woman
• Her MG remitted
• They tried it in other MG patients with no thymoma
• found hyperplasia in the thymus
• reported improvement in at least half of their patients.


Thymus

• The pathophysiology involves T-cell mediated immunity
• Thymic pathology in 80-90% of MG patients
• About 15% of MG patients have thymoma

Thymectomy

• Goal is stable remission
• Various success rates cited: 15%, 64%, 90%, depending on source
• Expert consensus is that thymectomy can be useful for some patients


Thymectomy

• Believed to be best performed within the first few years of diagnosis
• Usually recommended for patients < age 60


MGTX Trial

• Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy
• Estimated enrollment: 126
• Study Start Date: June 2006
• Study Completion Date: July 2016

Source: ClinicalTrials.gov  NCT00294658
Future Treatments?

• Studies ongoing with monoclonal antibodies
  – Rituximab
  – Eculizumab

Duchenne Muscular Dystrophy and Eteplirsen

What is Duchenne Muscular Dystrophy?
Neuromuscular Disorders

- Anterior horn cells ——— Motor neuron disease
- Roots ———— Radiculopathy
- Plexuses ———— Plexopathy
- Nerves ———— Neuropathy
- NMJ ———— NMJ disorder
- Muscle ———— Myopathy

Dystrophin

- First gene identified by positional cloning
- Large gene (the average gene consists of 3000 bases; the dystrophin gene comprises 2.4 million)
- Short arm of Myasthenia Gravis chromosome
Duchenne muscular dystrophy

- Early childhood weakness
- Gower sign
- Calf hypertrophy
- Wheelchair dependence by age 12
- Death from cardiomyopathy with conduction defects, respiratory weakness, & pneumonia
Duchenne muscular dystrophy

Dystrophin

Actin

“Revertant fibers” result from reading frame restoring mutations
Dystrophinopathy: Diagnosis

- Deletions or duplications in DNA isolated from peripheral blood
  - ~70% of Duchenne
  - ~85% of Becker
- Muscle biopsy
  - Immunostaining for dystrophin
  - Immunoblot analysis
  - Evaluation of related proteins

Duchenne Muscular Dystrophy and Eteplirsen

What is Eteplirsen?
What is Spinal Muscular Atrophy?

Neuromuscular Disorders

- Anterior horn cells --- Motor neuron disease
- Roots ------------ Radiculopathy
- Plexuses -------- Plexopathy
- Nerves ---------- Neuropathy
- NMJ ------------ NMJ disorder
- Muscle -------- Myopathy
Spinal Muscular Atrophy - Description -

- Loss of lower motor neurons
- Subtypes named for age of onset
- Progressive weakness

SMA Type 1

- Most severe
- Most common (60% of SMA)
- Very early onset. “Floppy baby syndrome”
- Weakness interferes with breathing, coughing, and swallowing.
- High mortality at a young age

SMA Type II

- Typical onset between 6 and 24 months
- Weakness is less severe
- Affected individuals unable to walk
SMA Type III

- Typical onset after 18 months
- Affected individuals may initially be able to walk, but as weakness worsens, they may become wheelchair-bound

SMA Type IV

- Onset in adolescence or adulthood
- Less severe, may still be progressive
- Rare

Spinal Muscular Atrophy - genetics -

- Caused by mutations in survival motor neuron 1 gene (SMN1)
- Results in deficiency of SMN protein
Spinal Muscular Atrophy - genetics -

• There is a second gene, called SMN2, that produces SMN protein in insufficient amounts

• The number of SMN2 gene copies correlates with clinical phenotype

Spinal Muscular Atrophy

- SMA is a rare, debilitating, autosomal recessive neuromuscular disorder caused by insufficient levels of SMN protein

Spinal Muscular Atrophy and Nusinersen

What is Nusinersen?
Nusinersen

- Antisense oligonucleotide
- Modifies splicing of the SMN2 precursor mRNA
- Increases the levels of full length SMN2
- Promotes increased production of functional SMN protein
**NURTURE Study Design**

- Phase 2, open-label, multicentre, multinational, single-arm study in 10 countries
- **Objectives:** to evaluate the efficacy and safety profile of intrathecal nusinersen in infants with genetically diagnosed and pre-symptomatic SMA
- **Enrollment:** up to 25 infants

**Key inclusion criteria:***
- Age ≥6 weeks at first dose
- Free of infection
- Genetic diagnosis of type 1, 2, or 3 SMA
- No previous treatment with nusinersen
- Written informed consent
- **Key exclusion criteria:***
- Age <6 weeks at first dose
- Infections
- Other neurological disorders
- History of, or at risk for, severe respiratory disorders
- Previous intrathecal medication
- Prior or ongoing motor function intervention
- Major congenital malformations or anomalies
- History of, or at risk for, severe gastrointestinal disorders

