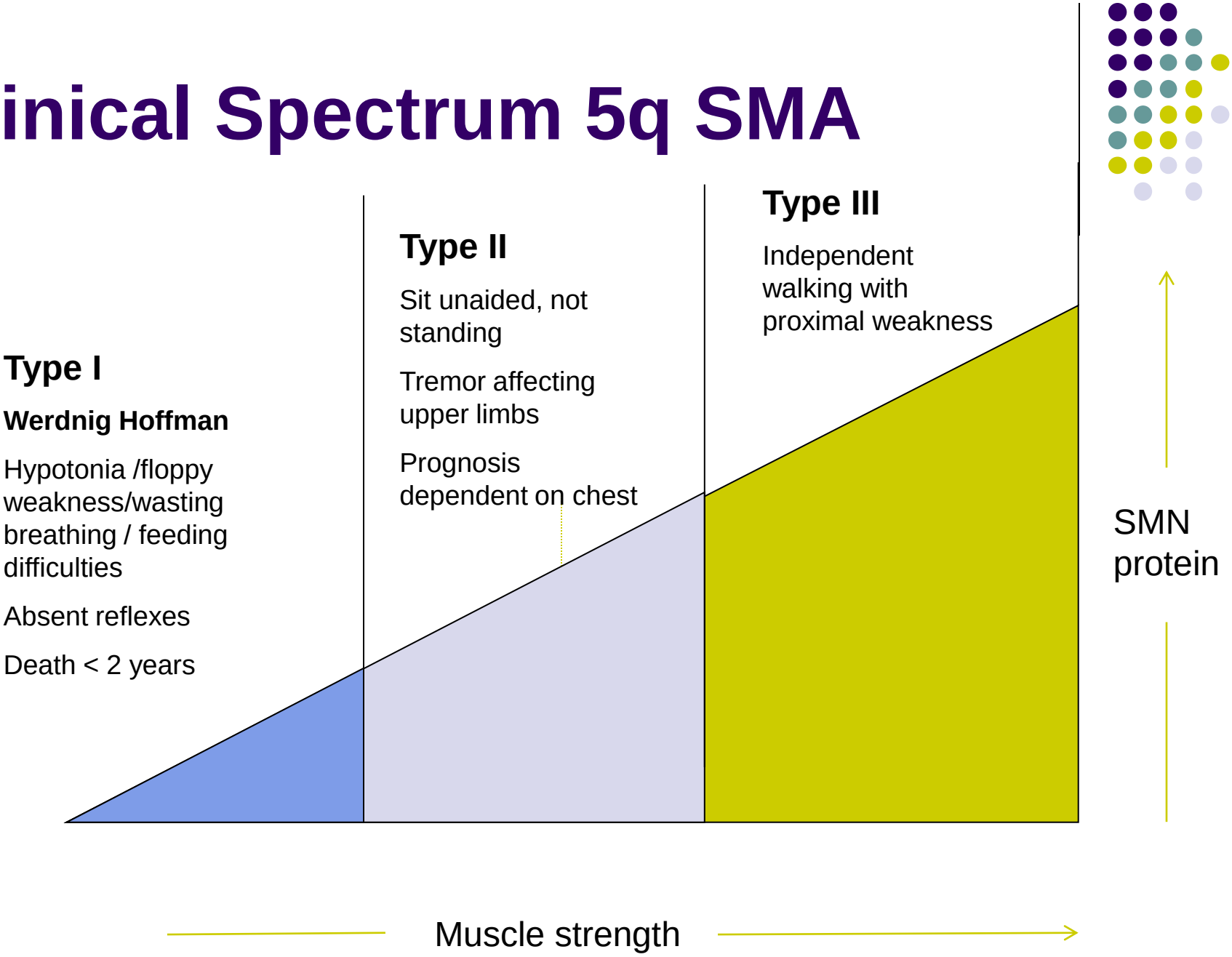
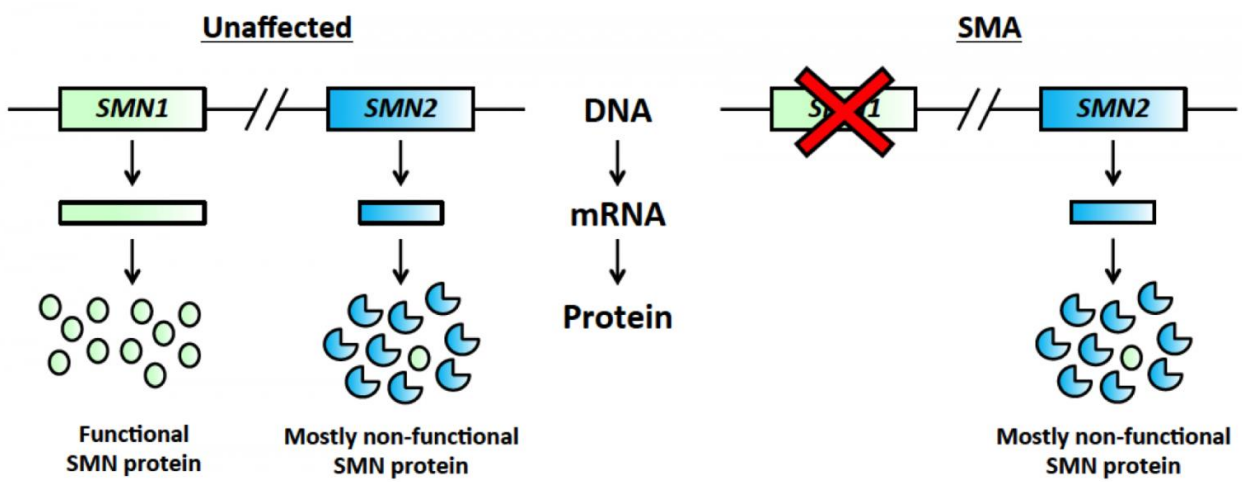
Spinal Muscular Atrophy Type 1

Treatment Landscape and Evolving Phenotypes

Clinical Spectrum 5q SMA



Clinical Spectrum 5q SMA



Clinical Presentation

- Essa
- 3rd child of 1st cousin parents
- 1st child born in 2014, little girl diagnosed with SMA at 6m, died in hospice at 11m
- 2nd child healthy girl now 3 yrs
- Born at term planned LSCS, active and moving all 4 limbs at birth
- Presented at 6 days with reduced spontaneous movements.

