Effects of nusinersen after one year of treatment in 123 children with SMA type 1 or 2: a French real-life observational study

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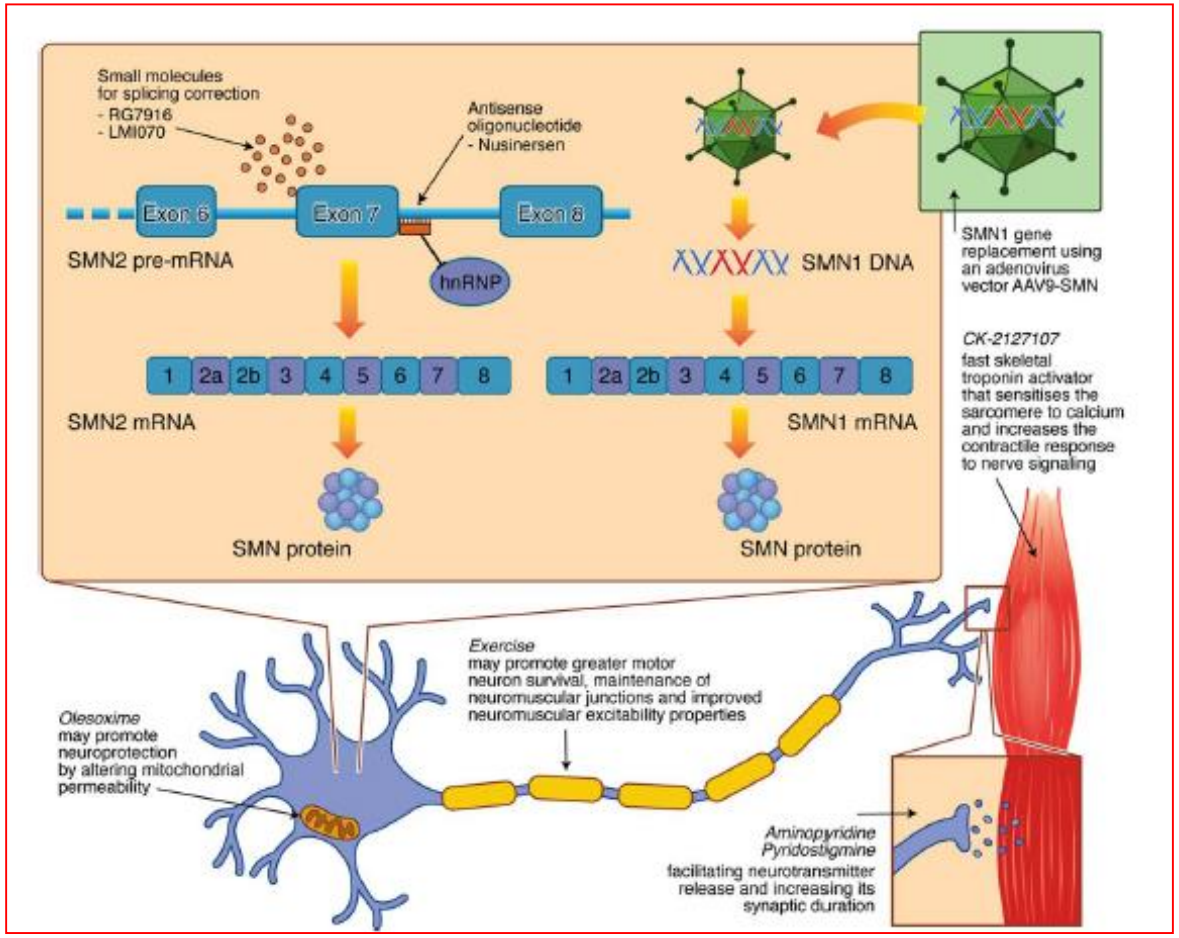
Filière FILNEMUS

Spinraza-Nusinersen©.

- Available in France since May 2017.
- Antisense oligonucleotide that acts as a splicing modifier targeting the intronic splicing silencer N1 in the *SMN2* intron and is delivered by repeated intrathecal injections



Spinraza-Nusinersen©.

- Nusinersen has shown some clinical efficacy in well-controlled clinical trials with prolonged survival after 2 years of age in different populations of SMA patients.
- However, these motor benefits seem to be somewhat offset by an increased use of invasive treatments such as gastrostomy and ventilatory support

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Research Report

Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany

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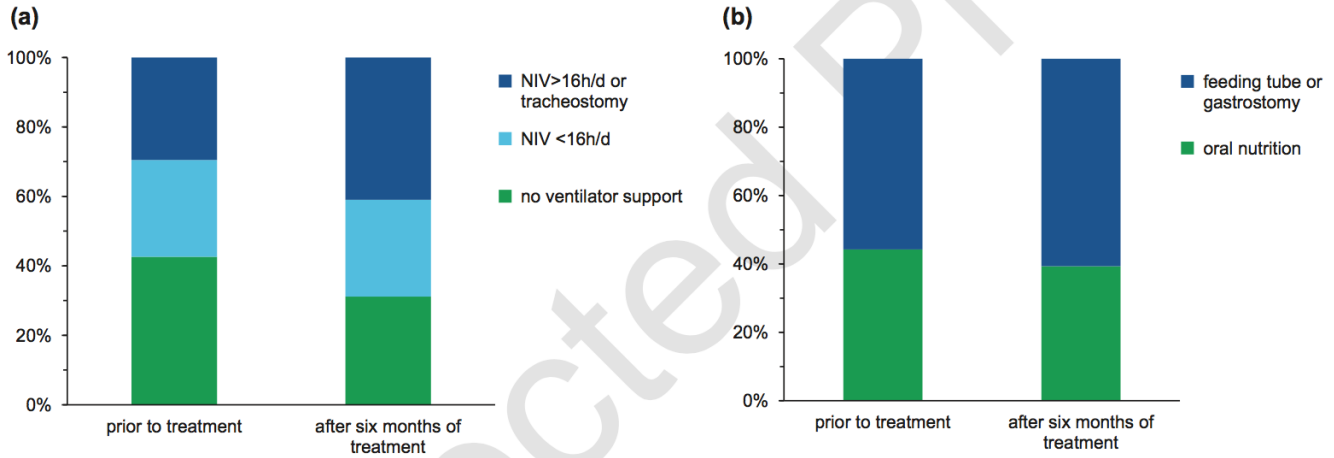


Fig. 3. Data at baseline and after six months of treatment regarding ventilator support (a) and nutrition (b).