**Study Endpoints**

- **Primary:**
  - Time to respiratory intervention (invasive or non-invasive ventilation for 48 hours/day continuously for ≥7 days or tracheostomy) or death
- **Secondary:**
  - Safety, tolerability and pharmacokinetics
  - Effect on development of SMA by assessing clinical milestones
  - Ability to crawl, stand or walk
  - Motor function milestones
  - Assessed using CHOP INTEND, HINE and WHOD
  - Survival (proportion of patients alive)
  - Growth parameters

**Study Overview: Interim Analysis**

- 22 infants screened
- 17 infants enrolled
- 17 infants treated
- Interim analysis data cutoff: 8 June 2016
- Efficacy analyses are based on 13 infants who have reached the final efficacy assessment visit (Day 64, age ≥2 months) or longer
Primary Endpoint: Time to Death or Respiratory Intervention

- At the time of the interim analysis, infants had been enrolled for up to ~13 months
- All infants were still alive
- No infants have required invasive ventilation or tracheostomy
- No infants have required non-invasive ventilation for ≥6 hours/day continuously for ≥7 days

Summary of HINE Motor Milestone Achievements

<table>
<thead>
<tr>
<th>Milestone</th>
<th>True no. of infants achieving milestone</th>
<th>2 copies of SMI0 ≤4</th>
<th>3 copies of SMI0 ≤4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head control</td>
<td>9</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Sitting</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Standing</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Walking</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

Conclusions

- Findings from the NURTURE interim analysis show that all the pre-symptomatic infants with SMA treated with nusinersen are alive without requiring chronic respiratory support and are exhibiting improvements in function and motor milestones
- Most infants are achieving motor milestone and growth parameter gains generally consistent with normal development
- The majority of infants are gaining weight
- To date, no new safety concerns have been identified
The ENDEAR Study

- ENDEAR is a Phase 3, randomised, double-blind, sham procedure controlled study to assess the clinical efficacy, safety and tolerability of intrathecal nusinersen in infants with SMA.

ENDEAR Study Design

- ITT and safety population: randomised and received 1 dose of study drug.
- Intent to treat population: ITT participants who received nusinersen dose/sham procedure control at least 2 months before cut-off date for interim efficacy analysis and/or were assessed at any of the Del 183, 300, or 364 visits.

ENDEAR Primary Endpoint: Definition of HINE Motor Milestone Responders

- Motor milestone responder definition: more HINE categories with improvement than worsening.
- Participants who die or withdraw are counted as non-responders.

Improvement: 2-point improvement in ability to sit, or maximal score, or 3-point improvement in any other milestone excluding voluntary grasp.

Worsening: 2-point worsening in ability to kick, or score zero, or 3-point worsening in any other milestone excluding voluntary grasp.
What is CMT 1-A?
Neuromuscular Disorders

- Anterior horn cells —— Motor neuron disease
- Roots ———————— Radiculopathy
- Plexuses ——————— Plexopathy
- Nerves ——————— Neuropathy
- NMJ ——————— NMJ disorder
- Muscle ——————— Myopathy

CMT 1-A  
- Description -

- CMT refers to inherited sensorimotor peripheral polyneuropathies
- 90 different genes
- CMT 1 is demyelinating

Sources:

CMT 1-A  
- Pathophysiology -

- Genetic disease
- Autosomal dominant
- Duplication of peripheral myelin protein-22 (PMP-22).
- Overexpression of PMP-22 causes abnormal myelin structure and function

Sources:
**CMT 1-A**  
**- Impressive-Sounding Numbers -**

- CMT Affects appx. 1 in 2,500 people in the United States
- CMT 1 accounts for about 55% of all cases of CMT
- CMT 1-A accounts for about 66% CMT 1

Sources:
- http://www.cmtusa.org/understanding-cmt/types-and-causes/

**CMT 1-A**  
**- So What’s the Deal? -**

- No effective treatment for any form of CMT
- Many agents have been evaluated
- Supportive care, orthotics, PT and OT are mainstay of treatment

Source:

**CMT in Hawai’i**

- Expected Prevalence:  
  - 568 people with CMT  
  - 206 people with CMT 1A
PTX3003 - Description -

- A “pleodrug”
- “a fixed dose combination of (RS)-baclofen, naltrexone hydrochloride and D-sorbitol selected via a Systems Biology approach and developed by Pharnext, with the aim to lower toxic PMP22 gene over-expression in CMT1A.”

