Spinraza (Nusinersen) The DANA experience

Dr. Moran Lavie
Director, pediatric pulmonology unit
Dana-Dwek children hospital
Tel Aviv medical center

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SMN gene

- SMA is caused by homozygous deletion or mutation of SMN1 (Survival Motor Neuron) gene that encodes the SMN protein

- a C>T base change creates SMN2 "backup gene" which forms an unstable protein with both limited half-life and function

- The copy number of the SMN2 gene varies between individuals, Severity of SMA phenotype is correlated with SMN2 gene copies

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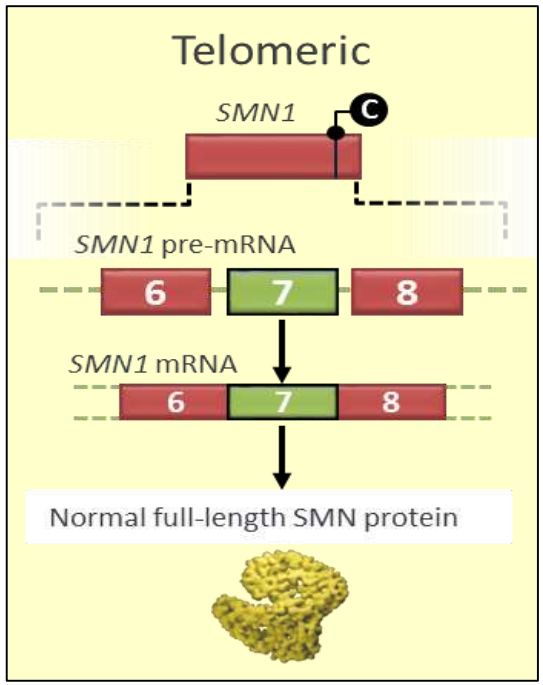

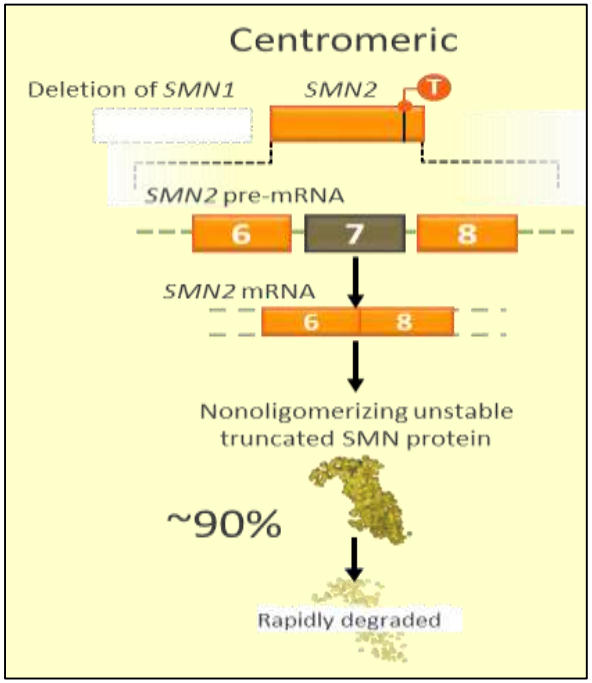

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SMA Disease Classification

- Based on **age of onset** and **maximum motor function achieved**[1]

Clinical Classification of SMA

SMA TYPE	Age of Onset	Motor Milestones	Average Age of Death (limited interventions)
I	< 6 months	Unable to sit w/o support	< 2years
II	< 18 months	Sit independently, cannot stand	2nd - 3rd decade
III	> 18 months	Stand and walk independently	Normal life expectancy
IV	Adolescent or Adult onset	Retain walking, muscle pain	Normal life expectancy

1. Kolb et al; Participants of the International Conference on SMA Standard of Care. J Child Neurol. 2010.

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SPINRAZA® (nusinersen)

- Modulation of the SMN2 - "Back-Up Gene"
- Antisense oligonucleotides (ASO) - synthetic strings of nucleotides that bind and alter the expression of target RNA → modify protein expression
- Repeated administration is required as they only affect the splicing not the gene itself (not a genetic Tx)
- Require intrathecal administration

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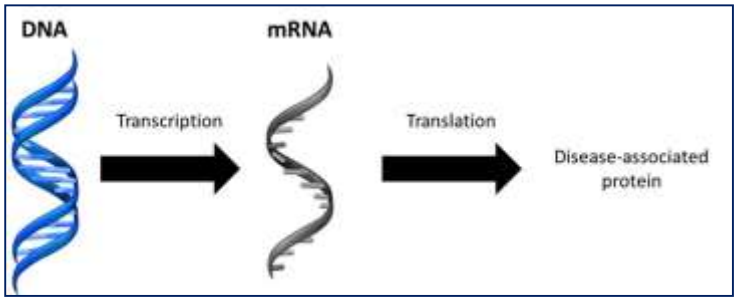