Methodology

- 23 French centers for rare pediatric diseases in the French FILNEMUS network for rare neuromuscular diseases.
- This multicenter study was commissioned by the neuromuscular commission of the French Society of Pediatric Neurology (Société Française de Neuropédiatrie), which holds monthly discussion group meetings.
- The data for this study were collected from **May 2017** (when nusinersen became available in France) until **February 2019**.

Methodology

- The inclusion criteria were:
  - A genetically proven SMA mutation (homozygous deletion of exon 7 on chromosome 5q13)
  - SMA type 1 or 2, as defined by the HAS (*Haute Autorité de Santé*, French National Authority for Health)
  - A complete clinical description at treatment onset (T0)
  - Treatment with intrathecal nusinersen injections for at least one year ± 2 months (Y1). (Patients were evaluated after 10, 12 or 14 months' treatment depending on the study center).

Datas/

- General datas:
  - date of birth
  - Gender
  - age at diagnosis
  - number of copies of the *SMN2* gene
  - age at treatment onset
- SMA type : Mercuri classification as 1a/b, 1c, or 2.

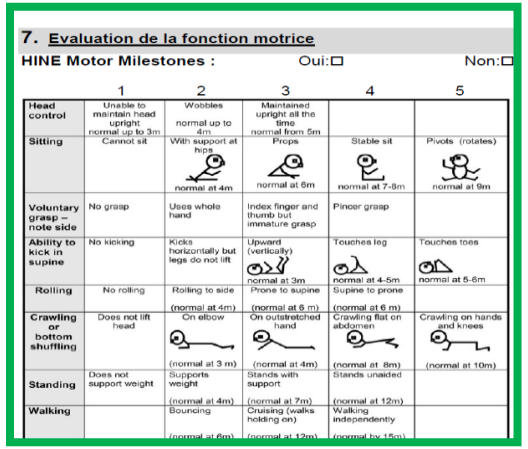
TABLE 1. Classification and Subtypes of Spinal Muscular Atrophy

Type	Age of Onset	Maximal Motor Milestone	Motor Ability and Additional Features	Prognosis[c]
SMA 0	Before birth	None	Severe hypotonia; unable to sit or roll[a]	Respiratory insufficiency at birth; death within weeks
SMA I	2 weeks (Ia) 3 months (Ib) 6 months (Ic)	None	Severe hypotonia; unable to sit or roll[b]	Death/ventilation by 2 years
SMA II	6 to 18 months	Sitting	Proximal weakness; unable to walk independently	Survival into adulthood
SMA III	<3 years (IIIa) >3 years (IIIb) >12 years (IIIc)	Walking	May lose ability to walk	Normal life span
SMA IV	>30 years or 10 to 30 years	Normal	Mild motor Impairment	Normal life span

[a]Need for respiratory support at birth; contractures at birth, reduced fetal movements.
[b]Ia joint contractures present at birth; Ic may achieve head control.
[c]Prognosis varies with phenotype and supportive care interventions.

Datas/ Motor development milestone achievement

- Modified Hammersmith Infant Neurologic Examination–Part 2 **(HINE-2)**
- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders **(CHOP INTEND)** less than 2 years old
- Motor Function Measure **(MFM)** :children older than 2 years
  - MFM20 for children between 2 and 5 years old
  - MFM32 for children above 6 years of age.
  - 3 domains:
    - D1, standing and transfer;
    - D2, axial and proximal motor function;
    - D3, distal motor function



7. Evaluation de la fonction motrice

HINE Motor Milestones : Oui:☐ Non:☐

	1	2	3	4	5
Head control	Unable to maintain head upright normal up to 3m	Wobbles normal up to 4m	Maintained upright all the time normal from 5m		
Sitting	Cannot sit	With support at hips normal at 4m	Props normal at 6m	Stable sit normal at 7-8m	Pivots (rotates) normal at 9m
Voluntary grasp – note side	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick in supine	No kicking	Kicks horizontally but legs do not lift	Upward (vertically) normal at 3m	Touches leg normal at 4-5m	Touches toes normal at 5-6m
Rolling	No rolling	Rolling to side (normal at 4m)	Prone to supine (normal at 6 m)	Supine to prone (normal at 6 m)	
Crawling or bottom shuffling	Does not lift head	On elbow (normal at 3 m)	On outstretched hand (normal at 4m)	Crawling flat on abdomen (normal at 8m)	Crawling on hands and knees (normal at 10m)
Standing	Does not support weight	Supports weight (normal at 4m)	Stands with support (normal at 7m)	Stands unaided (normal at 12m)	
Walking		Bouncing (normal at 6m)	Cruising (walks holding on) (normal at 12m)	Walking independently (normal by 15m)	

1. Mouvements spontanées (extrémités supérieures)	**9. Flexion de l'épaule et du coude**
1. Mouvements spontanées (extrémités inférieures)	9. Extension du genou
1. Préhension	9. Flexion de la hanche et dorsiflexion du pied
1. Tête sur la ligne médiane lors d'une stimulation visuelle	9. Contrôle de la tête
1. Adducteurs de la hanche	9. Flexion du coude
1. Se retourner à partir des jambes	9. Flexion du cou
1. Se retourner à partir des bras	9. Extension du cou/de la tête
1. Flexion des épaules et du coude et abduction horizontale	9. Incurvation de la colonne vertébrale

Datas/

- Nutritional support :
  - nasogastric tube
  - gastrostomy
- Ventilatory support:
  - non-invasive ventilation for more than 12 h per day.
  - tracheostomy-assisted ventilation for more than 12 h per day.
- Caregivers’ evaluations : Clinical Global Impressions-Improvement(CGI-I) scale with 7 ratings scored from very much improved (rating 1) to very much worse (rating 7).