Video

Progress

- Feeding well and regained birthweight with breast feeds
- Abdominal breathing pattern but normal overnight sleep study
- DNA day 10 confirmed homzygous deletion exons 7+8 SMN1 gene
- Priorities for management??
- Prognosis for Essa

Special Issue Article

Journal of Child Neurology
Volume 22 Number 8
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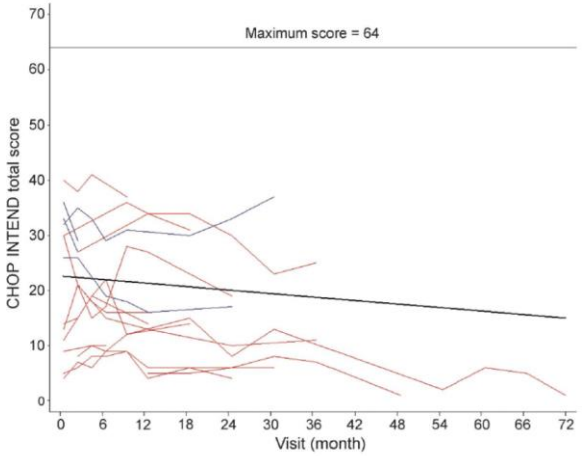
Consensus Statement for Standard of Care in Spinal Muscular Atrophy

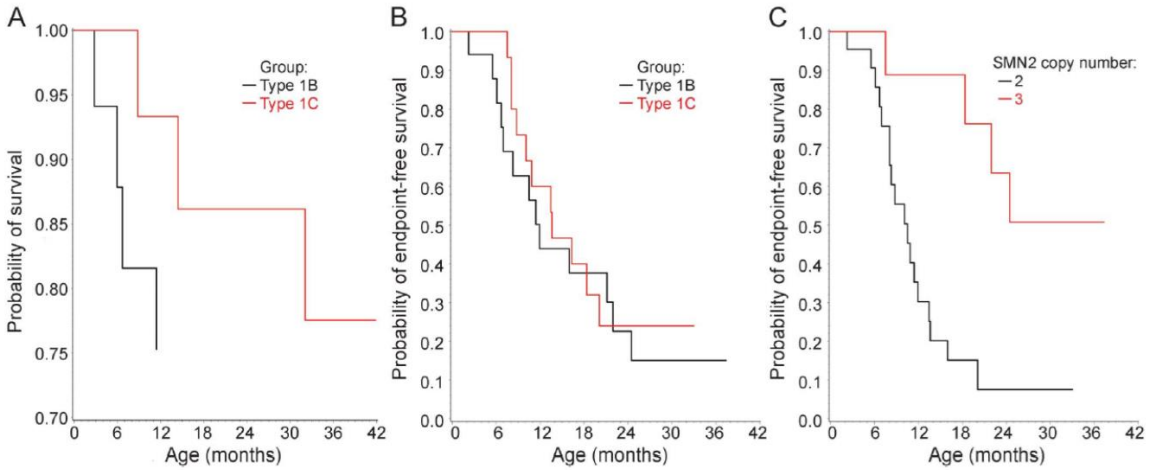
Ching H. Wang, MD, PhD, Richard S. Finkel, MD, Enrico S. Bertini, MD, Mary Schroth, MD, Anita Simonds, MD, Brenda Wong, MD, Annie Aloysius, MRCSLT, HPC, Leslie Morrison, MD, Marion Main, MCSP, MA, Thomas O. Crawford, MD, Anthony Trela, BS, and Participants of the International Conference on SMA Standard of Care

Figure 2 CHOP INTEND motor function in SMA-I: Longitudinal data



The CHOP INTEND longitudinal data are represented for each subject with 2 or more assessments. Those subjects enrolled within 3 months of diagnosis ("recent") are shown with a blue line and those enrolled more than 3 months after diagnosis ("chronic") are shown with a red line. CHOP INTEND = The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders; SMA-I = spinal muscular atrophy type I.

Figure 1 Time-to-event curves for SMA-I



Kaplan-Meier curves for SMA-I. (A) Probability of survival with advancing age by SMA-I subtype (type IB, n = 18; type IC, n = 16). (B) Probability of not reaching the combined endpoint of death or the need for a minimum of 16 hours/day of noninvasive ventilation support for a minimum of 14 continuous days, in the absence of an acute reversible illness or perioperatively, with advancing age by SMA-I subtype. (C) Probability of not reaching the combined endpoint with advancing age by *SMN2* copy number (2 copies, n = 23; 3 copies, n = 9). SMA-I = spinal muscular atrophy type I.

Observational study of spinal muscular atrophy type I and implications for clinical trials