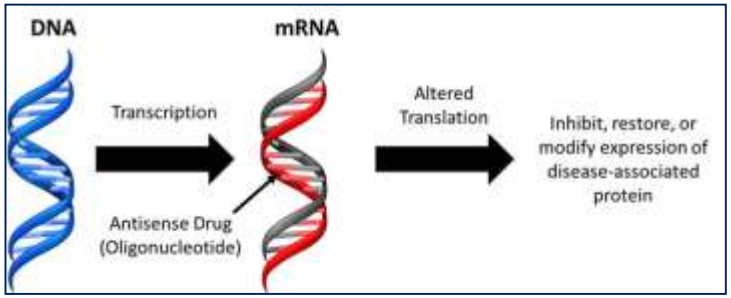

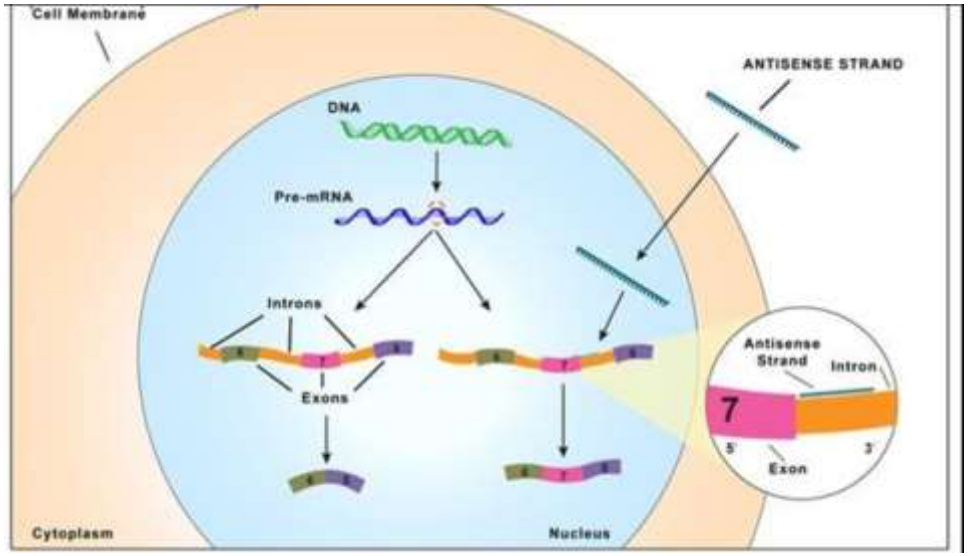

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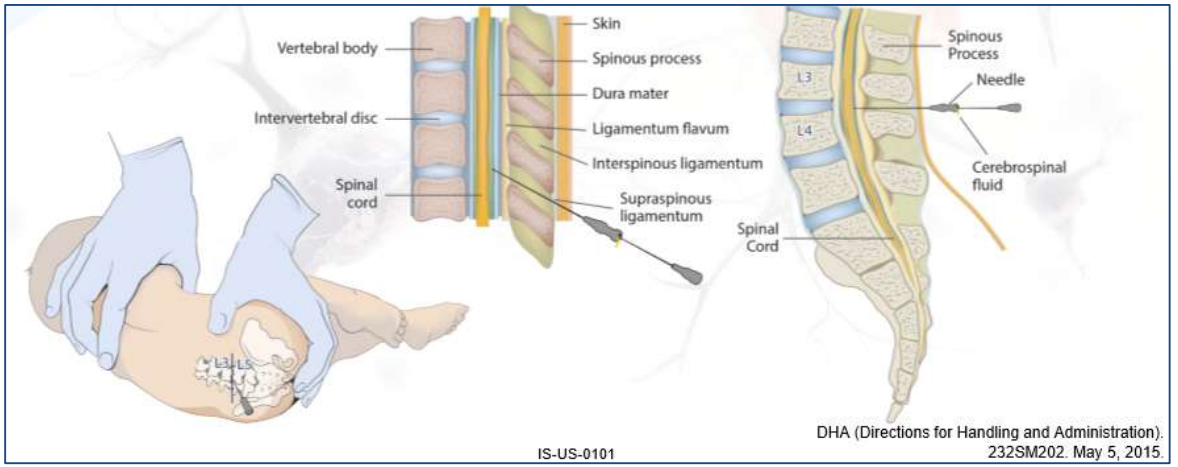
SPINRAZA® (nusinersen)



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SPINRAZA® (nusinersen) - Efficacy Outcomes

- Pre symptomatic <6 weeks of age at time of first dose

Pre-symptomatic Newborns | nurture Biogen Study

- SMA-I symptomatic <7 month of age at screen

endear Phase 3

- Symptomatic SMA-II Age 2-12 years at screen - Can sit but not walk

cherish Phase 3

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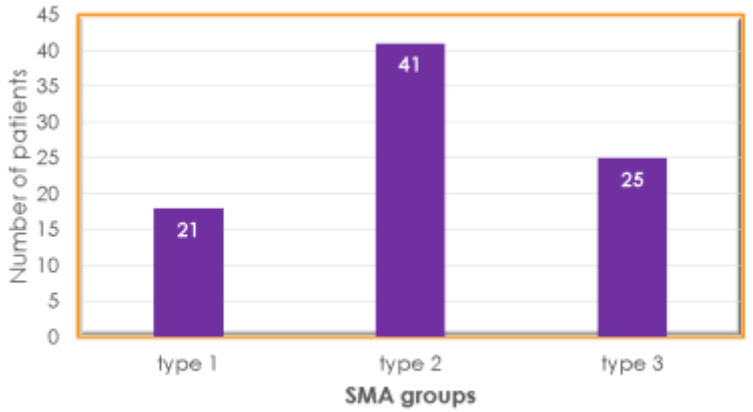
SMA in Israel

- ~110 patients
- All ethnicities
- Most - SMA type 2
- From 2013 – carrier screening



- חוזר משרד הבריאות 2016: בדיקות סקר באוכלוסייה לשם גילוי זוגות בסיכון ללידת ילדים עם מחלות תורשתיות חמורות