Nom : |__|__|__|

Prénom : |__|__|

Date de naissance: |__|__| |__|__| |__|__|__|__|

1. Histoire médicale : (1ère visite uniquement)

Age du diagnostic : |__|__|__| (mois)

Confirmation génétique :

Nb de copie *SMN1*: |__|__|

Nb de copie *SMN2*: |__|__|

Mise en place du traitement : |__|__| |__|__| |__|__|__|__|

Date de la visite : |__|__| |__|__| |__|__|__|__| **M0/M6/M10/M14**

Poids (g)	Taille (cm)	Pc (cm)	PTi(cm)	PTe (cm)
I__I__I __I__I. I__I	I__I__I __I	I__I__I __I. I__I	I__I__I __I. I__I	I__I__I __I. I__I

Mode de vie : domicile / centre

Scolarité : Normale / Normale +AVS / IEM / autre : .....

2. Statut respiratoire

Nombre d'hospitalisation : ..... / réa

Nombre d'infections respiratoires / dernière visite |__|__|

Capacité vitale forcée évaluée : Oui: ☐ Non: ☐

Mesure avec corset ☐ Mesure sans corset☐

	CVF (L)	CVF (%)
En position assise	|__|__|__|,|__|	|__|__|__|
En position couchée	|__|__|__|, |__|	|__|__|__|

Relaxateur de pression : Oui: ☐ Non: ☐

Mise en place de la ventilation (mois): |__|__|__|.|__|

Nombre d'heures de ventilation VNI : <12h ☐ 12h-18h☐ >18h☐

Trachéostomie Oui: ☐ Non: ☐

Si oui, date: |__|__| |__|__| |__|__|__|__|

Aide à la toux/ aspiration : Oui: ☐ Non: ☐

3. Statut orthopédique

- Scoliose: Oui: ☐ Non: ☐
  - Si Oui, âge de début (mois): |__|__|__|.|__|
  - Arthrodèse/ instrumentation sans greffe:Oui: ☐ Non: ☐
  - Si Oui, date : |__|__| |__|__| |__|__|__|__|
- Orthèses: Oui: ☐ Non: ☐

  Si Oui, préciser : ☐corset : ☐attèle membre supérieur: ☐attèle membre inférieur: Verticalisation Oui: ☐ Non: ☐
- Fauteuil roulant : Oui: ☐ Non: ☐
  - Si Oui: électrique : ☐ manuel: ☐

4. Oralité / Statut digestif

- Alimentation : ☐ mixée ☐normale
- Compléments caloriques : Oui: ☐ Non: ☐
- Sonde gastrique : Oui: ☐ Non: ☐
- Gastrostomie: Oui: ☐ Non: ☐
- Constipation : Oui: ☐Non: ☐
- Atteinte bulbaire : Oui: ☐ Non: ☐

5. Clinical Global Impressions – Improvement (CGI-I)

(La cotation de la CGI-I doit prendre en compte la situation au cours de la semaine écoulée) . D'après les parents, par rapport à la situation de leur enfant lors de la première consultation, la situation est :

1. ☐ Fortement améliorée (Very much improved)
2. ☐ Très améliorée (Much improved)
3. ☐ Faiblement améliorée (Minimally improved)
4. ☐ Inchangée (No change)
5. ☐ Plus mal (Minimally worse)
6. ☐ Pire (Much worse)
7. ☐ Fortement dégradée (Very much worse)

6. Effets secondaires liés au traitement

Texte libre : ..... vomissement, céphalées, fatigue, fièvre, ...

Difficultés d'injection : oui / non

Modalités : assis couché, MEOPA, ...

7. Evaluation de la fonction motrice

- **HINE Motor Milestones :** Oui:☐ Non:☐

	1	2	3	4	5
Head control	Unable to maintain head upright normal up to 3m	Wobbles normal up to 4m	Maintained upright all the time normal from 5m		
Sitting	Cannot sit	With support at hips  normal at 4m	Props  normal at 6m	Stable sit  normal at 7-8m	Pivots (rotates)  normal at 9m
Voluntary grasp – note side	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
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Crawling or bottom shuffling	Does not lift head	On elbow  (normal at 3 m)	On outstretched hand  (normal at 4m)	Crawling flat on abdomen  (normal at 8m)	Crawling on hands and knees  (normal at 10m)
Standing	Does not support weight	Supports weight (normal at 4m)	Stands with support (normal at 7m)	Stands unaided (normal at 12m)	
Walking		Bouncing (normal at 6m)	Cruising (walks holding on) (normal at 12m)	Walking independently (normal by 15m)	

Total Score : |__|__| (min 8, max 40)