Neurology® 2014;83:810-817

Revised Standards of Care 2018

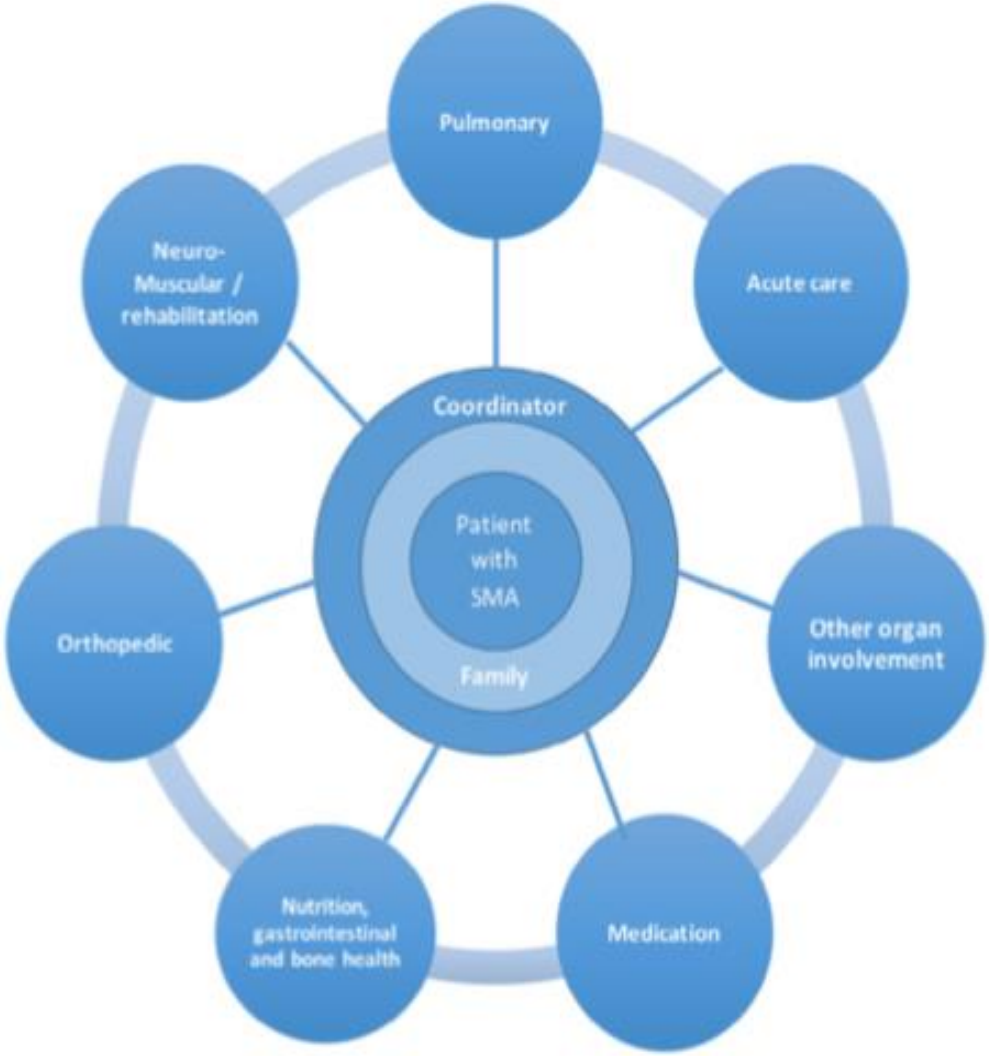


Fig. 2. Multidisciplinary approach.

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Neuromuscular Disorders 28 (2018) 103–115
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Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

Eugenio Mercuri [a,b,l,*], Richard S. Finkel [c,l], Francesco Muntoni [d], Brunhilde Wirth [e], Jacqueline Montes [f], Marion Main [d], Elena S. Mazzone [a,b], Michael Vitale [g], Brian Snyder [h], Susana Quijano-Roy [i,j], Enrico Bertini [k], Rebecca Hurst Davis [l], Oscar H. Meyer [m], Anita K. Simonds [n], Mary K. Schroth [o], Robert J. Graham [p], Janbernd Kirschner [q], Susan T. Iannaccone [r], Thomas O. Crawford [s], Simon Woods [t], Ying Qian [u], Thomas Sejersen [v] for the SMA Care Group

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Neuromuscular Disorders 28 (2018) 197–207
www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics

Richard S. Finkel [a,l], Eugenio Mercuri [b,l,*], Oscar H. Meyer [c], Anita K. Simonds [d], Mary K. Schroth [e], Robert J. Graham [f], Janbernd Kirschner [g], Susan T. Iannaccone [h], Thomas O. Crawford [i], Simon Woods [j], Francesco Muntoni [k], Brunhilde Wirth [l], Jacqueline Montes [m], Marion Main [k], Elena S. Mazzone [b], Michael Vitale [n], Brian Snyder [o], Susana Quijano-Roy [p], Enrico Bertini [q], Rebecca Hurst Davis [r], Ying Qian [s], Thomas Sejersen [t] for the SMA Care group

Timeline for Novel Therapies

2012	Cochrane Review: No effective Treatment
2017	Nusinersen gets FDA approval NEJM publishes Gene therapy paper
2018	Biogen open EAP for Nusinersen in type 1 infants in UK
2019	NICE approves MAA for Nusinersen (1-3, not 3a) in specialist centres FDA approves Zolgensma
2020	NICE approves Zolgensma SMA type 1 < 6m and 6-12m + MDT approval, Presymptomatic MAA and NHSE agreement > 13m prevalent population EAMS launched for Risdiplam SMA type 1 and 2 if cant have Nusinersen NICE approves Nusinersen in type 3a SMA
2021	NHSE commissions 4 centres to deliver Zolgensma NICE approves MAA for Risdiplam types 1-3 + presymptomatic > 2m UK trials for Myostatin inhibitors ? enhance effect of SMN upregulation

Timeline for Essa

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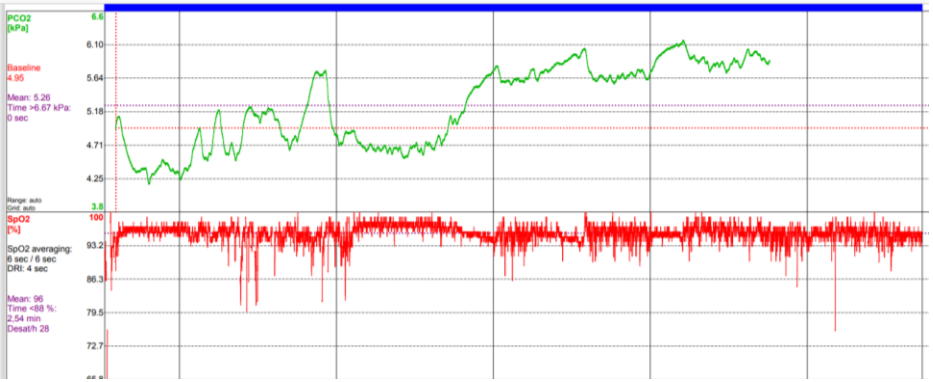
Management for Essa