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The DANA experience

PERGAMON

Neuromuscular Disorders 14 (2004) 56–69

www.elsevier.com/locate/nmd

Workshop report

117th ENMC Workshop: Ventilatory Support in Congenital Neuromuscular Disorders — Congenital Myopathies, Congenital Muscular Dystrophies, Congenital Myotonic Dystrophy and SMA (II) 4–6 April 2003, Naarden, The Netherlands

Carina Wallgren-Pettersson[a,*], Kate Bushby[b], Uwe Mellies[c], Anita Simonds[d]

[a]*The Folkhälsan Department of Medical Genetics, University of Helsinki, P.O. Box 211, Topeliuksenkatu 20, FIN-00251 Helsinki, Finland*
[b]*Institute of Human Genetics, University of Newcastle upon Tyne, Newcastle upon Tyne, UK*
[c]*Department of Pediatrics and Pediatric Neurology, University of Essen, Essen, Germany*
[d]*Royal Brompton & Harefield NHS Trust, London, UK*

Received 19 August 2003

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Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 25 (2015) 979–989

NMD

www.elsevier.com/locate/nmd

Workshop report

1st Italian SMA Family Association Consensus Meeting: Management and recommendations for respiratory involvement in spinal muscular atrophy (SMA) types I–III, Rome, Italy, 30–31 January 2015

V.A. Sansone [1,*,a], F. Racca [2,a], G. Ottonello [3], A. Vianello [4], A. Berardinelli [5], G. Crescimanno [6], J.L. Casiraghi [7] on behalf of the Italian SMA Family Association

[1] *Centro Clinico NEMO, Neurorehabilitation Unit, University of Milano, Milano, Italy*
[2] *Pediatric Anesthesiology and Intensive Care Unit, SS Antonio Biagio e Cesare Arrigo Hospital, Alessandria, Italy*
[3] *Famiglie SMA Scientific Committee, Milan, Italy*
[4] *Respiratory Pathophysiology Division, University – City Hospital of Padova, Padova, Italy*
[5] *I.R.C.C.S Istituto Neurologico Nazionale Casimiro Mondino, Pavia, Italy*
[6] *A.O. Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy*
[7] *SMA Family Representative, Milan, Italy*

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ScienceDirect

Neuromuscular Disorders 25 (2015) 353–358

www.elsevier.com/locate/nmd

Workshop report

203rd ENMC international workshop: Respiratory pathophysiology in congenital muscle disorders: Implications for pro-active care and clinical research 13–15 December, 2013, Naarden, The Netherlands

A. Rutkowski [a,*], M. Chatwin [b], A. Koumbourlis [c], B. Fauroux [d], A. Simonds [b], for the CMD Respiratory Physiology Consortium [1]

[a] *Cure Congenital Muscular Dystrophy and Kaiser SCPMG, Los Angeles, CA, USA*
[b] *Royal Brompton, London, UK*
[c] *Children's National Medical Center, Washington, DC, USA*
[d] *Hôpital Necker, Paris, France*

Received 9 October 2014

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The DANA experience

REVIEW

CURRENT OPINION

Respiratory complications, management and treatments for neuromuscular disease in children

MyMy C. Buu

Purpose of review
To summarize current literature describing the respiratory complications of neuromuscular disease (NMD) and the effect of respiratory interventions and to explore new gene therapies for patients with NMD.

Recent findings
Measurements of respiratory function focus on vital capacity and maximal inspiratory and expiratory pressure and show decline over time. Management of respiratory complications includes lung volume recruitment, mechanical insufflation-exsufflation, chest physiotherapy and assisted ventilation. Lung volume recruitment can slow the progression of lung restriction. New gene-specific therapies for Duchenne muscular dystrophy and spinal muscular atrophy have the potential to preserve respiratory function longitudinally. However, the long-term therapeutic benefit remains unknown.

Summary
Although NMDs are heterogeneous, many lead to progressive muscle weakness that compromises the function of the respiratory system including upper airway tone, cough and secretion clearance and chest wall support. Respiratory therapies augment or support the normal function of these components of the respiratory system. From a respiratory perspective, the new mutation and gene-specific therapies for NMD are likely to confer long-term therapeutic benefit. More sensitive and standard tools to assess respiratory function longitudinally are needed to monitor respiratory complications in children with NMD, particularly the youngest patients.

Keywords
lung, neuromuscular disease, respiratory complications, respiratory insufficiency, respiratory therapy

