

SMA Treatment Update

Adults with SMA

MDNSW Medical Information & Research Day

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What might one want to know?

- What treatments are out there for adults?
 - Currently available in Australia?
 - What outcome can one expect from current treatment?
 - What is required of the treatment?
 - Potential adverse effect?
 - What else is in the pipeline?
- Should one wait/ or should one go for it?

What treatments

- (Olesoxime – stopped development June 2018)
 - Cholesterol oxime family - preserve mitochondrial function
 - Neuroprotective for motor neurons
- Onasemnogene abeparvovec (Zolgensma)
 - Gene therapy replacing SMN gene
 - For children < 2 yo with SMA
 - Intrathecal
- Nusinersen (Spinraza)
 - Antisense oligonucleotide
 - SMN2 pre-mRNA splicing modifier
 - Intrathecal
 - For disease onset < 18 years
- Risdiplam (Evrysdi)
 - Small molecule
 - SMN2 pre-mRNA splicing modifier
 - Oral

SMA

- Survival motor neuron 1 (SMN1) gene
 - Chromosome 5q13.2
 - Homozygous deletions in SMN1 gene - 96%
- Survival motor neuron 2 (SMN2) gene
 - The paralogue
 - C>T substitution in exon 7
 - Affects RNA splicing
 - SMN protein 90% truncated, non-functional

Currently in Australia

- Nusinersen (Spinraza)

- Biogen, Cambridge, Massachusetts, USA
- Antisense-oligonucleotide -modify pre-mRNA splicing of SMN2
 - Increases functional SMN protein
 - Approvals – Italy: any 5q SMA 2017; Germany
- Loading doses then maintenance 12mg/5mL
 - Days 0, 14, 28, 63, then q 4 months
- Intrathecal
 - Image guidance



- Risdiplam (Evrysdi)

- Roche
- Small molecule - SMN2 pre-mRNA splicing modifier
 - Increases functional SMN protein
- Oral solution – refrigerated 2-8 C
- 5mg daily (for >20kg)



Some conjecture - Nusinersen

- Safe
 - Minor side effect
 - Inconvenience
 - Image-guidance
- Response - not age-dependent
- Suggestion of greater improvement in less severe disease/ better baseline function
 - ?sensitivity of scales used
- Cumulative effect
 - More benefit over longer period of time

JEWELFISH - Risdiplam

- Adverse events:
 - Upper respiratory tract infection 17%
 - Pyrexia 17%
 - Headache 16%
 - Nausea 12%, Diarrhoea 11%, Vomiting 8%

Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study

Tim Hagenacker*, Claudia D Wurster*, René Günther*, Olivia Schreiber-Katz, Alma Osmanovic, Susanne Petri, Markus Weiler, Andreas Ziegler, Josua Kuttler, Jan C Koch, Ilka Schneider, Gilbert Wunderlich, Natalie Schloss, Helmar C Lehmann, Isabell Cordts, Marcus Deschauer, Paul Lingor, Christoph Kamm, Benjamin Stolte, Lena Pietruck, Andreas Totzeck, Kathrin Kizina, Christoph Mönninghoff, Otgonzul von Velsen, Claudia Ose, Heinz Reichmann, Michael Forsting, Astrid Pechmann†, Janbernd Kirschner†, Albert C Ludolph‡, Andreas Hermann, Christoph Kleinschnitz

• July 2017- May 2019

• N = 124, prospective

f'up 6mo (80%), 10mo (61%), 14mo (35%) •
SMA type 2: 6mo n=45... 14mo n=20
SMA type 3: 6mo n=77... 14 mo n=37

– HFMSE... RULM, 6MWT

• Proportion of clinically meaningful improvement

(\geq + 3 points on HFMSE)

– 6 mo: 28%

• mean difference 1.73

– 10 mo: 35%

• mean difference 2.58

– 14 mo: 40%

• mean difference 3.12

(\geq +2 points RULM)

– 6mo: 23%

• Mean difference vs baseline (p<0.0001):

– HFMSE score +3.12

– RULM score +1.09

– 6MWT +46m

• 5 patients showed increased HFMSE of > 10

– All with SMA type 3

– 3-4 SMN2 copies

– Ambulant 3, non-ambulant 2

– Age 48-59 years

• 14 deteriorated

Hagenacker et al, Lancet Neurol 2020

- Subgroup analysis

- Mean HFMSE

- Ambulant > non-ambulant
 - Higher baseline > lower

- SMA 3 > SMA 2

Greater improvement in motor function correlate with lower severity of disease at baseline

- Not age-dependent

- Change in HFMSE

- RULM score at 14 mo







- Adverse effects – most commonly

- Headache (35%)

- Back pain (22%)

- Nausea (11%)

Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3

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- N = 116 (M68, F48), retrospective, F'up 6-14 mo
 - RULM, HFMSE, 6MWT... Spirometry, timed walk/rise, subjective
 - Ages 18-72, median 34 years
- SMA type 3, n= 103, (Sitters 51, Walkers 52)
 - HFMSE
 - 6mo: +1 (median difference), range -5-8 (p<0.0001)
 - 10mo: +2, range -3-9 (p<0.0001)
 - 14 mo: + 3, range -3-11 (p<0.0001)
 - RULM
 - Ceiling effect, no change
 - 6MWT
 - 6mo: +11m (p=0.0005), 10mo: =25m (p= 0.00019), 14mo: +20m (p=0.016)
 - Spirometry
 - FVC Walkers 14mo: median +7% (p=0.031); FEV1 all SMA3 14mo +3%, p=0.0499
- SMA type 2, n= 13
 - 14 mo: No significant improvements HFMSE
 - +ve trend on RULM – higher baseline showed improvement

Maggi et al, JNNP 2020

- Subjective clinical improvement
 - 6mo: 58.7%, 10mo: 59.5%, 14mo: 57.1%
- Adverse events
 - Headache (post LP)
 - at least once 2/3
 - Back pain 8.6%
 - 1.7% ceased Rx
- Image-guidance in 35% patients
 - SMA3:
 - Standard LP 82.5%; CT-guided 3.9%, X-ray guided 13.6% (8.2% manual-> image-guided)
 - SMA2:
 - 12/13 with image-guidance
 - CT-guided 53.8% (7); X-ray guided 38.5% (5 patients)
- Cumulative effect over time
 - Responders
 - HSMSE + 3, RULM +2, 6MWT +30m
 - 6mo: 56%; 10mo: 64%; 14mo: 70%
- SMN2 copy numbers 6MWT (SMA3) at 14 mo
 - 4 copies -> improved more
- Patients with very advanced disease
 - Residual motor function imp
 - Less clear effect on motor function - ?suitability of scales
- HFMSE changes – not correlate with:
 - age, gender, disease duration, baseline performance (RULM, 6MWT), ?SMN2 copy number

JEWELFISH - Risdiplam

(SUNFISH – DBRCT age 2-25 years, SMA2/ 3)

JEWELFISH

- Open-label study, evaluating safety
- N = 174, age 1-60 yrs, SMA types 1-3
 - 30% teenagers, 35% adults, 62% HFMSE < 10
 - Up to 3 years
 - Previously Rx – nusinersen (n=66), onasemnogene abeparvovec (n=14)
- Increased SMN protein level x 2 fold
- Stabilisation of motor function (MFM-32)
 - At 12 mo

JEWELFISH - Risdiplam

- Adverse events:
 - Upper respiratory tract infection 17%
 - Pyrexia 17%
 - Headache 16%
 - Nausea 12%, Diarrhoea 11%, Vomiting 8%

Treatment expectations and perception of therapy in adult patients with spinal muscular atrophy receiving nusinersen

Thomas Meyer^{1,2} | André Maier¹ | Zeljko Uzelac³ | Tim Hagenacker⁵ | René Günther^{6,7} | Olivia Schreiber-Katz⁸ | Markus Weiler⁹ | Robert Steinbach¹⁰ | Ute Weyen¹¹ | Jan Christoph Koch¹² | Dagmar Kettemann¹ | Jenny Norden¹ | Johannes Dorst³ | Claudia Wurster³ | Albert C. Ludolph^{3,4} | Benjamin Stolte⁵ | Maren Freigang⁶ | Alma Osmanovic⁸ | Susanne Petri⁸ | Julian Grosskreutz¹⁰ | Annekathrin Rödiger¹⁰ | Ramona Griep² | Marcel Gaudlitz² | Bertram Walter¹ | Christoph Münch^{1,2} | Susanne Spittel^{1,2}

- n=151 SMA2 n=51; SMA3 n=90
 - Median ~ 6.1mo (0.5-16mo)
 - Age 15-69 years
- ~10% symptoms improvement
 - On the MYMOP2 score – p <0.001
 - Self-selected 2 prioritised symptoms
 - Greatest gain in bulbar function, head stabilisation and arm function.

Meyer et al, Eur J Neurol 2021

- Treatment expectations and perception of therapy in adult patients with spinal muscular atrophy receiving nusinersen - PubMed (nih.gov)

Meyer et al, Eur J Neurol 2021

- How likely is it that you would recommend nusinersen to a friend who suffers from SMA?
 - Net promoter score (NPS)
 - Patients <12 mo: 53% promote
 - -> 13-24mo: 64%;
 - >24mo: 71% promote
- TSQM-9 (Treatment Satisfaction Questionnaire for Medication) – 9 questions, 3 domains
 - Effectiveness – 89% satisfied for symptom relief
 - Convenience – 64% difficult for admin of Rx (hospital stay for 2d in germany)
 - Global satisfaction – 93% thinks good outweigh bad

What's in the pipeline

- Nusinersen in higher doses (DEVOTE)
- Intravenous OAV101 (AVXS-101) in pediatric patients