- Treatment options
  - Supportive Care
  - SMN2 modifying drug

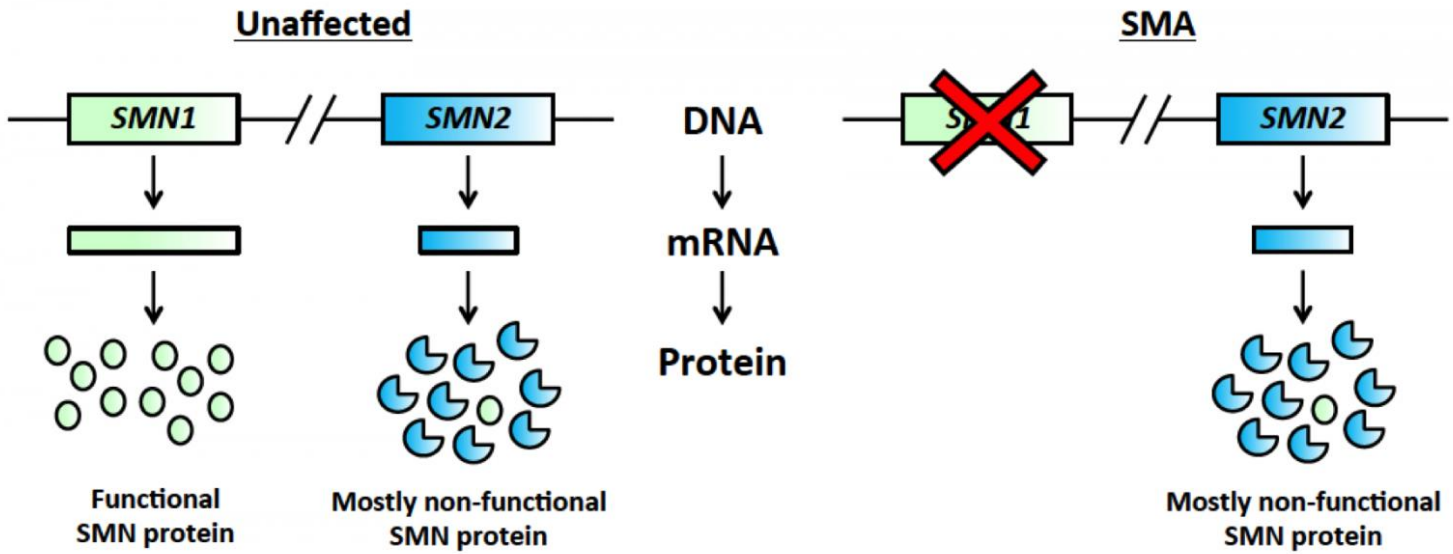


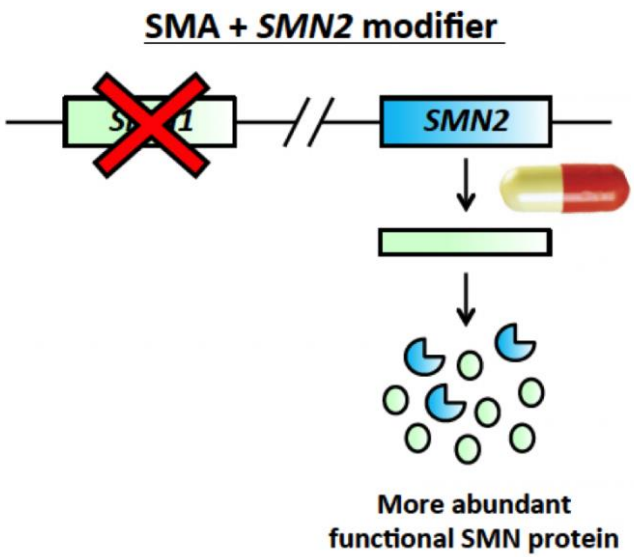
- Apply Standards of Care
  - 3 weeks: asynchronous breathing pattern, weak cough
  - VF confirms aspiration - PEG inserted. NBM
  - Sleep study: commences NIV post PEG

Disease Modifying Drugs

- To treat or not to treat…. Evolved since Essa's birth
  - What to use ??
- 2 modes of genetic modification
  - SMN2 'upregulation'
    - Nusinersen
    - Risdiplam > 2m
    - Managed Access Agreement (MAA)
      - Inclusion and Exclusion criteria
  - SMN1 replacement: Onasemnogene
- Balance between Risks and Benefits
  - Side effects
    - Relatively new drugs
    - Implementation has own issues/AEs
  - Benefits
    - Short term v long term
    - ? 1 treatment better than another
      - ? Combination..