- **Hammersmith scale**: Oui:☐ Non:☐

  Score: |__|__|
- **MFM score:** Oui:☐ Non:☐

  MFM Scale: MFM 20:☐ MFM 32:☐

  Score D1 (%) : |__|__|__|

  Score D2 (%) : |__|__|__|

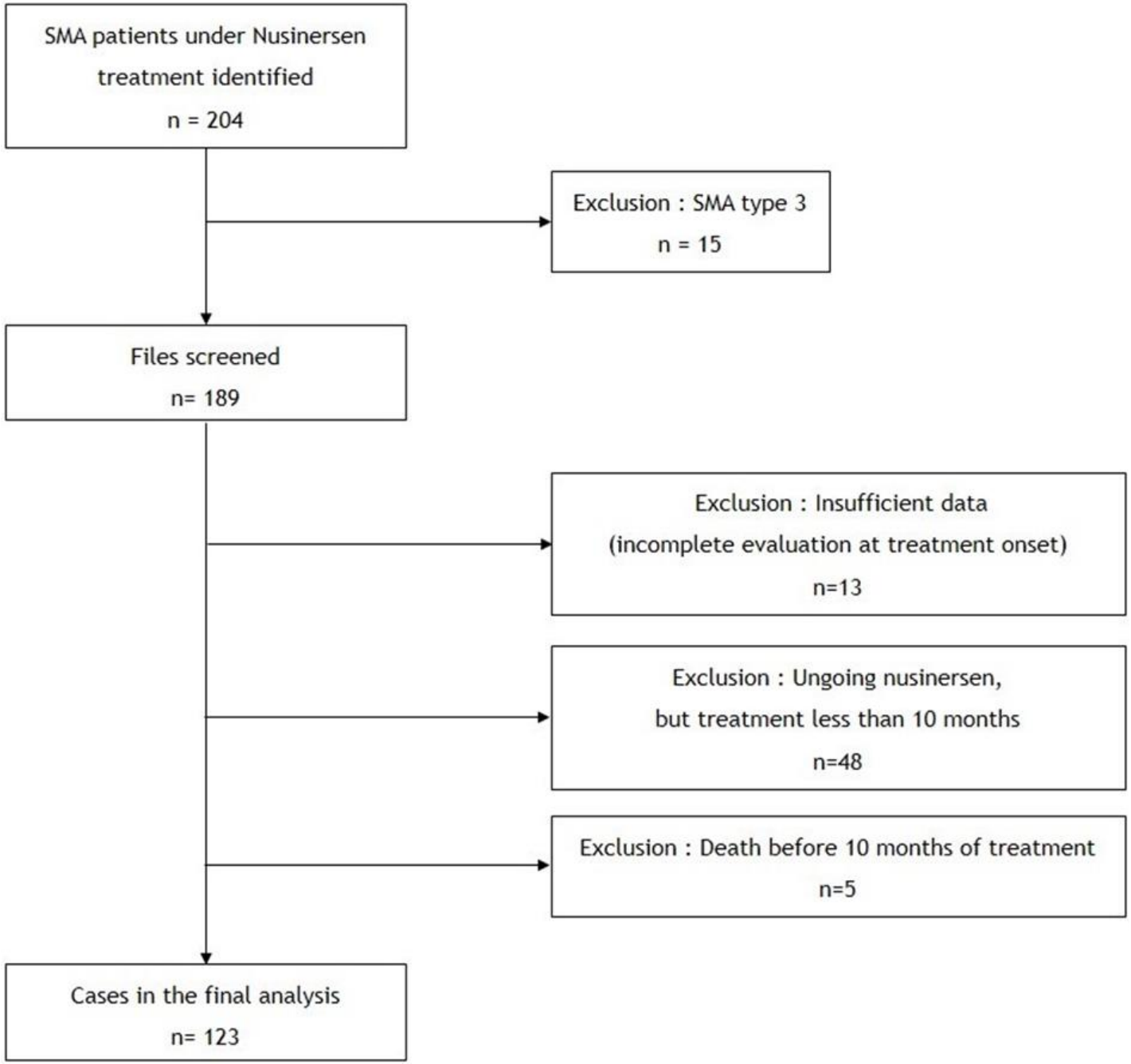
  Score D3 (%) : |__|__|__|

  Total score (%) : |__|__|__|

8. Kinésithérapie / Ergothérapie / Balnéothérapie :

- Kinésithérapie: Oui: ☐ Non: ☐
  - Si Oui, respiratoire: ☐ moteur: ☐ N par semaine : |__|__|
- Ergothérapie: Oui: ☐ Non: ☐, N par semaine: |__|__|
- Balnéothérapie: Oui: ☐ Non: ☐ , N par semaine: |__|__|
- Orthophonie: Oui: ☐ Non: ☐ , N par semaine: |__|__|

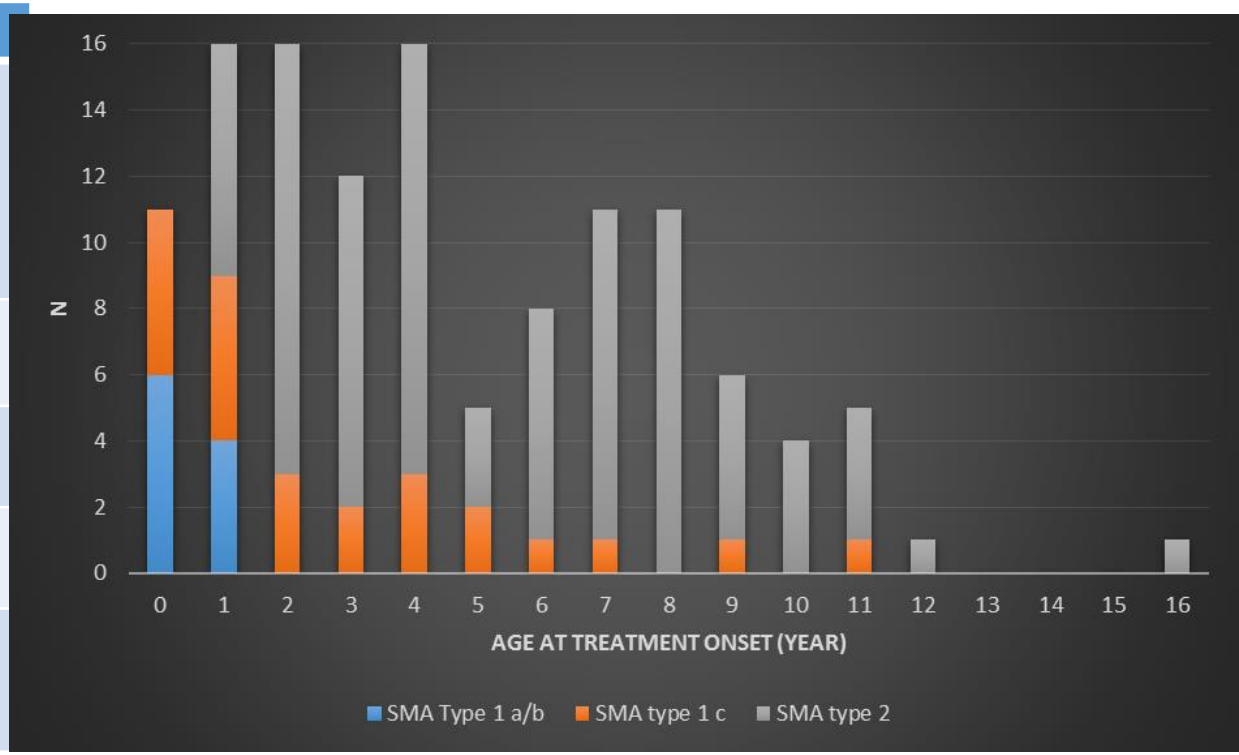
RESULTS


SMA patients under Nusinersen treatment identified
n = 204
Exclusion : SMA type 3
n = 15
Files screened
n= 189
Exclusion : Insufficient data
(incomplete evaluation at treatment onset)
n=13
Exclusion : Ungoing nusinersen,
but treatment less than 10 months
n=48
Exclusion : Death before 10 months of treatment
n=5
Cases in the final analysis
n= 123