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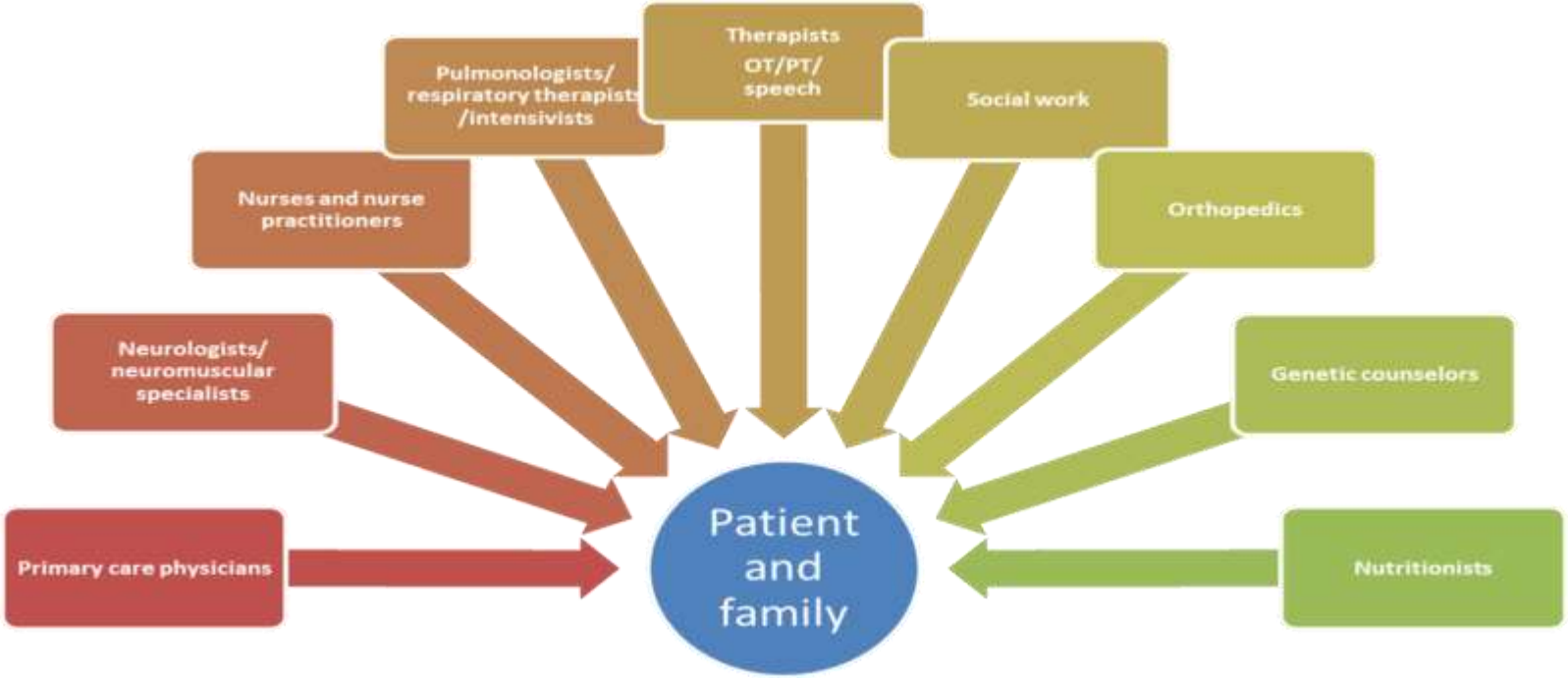
Consensus standard of care



SMA multidisciplinary clinic

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SMA Protocol

- ✓ Respiratory rate
- ✓ Dyspnea / paradoxical breathing
- ✓ Cough clinical assessment
- ✓ Physical examination
- ✓ Saturation
- ✓ Transcutaneous CO2
- ✓ Respiratory support
- ✓ Time off mechanical ventilation
- ✓ Chest XR – ap diameter, shape/chest circumference
- ✓ Sputum culture
- ✓ Spirometry – FVC, MIP, MEP, peak cough flow, peak expiration flow
- ✓ Physiotherapy assessment
- ✓ Echo – pulmonary HTN
- ✓ Polysomnography
- ✓ Scoliosis assessment

DATA BASE

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חדשות : בארץ

סל התרופות 2018: ה-sma בפנים, גמילה מעישון בחוץ

						Spinraza						
	ID	Type	DOB	DOD	Ethnicity	S1	S2	S3	S4	S5	S6	S7
1	22[redacted]9	1	[redacted]2.2016		2	03.04.2017	18.04.2017	09.05.2017	08.06.2017	15.10.2017	15.02.2018	
2	22[redacted]5	1	[redacted]0.2016		2	08.04.2017	22.03.2017	05.04.2017	03.05.2017	03.09.2017	04.01.2018	06.05.2018
3	34[redacted]1	1	[redacted]1.2016		2	30.03.2017	13.04.2017	27.04.2017	25.05.2017	25.09.2017	25.01.2018	24.05.2018
4	34[redacted]4	1	[redacted]9.2016		1	13.02.2017	27.02.2017	13.03.2017	12.04.2017	13.08.2017	14.12.2017	16.04.2018
5	34[redacted]9	1	[redacted].2016		1	31.01.2017	14.02.2017	28.02.2017	30.03.2017	30.07.2017	13.12.2017	11.04.2018
6	22[redacted]6	1	[redacted]6.2016	21.12.17	2	09.03.2017	23.03.2017	06.04.2017	08.05.2017	05.09.2017		
7	33[redacted]0	1	[redacted]8.2010		1	13.07.2017	27.07.2017	14.08.2017	14.09.2017	14.01.2018	14.05.2018	
8	32[redacted]8	1	[redacted]7.2008		1	21.08.2017	04.09.2017	18.09.2017	16.10.2017	18.02.2018	17.06.2018	
9	22[redacted]6	1	[redacted]7.2017		1	29.08.2017	12.09.2017	27.09.2017	25.10.2017	25.02.2018	25.06.2018	
10	20[redacted]7	2	[redacted]0.1998		1	15.08.2017	30.08.2017	14.09.2017	19.10.2017	22.02.2018	21.06.2018	
11	34[redacted]7	1	[redacted].2017		2	21.11.2017	5.12.2017	19.12.2017	16.01.2018	16.05.2018		
12	33[redacted]4	3	[redacted].2014		2	21.11.2017	5.12.2017	19.12.2017	18.01.2018	21.05.2018		

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The DANA 1 year experience

- 10 type I (companionate- Biogen)
- 1 type II (Court order) – post spinal fusion
- 1 type III (private funding)