SMN2 modification

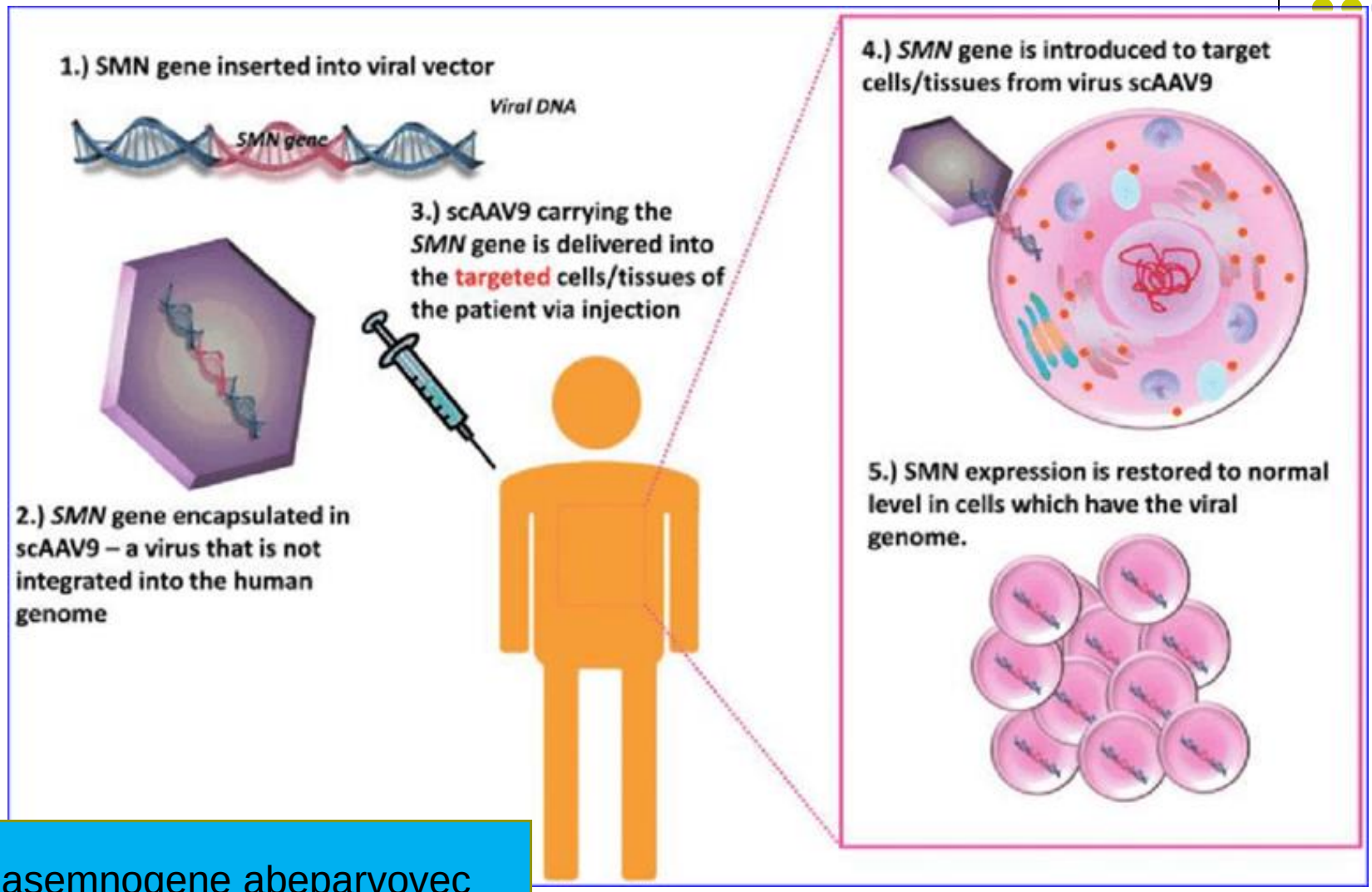




Nusinersen (Spinraza)

Risdiplam (Evrysdi)

SMN1 Gene Replacement



Onasemnogene abeparvovec (Zolgensma)

Nusinersen in type 1 SMA

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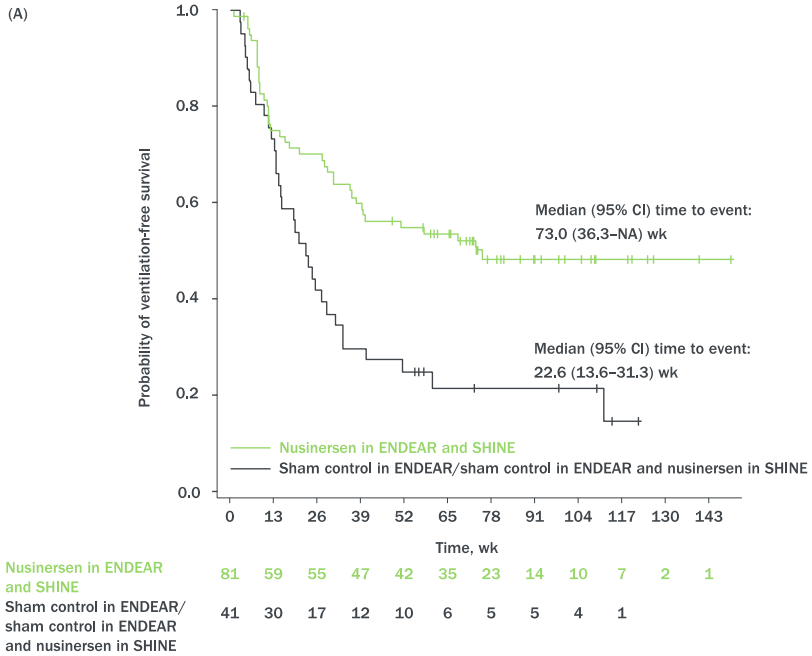
Figure 3. (A) Time to death or permanent ventilation and **(B)** time to death



ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

Nusinersen Conclusions:

- Longest data set,
- Endear study was RCT
- Significant improvement in survival
- Early treatment greater benefit
- Significant gain in motor skills
- Benefits appear sustained

P.266 | World Muscle Society Virtual Congress | 2020

Nusinersen in Infantile-Onset Spinal Muscular Atrophy: Longer-term Treatment Results From the Open-label SHINE Extension Study

89 infants, 64 treated

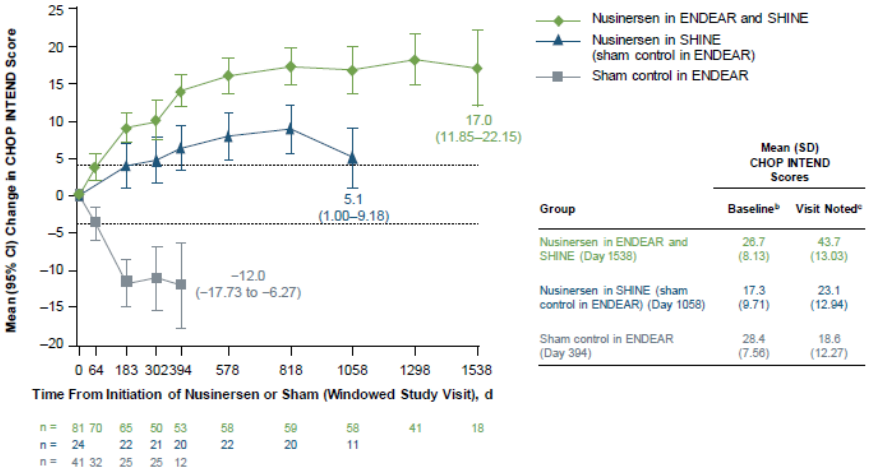
- 36% sit unaided
- 8% stand with assistance
- 5% walk with assistance

Results (3 of 4)

Motor Function

- CHOP INTEND was assessed for the full study period and included all participants in ENDEAR/SHINE (Figure 2).