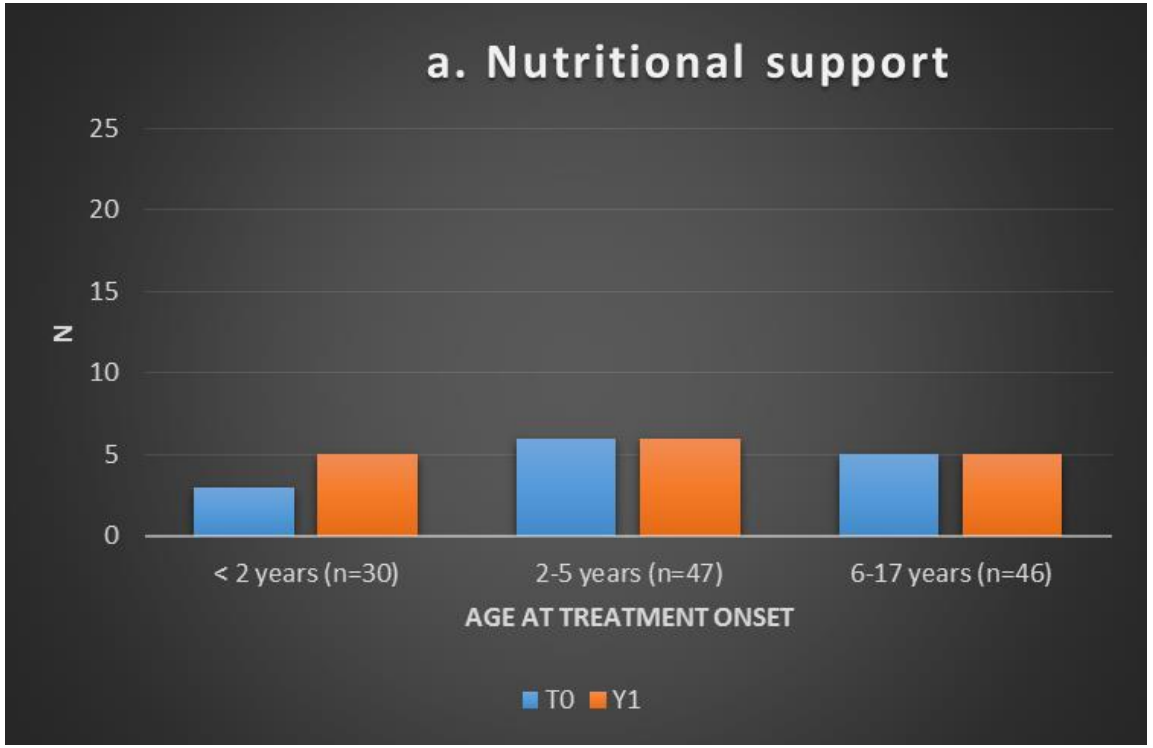
Population description:

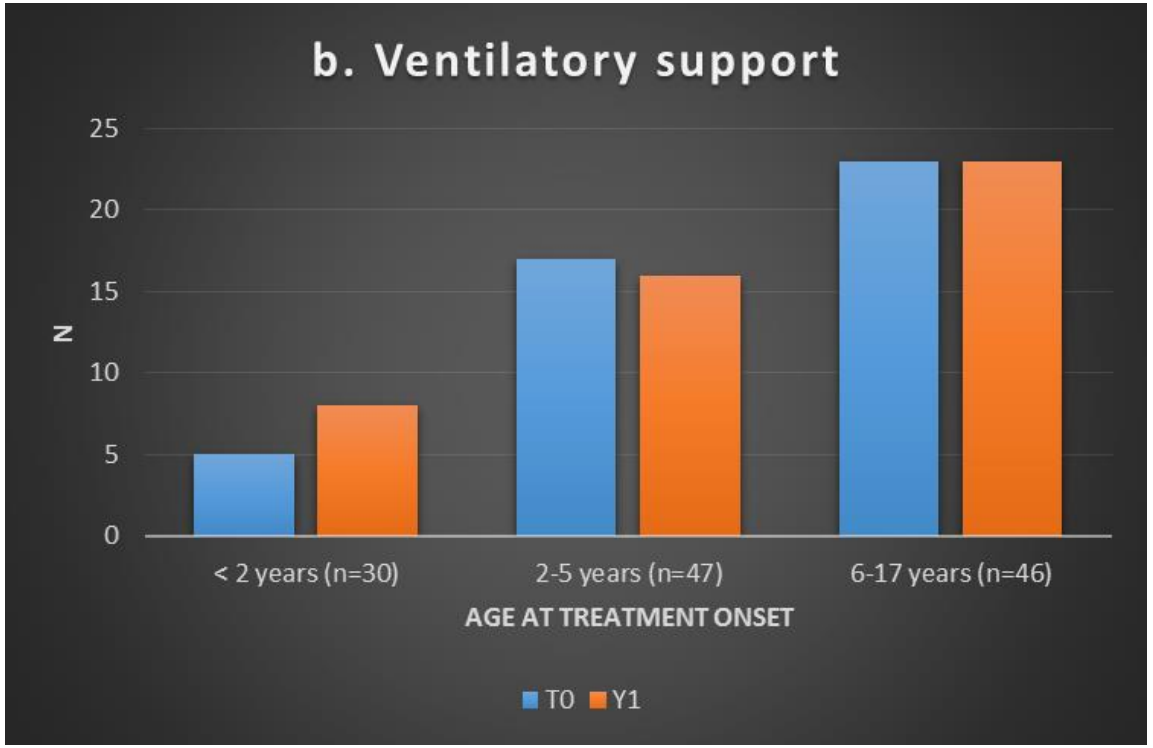
- 68 girls (55.3%) and 55 boys (44.7%)

SMA type	Age at treatment onset				SMN2 copy number				
	< 2 y	2-5 y	6-17 y	Total	2	3	4	ND	Total
Type 1a/b	10	0	0	10	6	4	0	0	10
Type 1c	11	10	3	24	7	16	0	1	24
Type 2	9	37	43	89	5	76	3	5	89
Total	30	47	46	123	18	96	3	6	123