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Baseline

	Name	Type	Sex	Ethnicity	Age	Resp. support	Resp. support from age	When	Prior resp. hosp.	Cough assist (times/d)
1	A. R. H.	1	M	A	12m	NIV	4m	Continous	4	1
2	B. Y.	1	M	A	16m	NIV	9m	Day+night sleep	4 (1 int.)	3
3	H. L.	1	F	A	4m	NIV	4m	Day+night sleep	1	1
4	L. M.	1	M	J	12m	NIV	6m	Night sleep	3 (1 int.)	3
5	N. D.	1	F	J	8m	NIV	6m	Continous	1	3
6	R. R.	1	F	A	14m	NIV	6m	Continous	1	2
7	Y. C.	1	F	J	6y	NIV	12m	Continous	Numerous	2
8	R. L.	1	F	J	8.5y	NIV	8y	Night sleep	5 (4 int.)	Exacerbations
9	M. T.	1	F	J	2m	No	5m	No	No	No
10	S. Y.	2	M	J	19y	NIV	12y	Night sleep	Multiple in infancy	Exacerbations
11	E. F.	1	F	A	3m	No	3m	No	1	No
12	A. Y.	3	M	A	3.5y	No	No	No	No	No

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The NEW ENGLAND JOURNAL of MEDICINE

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*

ABSTRACT

endear Phase 3

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Endear

- 81 - nusinersen group 41 – control
- 15% of infants in the nusinersen group and 8% in the control group had received permanent assisted ventilation at 3 months
- 31% and 48%, respectively, had received permanent assisted ventilation at 13 months
- Overall, 23% of the infants in the nusinersen group and 32% in the control group received permanent assisted ventilation. P = 0.13

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Tal

- SMA-I
- At diagnosis age 5wk –

✓ Hypotonia, eats well, sometimes cough during eating, gains weight

✓ RR - 72 , Sat – 99% RA

✓ Paradoxical breathing, retractions, normal sounds

✓ Normal blood gas

✓ Chest XR

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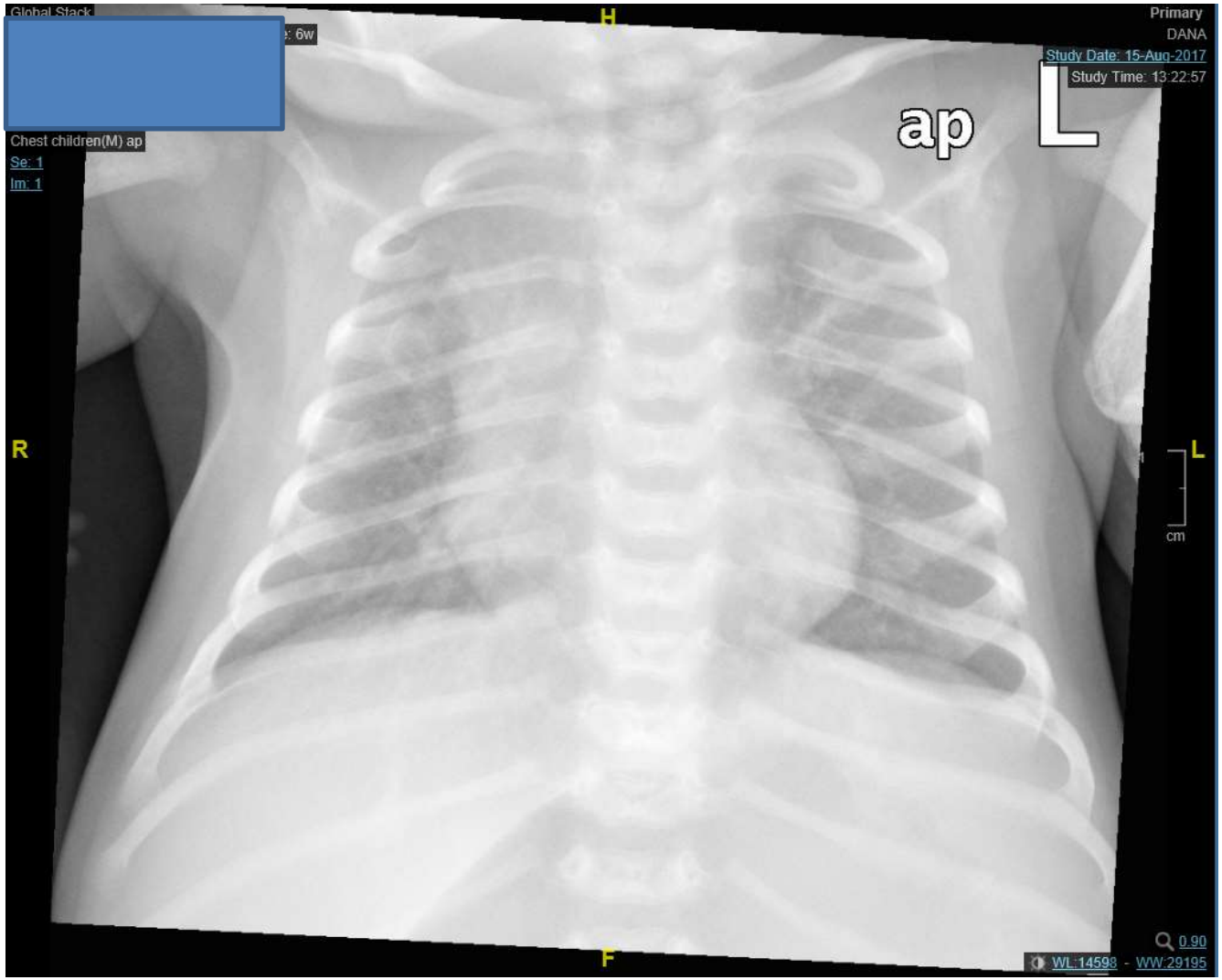
Chest XR -Tal