Figure 2. Children Treated With Nusinersen Showed Clinically Meaningful Improvements in CHOP INTEND Scores Over Time[a]



Group	Mean (SD) CHOP INTEND Scores: Baseline[b]	Visit Noted[c]
Nusinersen in ENDEAR and SHINE (Day 1538)	26.7 (8.13)	43.7 (13.03)
Nusinersen in SHINE (sham control in ENDEAR) (Day 1058)	17.3 (9.71)	23.1 (12.94)
Sham control in ENDEAR (Day 394)	28.4 (7.56)	18.6 (12.27)

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
Denominator is the number of participants with a value windowed to the analysis visit. Results displayed where n > 5.
[a]A change of 4 points in the CHOP INTEND score is considered to be outside of the range of test variability and clinically meaningful[7]; CHOP INTEND is assessed until participants have reached the maximum score of 64.
[b]This is baseline in ENDEAR for nusinersen in ENDEAR/SHINE and ENDEAR sham groups, and at start of nusinersen treatment for the group that received nusinersen in SHINE (previous sham).
[c]Last visit shown on the graph for the group noted in the left column.

7. Glanzman AM, et al; Pediatric Neuromuscular Clinical Research Network for Spinal Muscular Atrophy (PNCR), Muscle Study Group (MSG). *Pediatr Phys Ther*. 2011;23(4):322-326.

Given by IT injection usually under LA in infants
Loading doses day 1, 14, 28 and 63, then every 4 months
Generally very well tolerated

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ORIGINAL ARTICLE

Risdiplam in Type 1 Spinal Muscular Atrophy

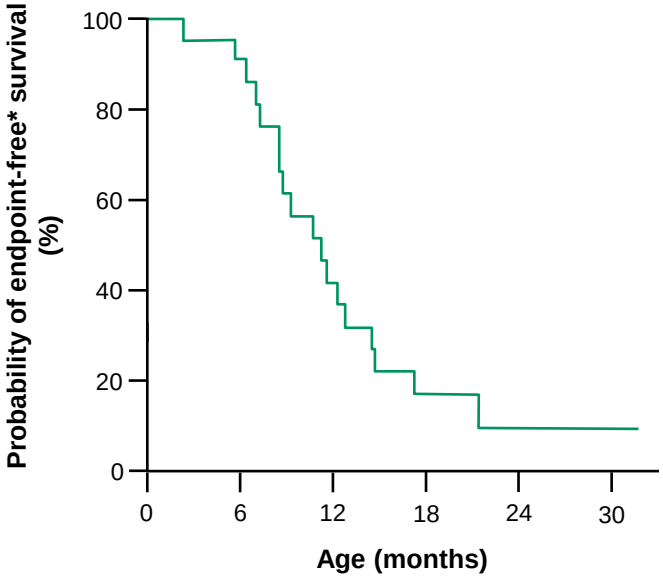
Giovanni Baranello, M.D., Ph.D., Basil T. Darras, M.D., John W. Day, M.D., Ph.D., Nicolas Deconinck, M.D., Ph.D., Andrea Klein, M.D., Riccardo Masson, M.D., Eugenio Mercuri, M.D., Ph.D., Kristy Rose, Ph.D., Muna El-Khairi, Ph.D., Marianne Gerber, Ph.D., Ksenija Gorni, M.D., Ph.D., Omar Khwaja, M.D., Ph.D., Heidemarie Kletzl, Ph.D., Renata S. Scalco, M.D., Ph.D., Timothy Seabrook, Ph.D., Paulo Fontoura, M.D., Ph.D., and Laurent Servais, M.D., Ph.D., for the FIREFISH Working Group*

Risdiplam is an liquid preparation – given as once daily medication
Firefish : open label study in type 1
Sunfish: RCT in later onset

3 yr data from Firefish
Generally well tolerated most AEs/SAEs reflect the condition
Some GI disturbance and rash
AEs reduce with time
Majority of infants feeding orally

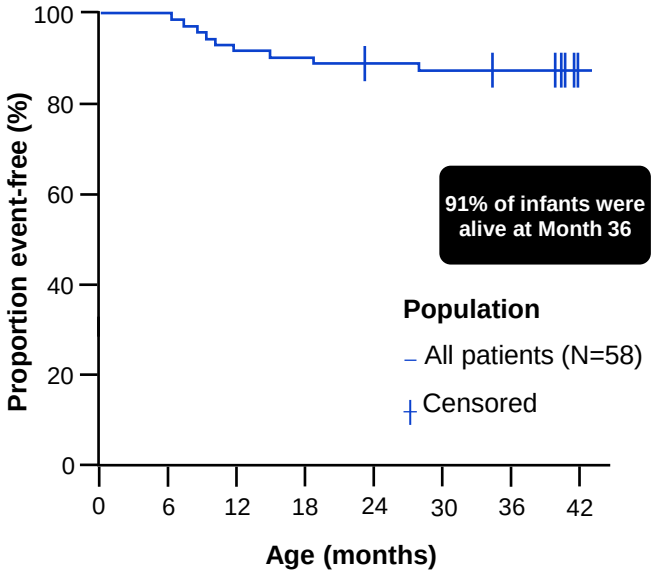
3 year follow up Firefish OLE

Natural history (PNCR) data for infants with Type 1 SMA and two *SMN2* copies[1]



n=23

84% of infants† were event free‡ after 36 months of treatment



Number of patients at risk

All patients	58	58	52	51	49	48	47	41§

In natural history, median age (IQR) for reaching death or permanent ventilation for infants with two *SMN2* copies was 10.5 (8.1–13.6) months[1]

Median time to reaching death or permanent ventilation in pooled FIREFISH Part 1‖ and Part 2 was not estimable due to lack of events

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ESTABLISHED IN 1812 NOVEMBER 2, 2017 VOL. 377 NO. 18

