The NorthStar Ambulatory Assessment in Duchenne Muscular dystrophy: considerations for the design of clinical trials

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on behalf of UK NorthStar Clinical Network

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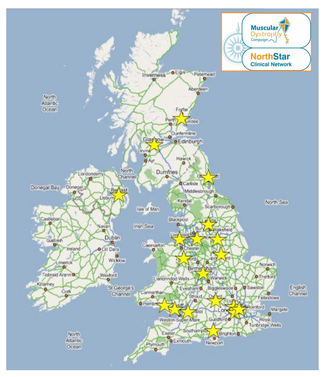
Background

With the emergence of experimental therapies for DMD, it is crucial to understand the natural history of this disorder to properly design clinical trials
The aims of this study are:

1) to assess the motor function decline in DMD boys treated according to the standards of care;
2) to describe the rate of motor function decline in different skippable population
3) to describe the natural history of DMD boys who were treated with steroids below five year of age

NorthStar Clinical Network

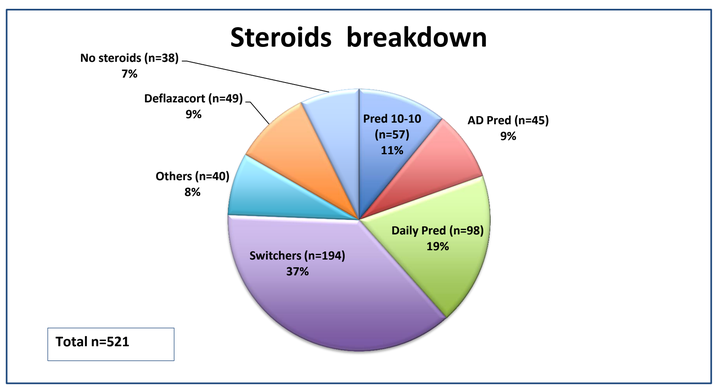
This is a collaboration of 20 neuromuscular centres in the UK, collecting in a web-based database longitudinal data on ambulant DMD boys treated with steroids . To date, there are over 500 patients registered in the database.

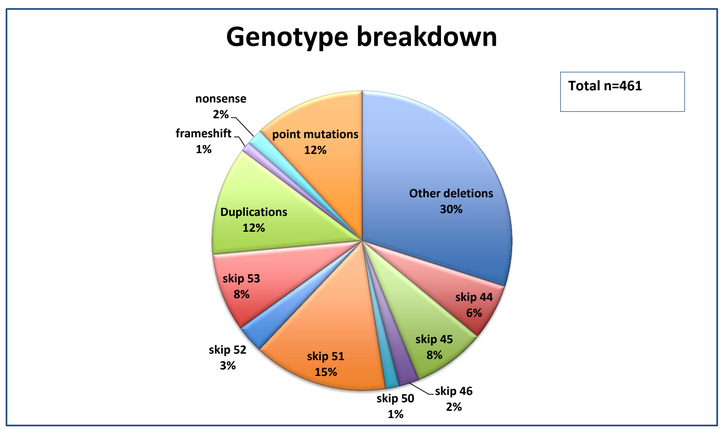


Methods

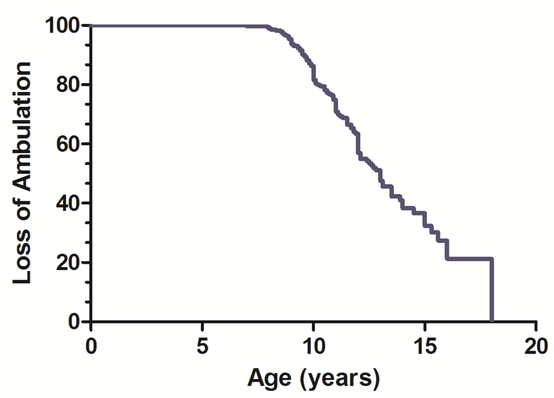
Through the UK NorthStar Network and database, clinical data systematically collected from 2004-2012 on **483** DMD boys followed-up in 17 UK neuromuscular centres were included in the analysis.
Our study focuses on the NorthStar Ambulatory Assessment (NSAA) as a primary outcome measure.
Additionally , for the analysis of the genetic subpopulation, we included data from **84** DMD boys followed-up in Rome.

General characteristics





Age at loss of ambulation

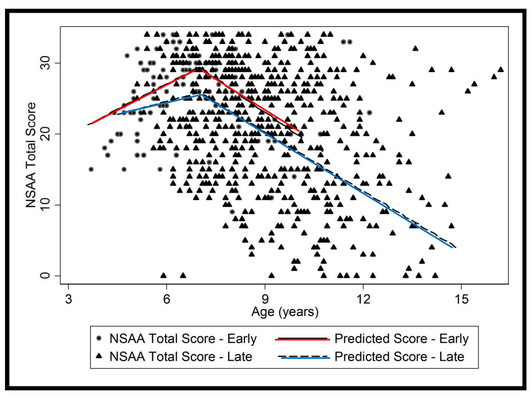


Age at loss of Ambulation

Loss of ambulation (LOA) was reported in 129 individuals.
Median LOA = 13 years (including all treatment regimen)
Two years prior to loss of ambulation, the mean total score for the NSAA was 13.5 units.