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Tal

- Initiation of Spinraza – 2m
- After initiation of Tx 5 months –

✓ Hypotonia, eats well and gains weight
✓ No respiratory exacerbations
✓ Cough assist * 2 daily
✓ RR - 46 , Sat – 99% RA
✓ Bell shape chest. Paradoxical breathing, retractions, fine crackles bil.
✓ Normal blood gas
✓ Chest XR

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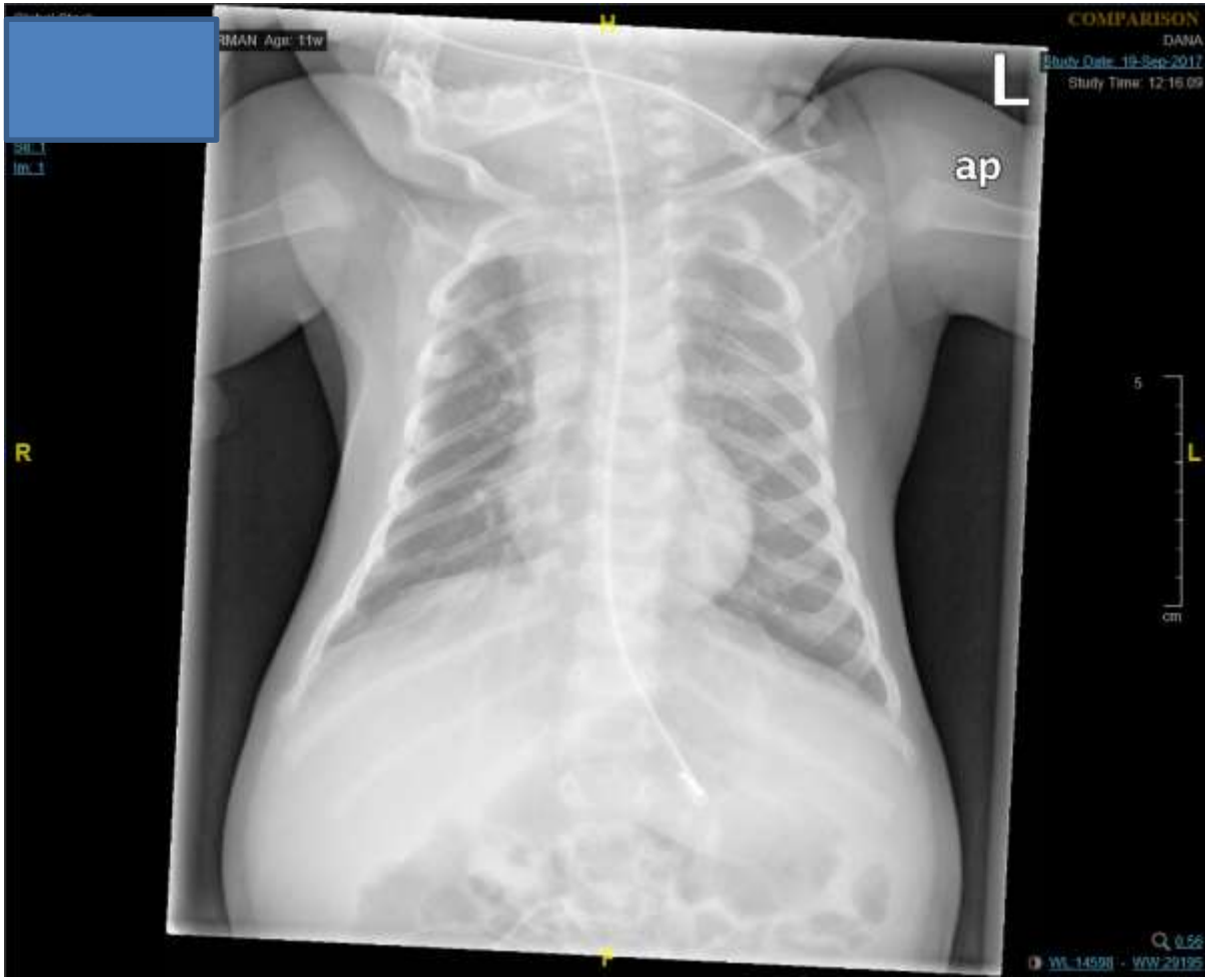
Chest XR -Tal