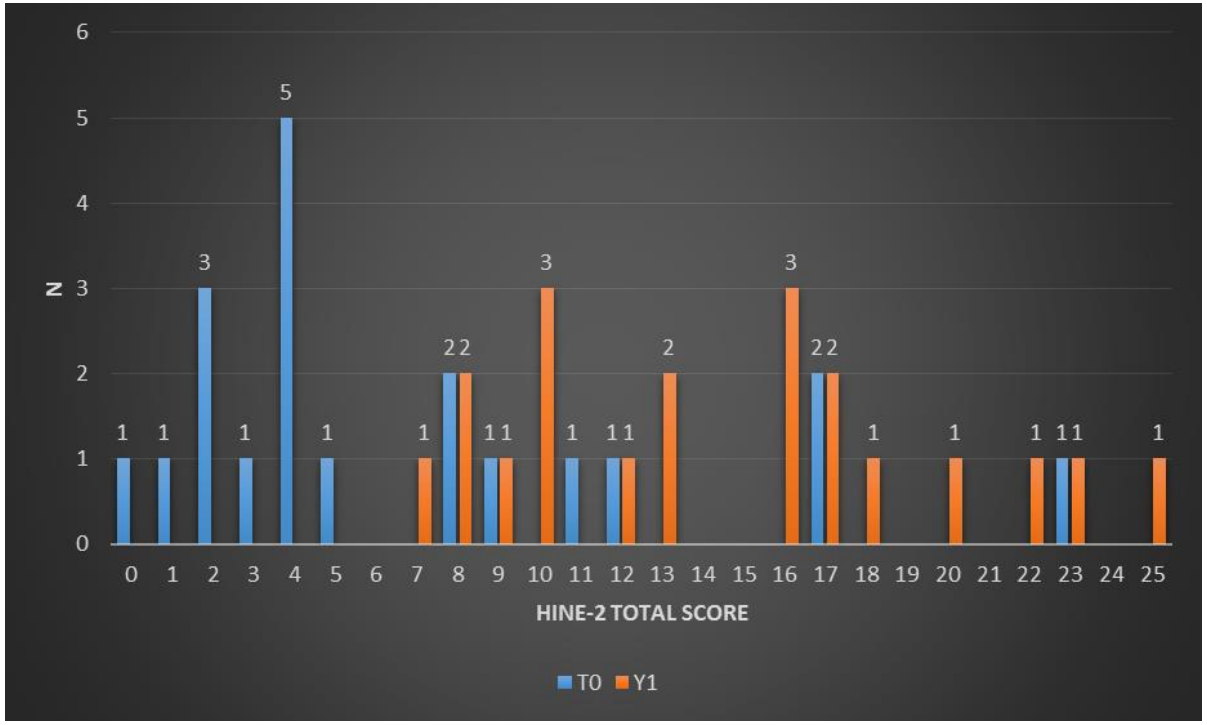
Nutritional and Ventilatory supports





Motor Milestone (HINE-2) , children < 2 years

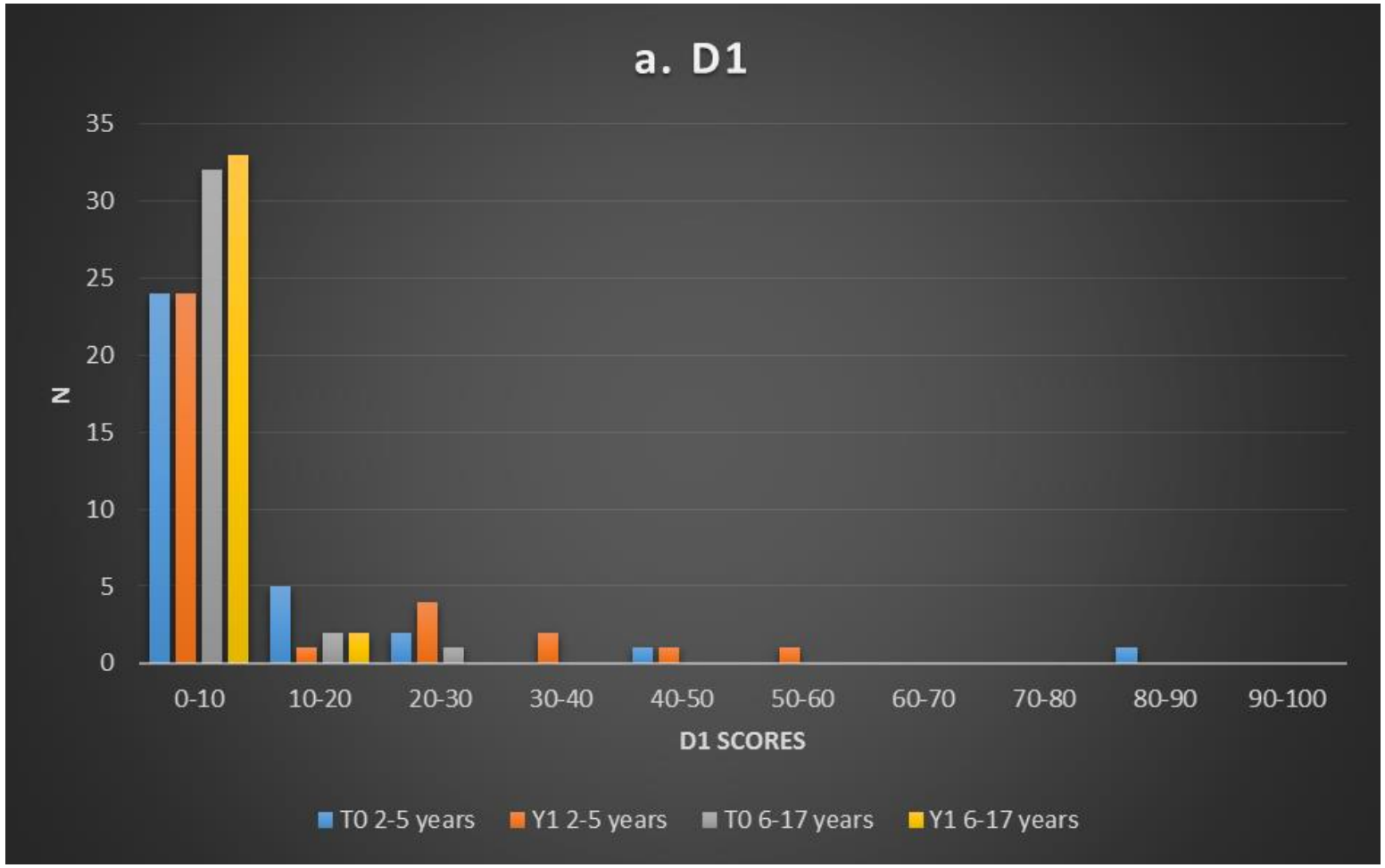
HINE-2 score	T0	Y1	p
Head control (0-2) (n=17)	1.2 / 1 (0-2)	1.9/ 2 (1-2)	0.008
Sitting (0-4) (n=17)	1.4 / 1 (0-4)	2.8 / 3 (0-4)	<0.0001
Voluntary grasp – note side (0-3) (n=17)	2.2 / 2 (0-3)	2.8 / 3 (2-3)	0.008
Ability to kick in supine (0-4) (n=17)	1.4 / 1 (0-4)	3.2 / 4 (1-4)	<0.0001
Rolling (0-3) (n=17)	0.6 / 0 (0-3)	1.8 / 2 (0-3)	0.001
Crawling or bottom shuffling (n=17)	0.6 / 0 (0-4)	1.1 / 1 (0-4)	0.008
Standing (0-3) (n=17)	0.1 / 0 (0-2)	0.6 / 0 (0-3)	0.016
Walking (0-3) (n=17)	0.1 / 0 (0-1)	0.3 / 0 (0-2)	0.25
HINE- 2 Total score (0-26) (n=20)	7 /4 (0-23)	14.5/ 14.5 (7-25)	<0.0001