We found no evidence of a significant difference in time of LOA when comparing the different skippable subgroups to the general DMD population .

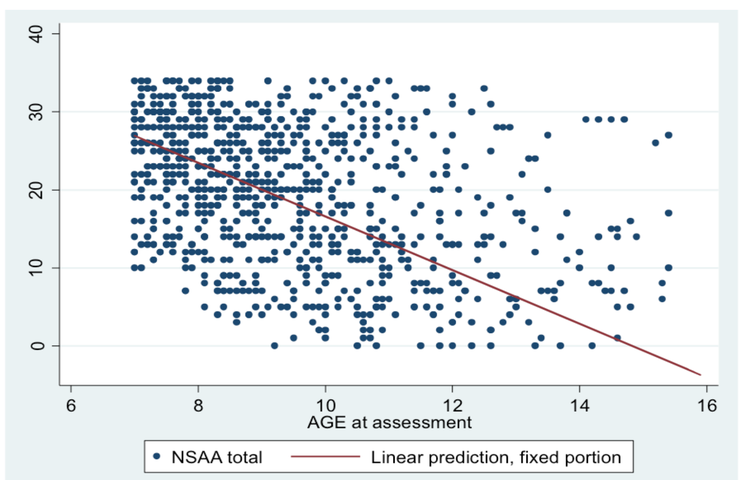
Young DMD and early treatment

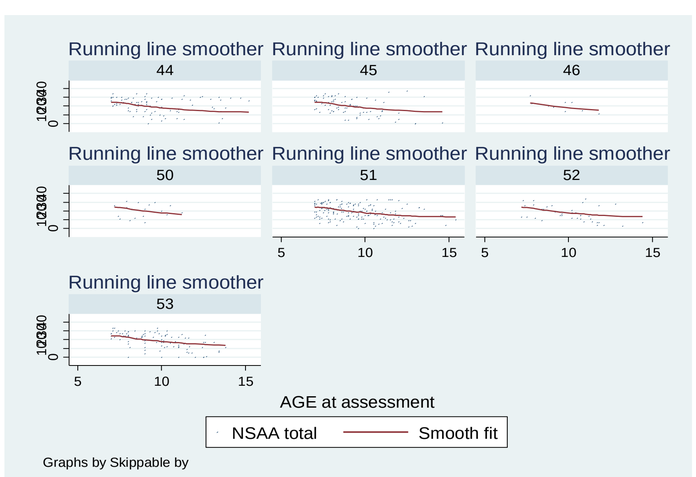


NSAA total score fitted model for < 7 years old

We compared boys who started steroids before 5 years with boys who started steroids between 5 and 9 years of age
Late starters on daily or intermittent prednisolone (n =222): mean age= 6.7 years
Early starters (n = 36): mean age = 4.5 y, the earliest steroids were started= 3.4 years; 19 on intermittent and 17 on daily prednisolone
Boys on steroids <5 y.o. gain better motor function increasing by an extra **2 units** in NSAA per year up to 7 years of age (p=0.04), with a mean NSAA of 29 vs 25.

NorthStar Ambulatory Assessment





Skippable by (yes vs. no)	Interaction coefficient	P value
44 (n=44)	1.29	0.004**
45 (n=48)	-0.36	0.49
46 (n=16)	1.29	0.003**
50 (n=14)	1.59	0.24
51 (=84)	-0.25	0.39
52 (n=16)	-0.85	0.08*
53 (n=63)	-0.78	0.05*

NSAA total score fitted model for > 7 years old

We previously reported that DMD boys gain motor function up to age of 7, when they start declining (Ricotti et al JNNP 2012).

In the analysis we included all the treatment groups.
The slope of decline is approximately **3.5 units** in NSAA per year.
At 8 years of age the population average NSAA score is of 24.
At 10 years of age it is estimated to be 17 units.
We adjusted the model for previous time on steroids.

NSAA total score fitted model and interaction for skippable genotype subgroups

For this analysis we included 24-monthsl longitudinal data on 84 DMD boys form the Italian NorthStar network.

When compared with the whole cohort of DMD boys, Individuals skippable by exon 44 and 46 do better declining at a slower rate of more than 1 NSAA unit per year. While populations skippable by exon 53 and 52 show a faster decline compared to the general DMD population, at an average rate of 0.8 NSAA unit per year.
We found no significant difference in the other skippable cohorts.

Conclusion

Our study provides insights on the current natural history in a large cohort of DMD boys, which help when selecting inclusion criteria in the design of clinical trials.
Including all the steroid treatment groups, after age 7, when motor function decline starts, we observed that the rate of decline on the NSAA is of about 3.5 units per year. Two years prior to loosing ambulation the average NSAA total score was 13.5.
When compared to the general DMD population, boys with mutation skippable by exon 44 and 46 decline at a lesser rate (p=0.004); while boys with mutation skippable by exon 53 and 52 decline faster (p=0.05). Finally, our data support early intervention with steroids: boys who started treatment before 5 years old gain better motor function until age 7 (p=0.04).

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