Sources:
- https://clinicaltrials.gov/ct2/show/NCT02579758

What is PTX3003?

- From Phase 2 trial, High Dose:
  - 6 mg baclofen
  - 0.7 mg naltrexone
  - 210 mg sorbitol

- Uncertain what doses being tested in Phase 3 trial

Sources:
Other treatments tried for CMT 1-A

- Vitamin C
- Vitamin A
- Vitamin E

Sources:

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PTX3003

- “Pharmacology-network based drug repurposing”

Source:  Chumakov, I. et al. 2014. Polytherapy with a combination of three repurposed drugs (PTX3003) down-regulates Pmp22 over-expression and improves myelination, axonal and functional parameters in models of CMT1A neuropathy. Orphanet Journal of Rare Diseases 9:201

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PTX3003 - How Does it Work? -

- “The proprietary R&D platform of Pharnext is based on network pharmacology. It allows the development of synergistic combinations of repositioned drugs – pleodrugs – which benefit from an outstanding safety profile and IP with strong enforceability.”

Source:  https://www.pharnext.com/en/
PTX3003

- “Eventually, three drugs – (RS)-baclofen, naltrexone and D-sorbitol – were chosen for testing in the relevant cellular and animal models of CMT1A.”

Source: Chumakov, I. et al. 2014. Polytherapy with a combination of three repurposed drugs (PTX3003) down-regulates Pmp22 over-expression and improves myelination, axonal and functional parameters in models of CMT1A neuropathy. Orphanet Journal of Rare Diseases 9:201
PTX3003
- What’s the Evidence? -

- Preclinical studies
- Phase II study
- Recruitment now in process for Phase III
PXT3003 Phase 2 Trial

- 80 adult patients with mild-to-moderate CMT1A received in double-blind for 1 year Placebo or one of the 3 doses of PXT3003 tested
- Efficacy was assessed using the Charcot-Marie-Tooth Neuropathy Score (CMTNS) and the Overall Neuropathy Limitations Scale
- This trial confirmed the safety and tolerability of PXT3003.
- The highest dose (HD) showed consistent evidence of improvement beyond stabilization.
- CMTNS showed significant improvement of 8% (0.4% - 16.2%) in the HD group versus the pool of all other groups
- ONLS showed significant improvement of 12.1% (2% - 23.2%)
- HD group had significantly more patients who did not deteriorate over one year
### PXT3003 Phase 3 Clinical Trial

- **Estimated Enrollment:** 300
- **Study Start Date:** December 2015
- **Estimated Study Completion Date:** December 2017
- **Estimated Primary Completion Date:** December 2017 (Final data collection date for primary outcome measure)

Source:

- [https://clinicaltrials.gov/ct2/show/NCT02579759](https://clinicaltrials.gov/ct2/show/NCT02579759)
Study PXT3003-02 eligibility criteria

Inclusion criteria:
- Male or female aged from 16 to 65 years
- Patient with a proven genetic diagnosis of CMT1A
- Mild to moderate severity assessed by CMTNS= + with a score ≥2 and ≤12
- Muscle weakness in at least 5 toes
- Motor nerve conduction of the median nerve of at least 55 m/sec.
- Signed written informed consent
- Able to comply with all study procedures and scheduled visits.

Exclusion criteria:
- Other significant neurological disease or major systemic disease
- Ulcerative or gastrointestinal disease (e.g. diabetes, PI) with unstable medical illness since last 30 days
- Hematologic disease, hepatitis or liver failure, renal failure
- Lived previously in 6 months before randomisation or disabled before trial completion
- Currently receiving any vitamin, mineral supplements or medications other than vitamins
- Alcohol or drug abuse, or non-compliance with treatment or other experimental protocols.
- Unauthorized concurrent treatments (vaccination, chemotherapy, surgery, pharmacological forms, opioids, dentrifices and potentially harmful drugs such as anesthetics, chemotherapy, anti-cancer drugs)
- Female or childbearing patients (without contraceptive measures), pregnant or breastfeeding
- Known hypersensitivity to any of the individual components of PXT3003
- Paraphys (contra-indication to surgery, and it may also induce neurotoxicity)
- Individuals to complete the study follow-up (tissue workers, transplant workers, tourists or any others for whom follow-up evaluation is not assumed)
- Inability to provide written informed consent or to comply with evaluation procedures
- Participation in another trial of investigational (drug) within the past 30 days
- Only one patient per family living in the same household, to avoid violation of confidentiality and risk of inversion of the blind treatments which could jeopardize the interpretation of study results.

That's all Folks!