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Phatma

- SMA-I
- At diagnosis age 5wk –

✓ Hypotonia, eats well and gains weight

✓ RR - 60, Sat – 95%RA

✓ Paradoxical breathing, retractions, normal sounds

✓ Normal blood gas

✓ Chest XR

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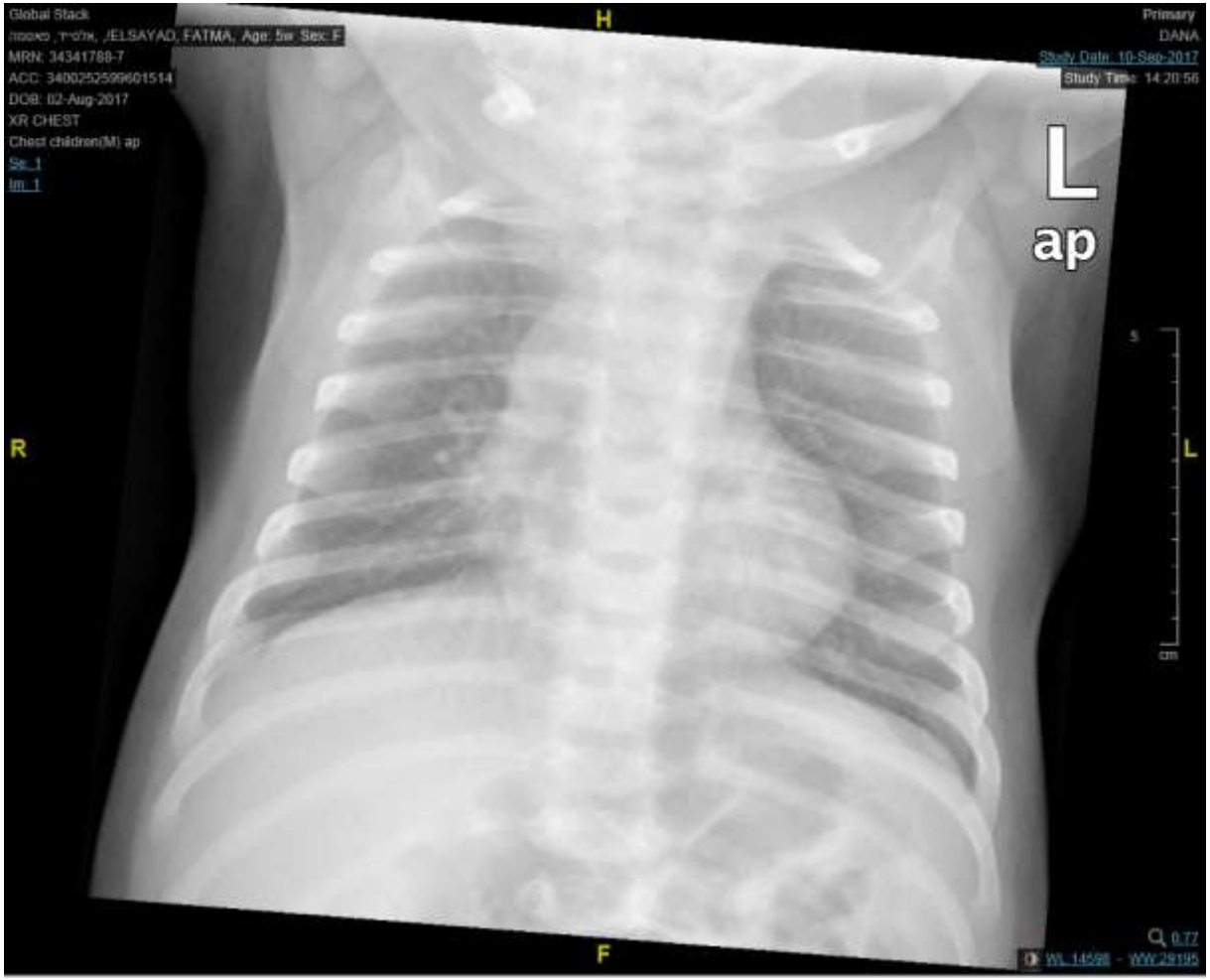
Chest XR - Phatma



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Phatma

- age 12 wk –
- ✓ Hypotonia, tired when eats
- ✓ No Tx, no electricity…
- ✓ RR – 56 , Sat – 95% RA
- ✓ Bell shape, paradoxical breathing, retractions, normal sounds
- ✓ Normal blood gas
- ✓ Chest XR – bell shape

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חדשות בריאות

התינוקת פטמה שזקוקה לתרופה

איכילוב: בת 3 חודשים במצב קריטי כי אין מימון לתרופה

התינוקת לוקה בניוון שרירים מסוג SMA, ורק תרופה שעלותה 2.5 מיליון שקל בשנה תציל את חייה. ועדת סל התרופות טרם אישרה אותה, והחברה שסיפקה "טיפולי חמלה" לא מממנת אותם עוד. רופאיה: "המקרה שלה הוא הכי דחוף מכל הילדים שחולים במחלה"

שרית רזנבלום פורסם: 09.11.17 , 14:05

דרמה אנושית בבית החולים איכילוב: תינוקת בת שלושה חודשים הלוקה בניוון שרירים מסוג SMA, שמצבה קריטי, אינה מקבלת את התרופה שנדרשת להצלת חייה - מכיוון שאין לכך מימון.

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Phatma

- Initiation of Spinraza – 3m
- age 4 months –

✓ Full respiratory support NIV

✓ Cough assist * 6 daily

✓ Gastrostomy

✓ Recurrent hospitalizations d/t respiratory exacerbations , RUL atelectasis, pneumothorax secondary to recurrent bronchoscopies