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar

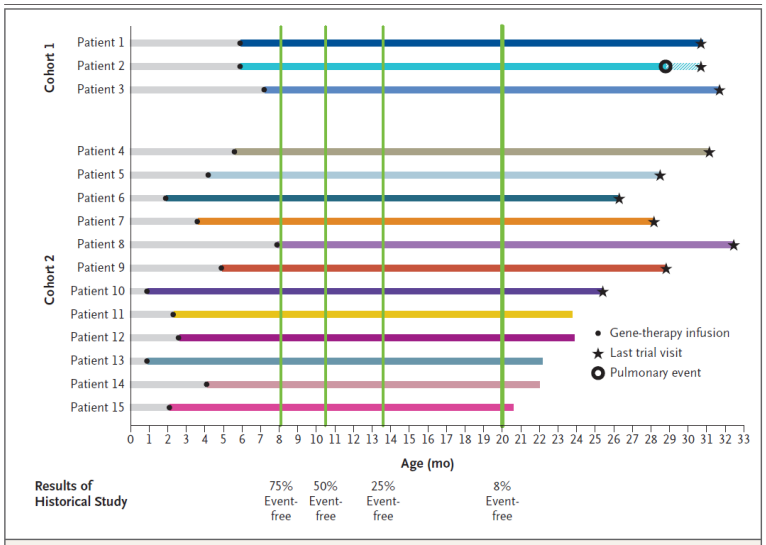
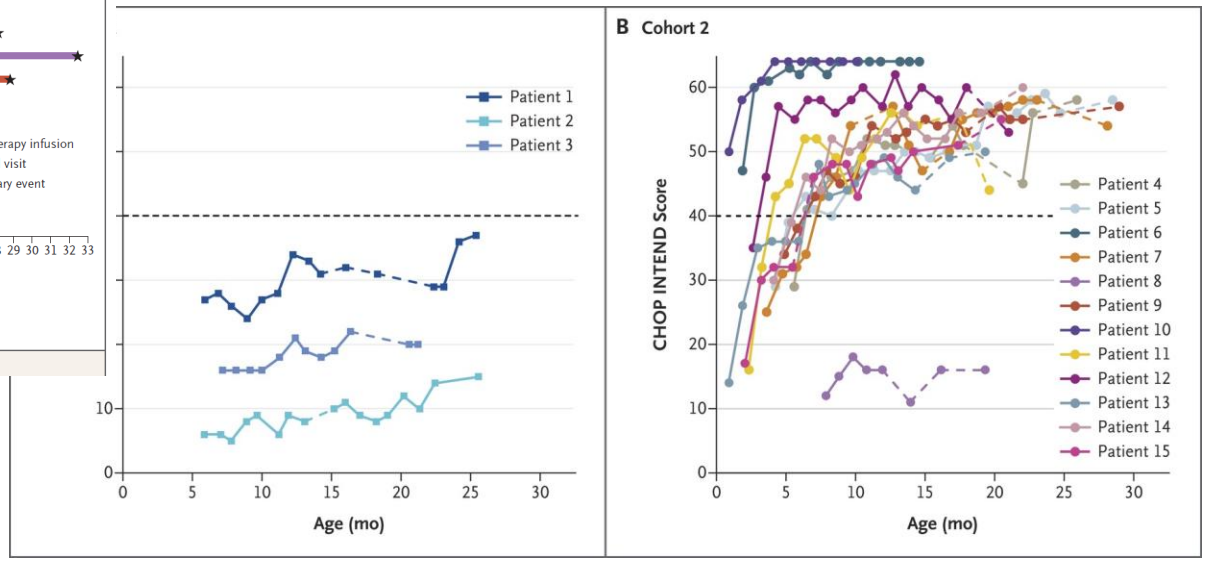


Figure 1. Survival Free from Permanent Ventilation in the 15 Study Patients.

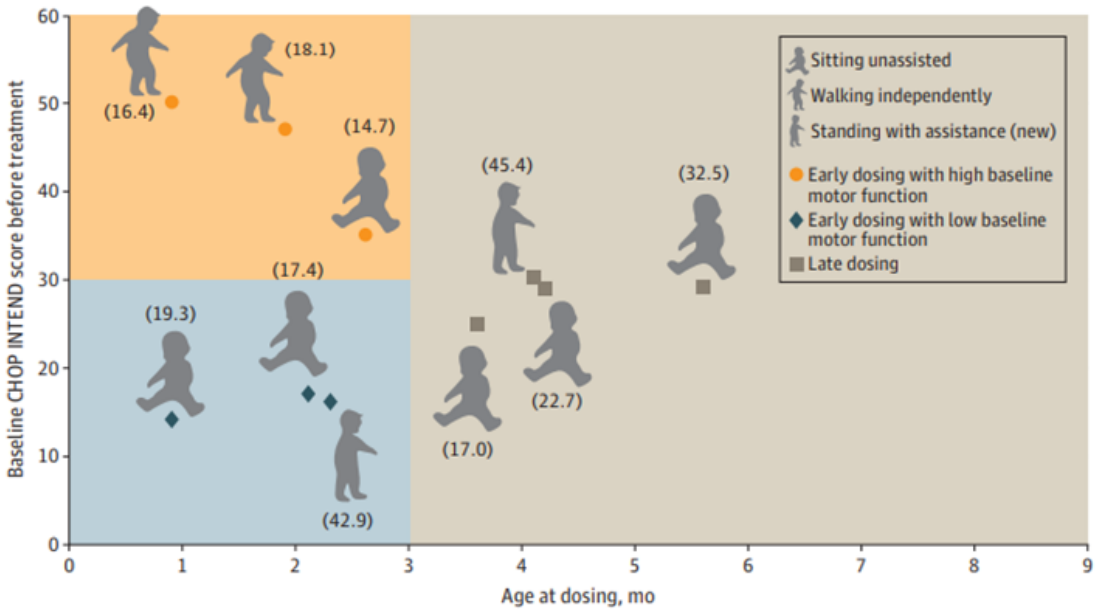


JAMA Neurology | Original Investigation

Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy

Jerry R. Mendell, MD; Samiah A. Al-Zaidy, MD; Kelly J. Lehman, MSN; Markus McColly, BA; Linda P. Lowes, PT, PhD; Lindsay N. Alfano, PT, DPT; Natalie F. Reash, PT, DPT; Megan A. Iammarino, PT, DPT; Kathleen R. Church, MSW; Aaron Kleyn, PhD; Matthew N. Meriggioli, MD; Richard Shell, MD

Figure 2. Greatest Development Milestones Achieved During the START Long-term Follow-up Study



5 yrs ‘extension’ results in 10/12 early treatment group

- No loss of skills
- 2 walking, 2 standing and 6 sitting with support
- None on permanent ventilation, 6/10 some NIV

Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicentre, phase 3 trial

*Eugenio Mercuri, Francesco Muntoni, Giovanni Baranello, Riccardo Masson, Odile Boespflug-Tanguy, Claudio Bruno, Stefania Corti, Aurore Daron, Nicolas Deconinck, Laurent Servais, Volker Straub, Haojun Ouyang, Deepa Chand, Sitra Tauscher-Wisniewski, Nuno Mendonca, Arseniy Lavrov, on behalf of the STR1VE-EU study group**

33 patients, median age at treatment 4.1 months

- 32 survived and 31 without ‘permanent ventilation’
- 14/32 achieved primary endpoint : sitting for 10s at 18m
- 55% had hepatotoxicity with 33% requiring > 2m steroids for transaminitis

Generally risks of treatment increase with amount of viral load ie weight of child

Treatments In Conclusion

- All the drugs work and change natural history
- No ‘head to head’ trials
- All show greater benefits when given earlier in disease course
  - Greatest benefits when presymptomatic
  - Need Early Diagnosis = Newborn screening
- ? Role for Combination therapy
  - Gene therapy + SMN2 upregulator
  - Any drug + myostatin inhibitors

Back to Essa

- Nusinersen only option in March 2020
  - Parents opted for treatment
- Had 7 doses of Nusinersen, last May 2021
- Referred for GT in Aug 2021
- Received treatment in Sept 2021

Functional outcome 28m

	2 weeks	6 months	13 months	19 months	22 months	28 months
WHO (Max 6)	0	0	0	0	1	2
HINE (Max 26)	2	3	9		17	20
CHOP intend (Max 64)	13	46	45	48	52	54
RHS (Max 69)			5		6	13
HFMSE (Max 66)			3		10	17

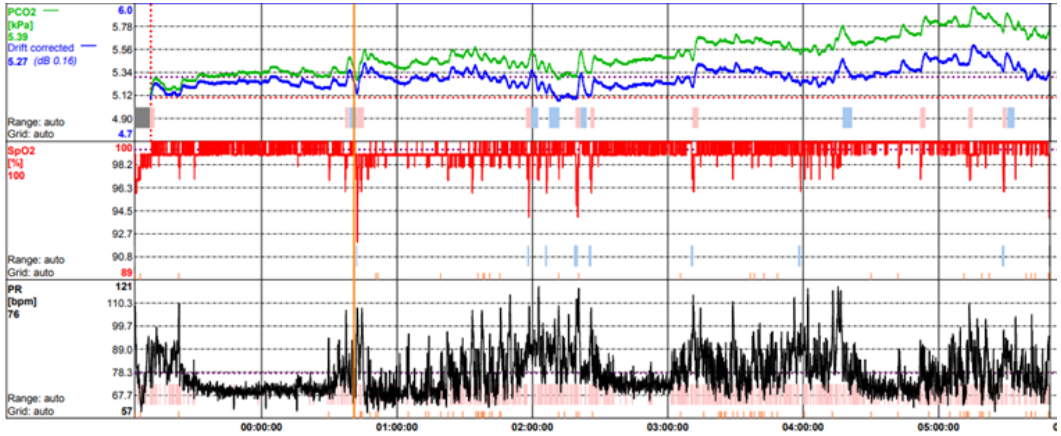
Nusinersen
1st Dose 3w

Zolgensma
19 months

Sitting securely and can pivot
Rolls across floor
Stands with support for 10s with hands held
But:
No expressive and ? receptive language
Limited play skills, poor eye contact and challenging behaviour

Essa feeding and respiratory

- NGT post VF 7 weeks
- PEG sited at 8 weeks
- Steroids 4m
- Cognitive outcome
  - Limited play
- NIV started 8 weeks
- Chest infections:
  - 6 admissions – 3 post GT
- Cough Assist 22 months
- 28m off regular NIV



On going Management Challenges

- 2017/18 Standards of care need updating
  - Written pre treatment access
  - Now seeing ‘new’ phenotypes
    - Surviving SMA 1 infants → children …

- Management of ‘predictable’ issues
  - Hips
  - Spine

Ongoing Management Challenges ..

- Management of ‘Unexpected’ Issue
  - Infants with SMA said to be ‘bright’
  - Increasing reports of
    - Cognitive delay
    - Delayed and/or disordered speech
    - ? More often seen in more severely affected
- Managing Expectations of parents + HCPs
  - Setting realistic outcomes for ‘Miracle’ drugs
  - Supporting parallel planning and limitation of treatment
- Access to treatments
  - MAAs for Novel therapies
  - No ‘guarantee’ that NHS will continue reimbursement given costs for ‘single’ drugs in all cases
  - Pressure for combination therapies
    - Data on safety and effectiveness needed

Ongoing initiatives in UK

- National ‘Audit’ Collection
  - SMA REACH project – collecting standardised data on all those living with SMA
  - iSMAC
- Treat NMD
  - Disease Registry
  - PROMS study
- Physiotherapy guidelines
- Themed Workshops
- Newborn Screening Alliance

Aims of SMA Care UK

- Similar model to DMD Care UK
  - Concept supported by SMA UK, MDUK and Treat SMA and REACH network
- Work with clinical experts and those living with SMA both nationally and international
  - Drawing on existing knowledge and building on existing initiatives
- Steering committee:
  - Identify priorities
  - Appoint individual Working groups
  - Overall oversight
- Individual Working groups
  - Collate/seek evidence to support EB care
  - Produce consensus guidelines
  - Plans for dissemination
    - Clinical networks - NM, community, other
    - Patient Friendly information
- Support equal access to best possible care
- Driver to improve service
- Drafting funding proposal with SMAUK and Newcastle University

Proposed Work Streams

Diagnosis +NBS

Transition

Cognitive and Speech Development

PROMs

Physiotherapy + Rehabilitation

Spine

Hip

Psychosocial care

SMA Care to be Comprehensive

- Whole Disease Spectrum
- All ages

??

Summary

- Huge progress in management of SMA 1
- Novel therapies alter disease trajectory
  - ? Optimal drugs for specific patients
  - Access to drugs given costs
  - Balancing expectations with reality
- New challenges in managing evolving issues in treated infants
  - Postural management
  - Cognitive development
- Excellent resources to try and help move forward