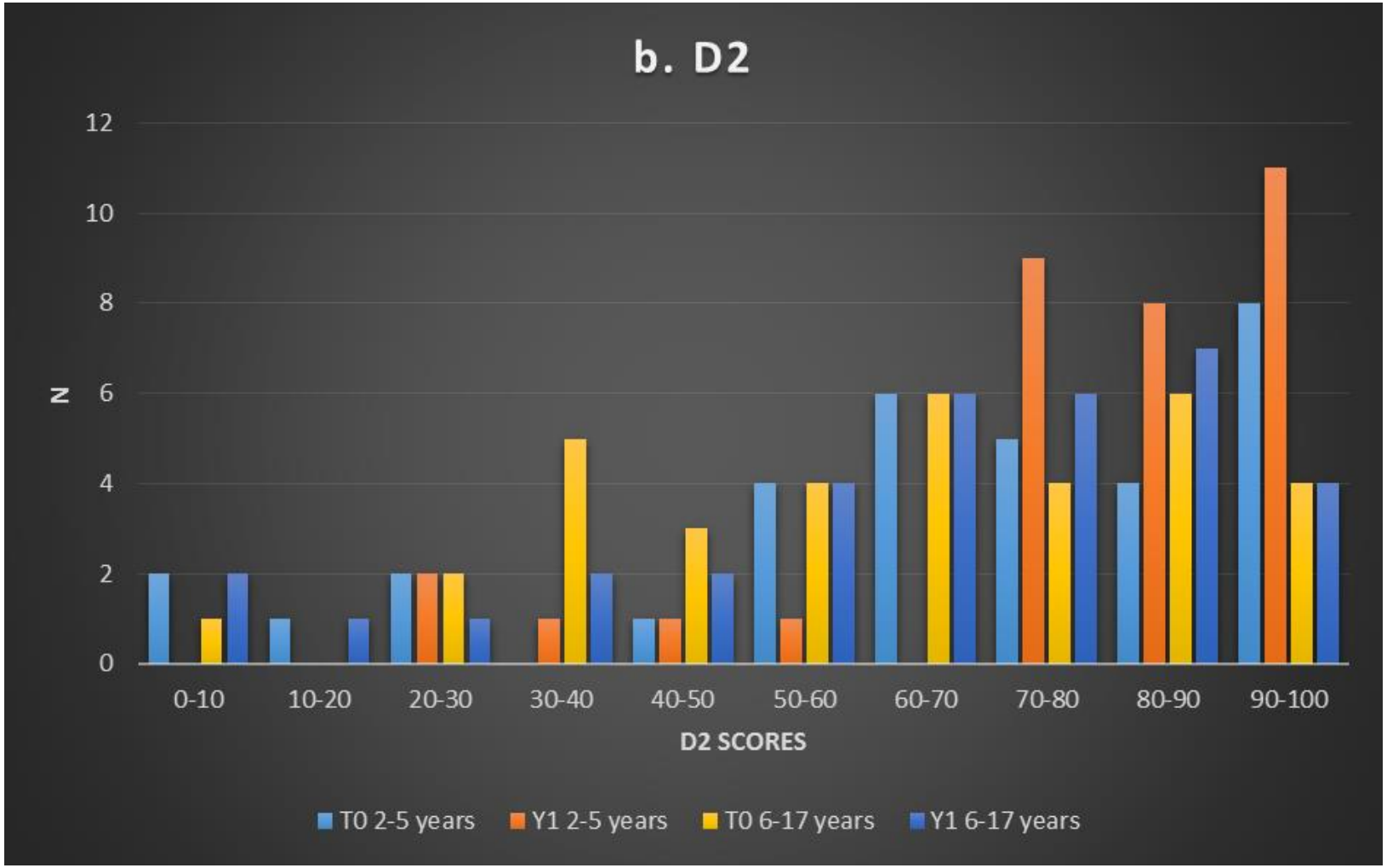
Motor Function Measure scores in children > 2 years.