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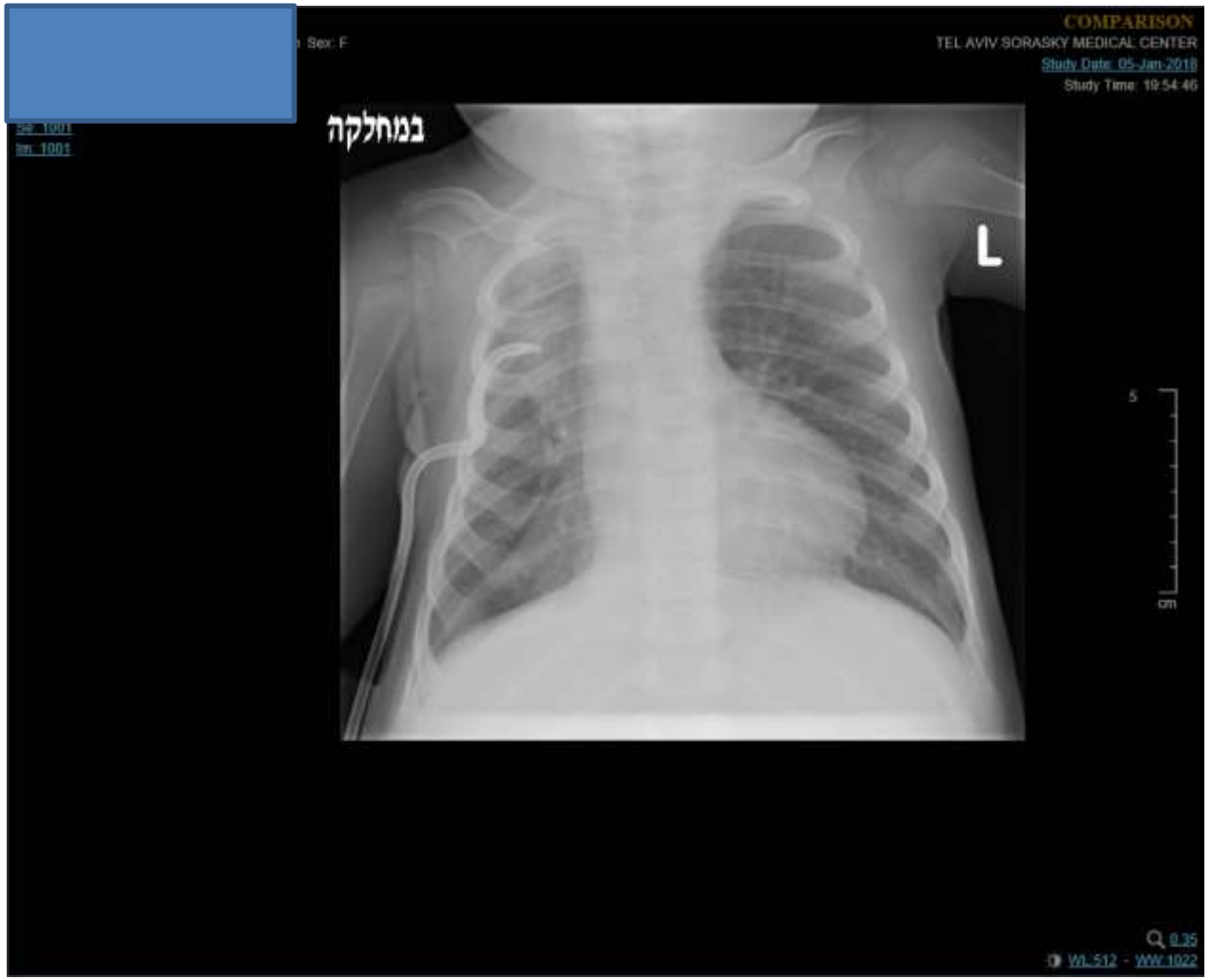
Chest XR - Phatma



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The NEW ENGLAND JOURNAL of MEDICINE

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

Fifteen patients with SMA1 received a single dose of intravenous adeno-associated virus serotype 9 carrying SMN complementary DNA encoding the missing SMN protein.

In patients with SMA1, a single intravenous infusion of adeno-associated viral vector containing DNA coding for SMN resulted in longer survival, superior achievement of motor milestones, and better motor function than in historical cohorts. Further studies

at least 16 hours per day for at least 14 consecutive days (considered equivalent to permanent ventilation) was 10.5 months.[4] In one cohort of

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The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

The Dilemma of Two Innovative Therapies for Spinal Muscular Atrophy

Ans T. van der Ploeg, M.D., Ph.D.

Nusinersen for Spinal Muscular Atrophy
Are We Paying Too Much for Too Little?

Vinay Prasad, MD, MPH

Nusinersen, one of several recently approved drugs intended for use in a rare disease, boasts an eye-popping price tag. Biogen Pharmaceuticals announced that nusinersen will cost $750 000 for the first year of treatment and $375 000 each year thereafter (prescribed indefinitely) for patients with spinal muscular atrophy (SMA).[1] Other recently approved costly thera-

$750 000 for the first year of treatment and $375 000 each year

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חדשות בריאות

סל התרופות לשנת 2018: רבע מהתקציב - ל-128 חולים

ועדת הסל הקצתה 117 מיליון שקל למחלות נדירות. הטיפול ל-SMA יתוקצב, אך התרופה היקרה לדושן נשארה בחוץ. יו"ר הוועדה מתח ביקורת על חברות התרופות: לא נסבול מחירים מנופחים וחזיריים

עידו אפרתי | התראות במייל
09:25 29.12.2017 | עודכן ב: 12:15

כל החדשות בריאות

תרופה מצילת חיים במחיר אסטרונומי מכניסה את מערכת הבריאות למלכוד

התרופה ספינרזה לטיפול במחלת ניוון שרירים עולה כ-2 מיליון שקל בשנה לכל חולה ■ הממשלה תידרש למצוא פתרון יצירתי במיוחד כדי להתמודד עם ההתנגשות בין עיקרון השוויון, תינוקות חולים, מעורבות של פוליטיקאים ומחירי תרופות בלתי־נתפשים

רוני לינדר-גנץ | התראות במייל
07:32 12.11.2017

DANA-DWEK
Children's Hospital

The Team

Dana

- ✓ Pulmonology – Dr. Sadot, Prof. Amirav, Dr. Diamant
- ✓ Neurology – Prof. Fatal, Dr. Sagi
- ✓ Gastroenterology, Endocrinology, Cardiology, Nephrology, Orthopedics, Genetics.
- ✓ Multidisciplinary team

Alin

- ✓ Dr. Beeri, Dr. Frenkel

Medical centers and home care doctors

TEL-AVIV SOURASKY
MEDICAL CENTER