Age at treatment onset		T0	Y1	p
	MFM total score	42/44 (4-87)	47 / 50 (6-78)	< 0.001
All patients (n=68)	MFM D1	7 / 4 (0-83)	7 / 3 (0-50)	0.245
	MFM D2	63 / 67 (1-100)	71 / 76 (2-100)	< 0.001
	MFM D3	74 / 81 (10-100)	81 / 88 (14-100)	< 0.001
2-5 years (n=33)	MFM total score	45 / 45 (10-87)	52/ 53 (16-78)	< 0.001
	MFM D1	10 / 4 (0-83)	10 / 4 (0-50)	0.144
	MFM D2	66 / 71 (1-100)	77 / 83 (22-100)	< 0.001
	MFM D3	74 / 83 (24-100)	84 / 92 (38-100)	0.001
6-17 years (n=35)	MFM total score	40/43 (4-60)	43/47 (6-63)	0.099
	MFM D1	4 / 3 (0-25)	3 / 3 (0-13)	0.651
	MFM D2	61/63 (6-96)	64/69 (2-97)	0.457
	MFM D3	73 / 81 (10-100)	79 / 86 (14-100)	0.04

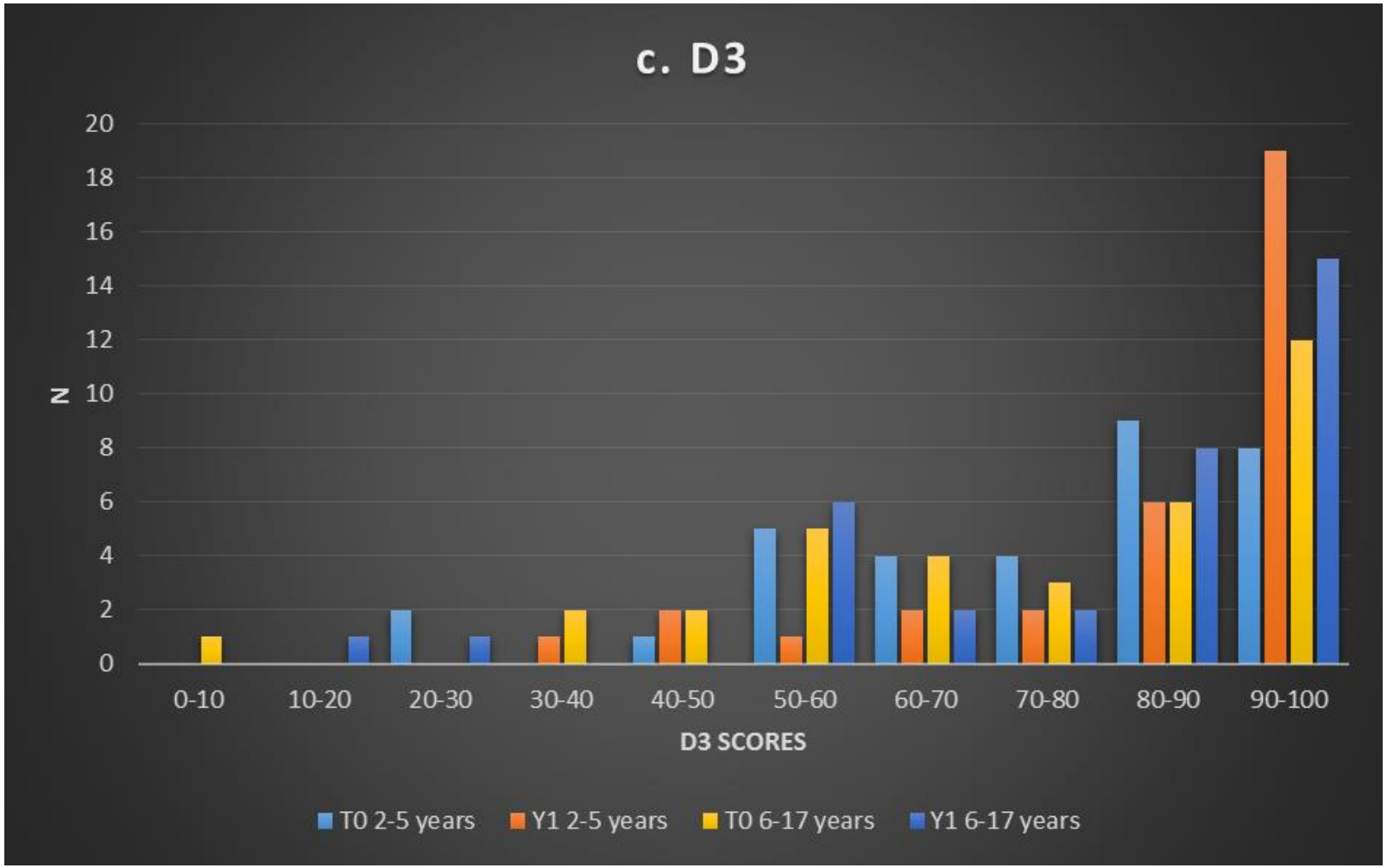
MFM : D1


a. D1
35
30
25
20
15
10
5
0
N
0-10
10-20
20-30
30-40
40-50
50-60
60-70
70-80
80-90
90-100
D1 SCORES
T0 2-5 years
Y1 2-5 years
T0 6-17 years
Y1 6-17 years

MFM: D2


b. D2
12
10
8
6
4
2
0
N
0-10
10-20
20-30
30-40
40-50
50-60
60-70
70-80
80-90
90-100
D2 SCORES
T0 2-5 years
Y1 2-5 years
T0 6-17 years
Y1 6-17 years

MFM: D3


c. D3
20
18
16
14
12
10
8
6
4
2
0
N
0-10
10-20
20-30
30-40
40-50
50-60
60-70
70-80
80-90
90-100
D3 SCORES
T0 2-5 years
Y1 2-5 years
T0 6-17 years
Y1 6-17 years

General considerations

- Caregiver evaluations :105 patients
  - No caregiver rated their patient's condition as minimally, much or very much worse (ratings 5, 6 and 7, respectively),
  - 13% observed no change (rating 4),
  - 35% a minimal improvement (rating 3)
  - 46% considered that the patient's condition was much improved (rating 2)
  - 6% very much improved (rating 1)
- Adverse events rare (n=95 /525)
  - technical difficulties for lumbar puncture (n=55) with fluoroscopic guidance required in 17 cases,
  - headache (n= 23),
  - post lumbar puncture syndrome (n=6),
  - nausea and vomiting (n= 4),
  - asthenia (n=4),
  - back pain (n=2), fever (n=1).

Conclusions

- Nusinersen changes the natural history and standard care of children with SMA, particularly for severe forms and in younger children
- In spite of these improvements, patients with SMA types 1 and 2 treated with nusinersen still require intensive support care and remain severely disabled
- Nevertheless, it seems there the use of corset is less necessary for younger child, with early treatment
- There is real optimism among caregivers after one year of treatment
- This treatment raises new ethical challenges.