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OUTCOMES IN PATIENTS WITH SPINAL MUSCULAR ATROPHY GIVEN NUSINERSEN, ONASEMNOGENE ABEPARVOVEC OR NO TREATMENT: AN ANALYSIS BASED ON RESTRICTED MEAN SURVIVAL TIME

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AN ANALYSIS BASED ON RESTRICTED MEAN SURVIVAL TIME

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The two authors contributed equally to this paper.
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Word count: 2,167 (excluding abstract, references, and tables).
Abstract (word count 197, max 200)

Objectives

Spinal muscular atrophy (SMA) is a rare neuromuscular disorder. Currently there are two approved drug treatments for SMA: nusinersen and onasemnogene abeparvovec (OAX). The purpose of the present study was to analyse and compare the event-free survival observed in patients with infantile-onset of SMA receiving nusinersen, OAX or no treatment. The comparison was based on the restricted mean survival time (RMST).

Methods

The cohorts included in our analyses (nusinersen, 17 patients; OAX, 10 patients; no treatment, 23 patients) were obtained from a standard PubMed search. For each cohort, the values of RMST were determined from the Kaplan-Meier curves reported in these studies (end-point: death or need for permanent ventilation). The RMST was calculated using a model-independent method.

Results

The RMST of nusinersen at 33 months of follow up was 25.05 months (95% confidence interval [CI], 23.86 to 26.23) vs 13.90 (95%CI 12.73 to 15.06) for no treatment. The RMST of OAX at 57 months was 57.00 vs 18.32 (95%CI 16.89 to 19.76) for no treatment.

Conclusion

Our analyses defined a robust methodological framework to quantify the outcomes of these treatments. This study needs to be repeated after these treatments have achieved a longer follow-up than that presently available.

KEYWORDS: spinal muscular atrophy; nusinersen; onasemnogene abeparvovec; restricted mean survival time; Kaplan-Meier; pharmacoeconomics.
1. Introduction

The restricted mean survival time (RMST) is a relatively new parameter proposed to improve the analysis of survival curves. In comparison with traditional analyses based on the hazard ratio (HR) and the median, the RMST has the advantage of capturing the overall shape of the survival curve, including long-term survivors. Like the median, the RMST is expressed on a scale of time. In comparison with the hazard ratio (HR), the RMST provides much better information on the outcomes obtained with different treatments [1-4].

The literature on the RMST has shown an extraordinary growth in 2019 and 2020 [5,6]. In this context, a model-independent method drawn from the field of pharmacokinetics [7] has been developed in 2020 to simplify the calculation of the RMST [8]. A technique for estimating the 95% confidence interval of RMST [9] has also been made available thus extending the application of the model-independent approach. Finally, the model-independent method of RMST calculation has already been employed to study patients with different types of cancer [10-13].

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by degeneration of spinal motor neurons (SMN), is caused by deletions or mutations in the Survival Motor Neuron 1 (SMN1) gene and is the most common genetic cause of childhood mortality [14]. Survival is dependent upon a small amount of normal SMN protein translated by the backup SMN2 gene. SMN2 gene differs from SMN1 by 11 nucleotides and, due to a splice site variant, usually excludes exon 7, so that only 10-25% of SMN2 generates full-length functional SMN protein.

Currently there are two approved drug treatments for SMA: nusinersen (Spinraza, FDA and EMA approved) [15,16] and onasemnogene abeparvovec (OAX) (Zolgensma, FDA approved) [17,18]. On 26 March 2020, also the EMA committee for human medicines has recommended OAX for conditional approval.
Nusinersen is an antisense oligonucleotide specifically designed to alter splicing of SMN2 pre-mRNA, increasing the amount of functional survival motor neuron. It is administered by intrathecal injection and the treatment requires multiple loading doses followed by a maintenance dose. OAX is an adeno-associated virus vector-based gene therapy designed to replace the function of the missing or nonworking SMN1 gene with a new, working copy of a human SMN1 gene. The treatment consists of a one-shot intravenous administration.

In the present paper focused on infantile-onset treatment of SMA, we studied the outcomes observed with these two drugs by focusing on the end-points of ventilation-free survival and death. Our analyses were based on the RMST.

2. Patients and Methods

2.1 Study design and literature search

Our study was aimed at applying the RMST to patients with infant-onset SMA receiving nusinersen, OAX, or no treatment. Death and/or ventilation free survival were the end-points of our analysis.

The criteria for including previously published patient cohorts in our analysis were the following: (1) initiation of treatment with nusinersen or OXA at age <3 years; (2) assessment of treatment outcomes using the end-point of death and/or freedom from ventilation; (3) inclusion of the study with the longest follow-up when two or more separate reports were available based on the same patient cohort. Nusinersen and OAX were selected because both have received approval by FDA and EMA.

A PubMed search based on the keyword “spinal muscular atrophy” (filter: clinical trial) identified 106 trials eligible for our analysis. After examining the abstract (and, if needed, the full text) of
these 106 papers, we selected the clinical studies (N=6) that met the three above-mentioned inclusion criteria. After removing duplicate entries, two trials were identified that met the criteria of our analysis. Finally, the PubMed search described above was supplemented by the expert opinion of the clinicians responsible for the prescription of nusinersen and/or OAX in the Tuscany region (Italy).

### 2.2 Statistical analysis

The RMST is defined as the area under a survival curve (AUC) and represents mean survival; its calculation can be made according to a lifetime perspective or truncated (“restricted”) at a pre-determined time-point of the follow-up (which is called “milestone”; abbreviation, t*). In our study, the model-independent values of RMST were determined according to the AUC calculation previously described [8,9]. Briefly, this estimation procedure retrieves the published graphs of the survival curves, then reconstructs the survival percentage-vs-time data points with a digitizer [22], and finally calculates the model-independent value of RMST. An Excel datasheet is used to apply the trapezoidal rule [23] (typical of pharmacokinetics). To improve the phase of data input, the procedure has been transferred into an executable file compatible with Windows.

Our analysis examined the time-to-event Kaplan-Meier survival curves of the clinical trials selected through the literature search; in these curves, the event was death or the need for permanent ventilation. The 95% confidence intervals (CIs) for RMST were calculated for each curve as previously described [9].

Finally, in performing pairwise (direct and indirect) comparisons between treatments, the value of t* was kept the same for the two alternatives being compared.
3. Results

3.1 Cohorts included in our study.

The cohort treated with nusinersen included in our analysis was obtained from an open-label, escalating dose phase 2 study, published by Finkel et al.[15], which included 17 patients; these patients were of either gender, aged between 3 weeks and 7 months, with onset of SMA symptoms between 3 weeks and 6 months. All had SMN1 homozygous gene deletion or mutation; the duration of follow-up ranged from 2 to 32 months.

The cohort treated with OAX was obtained from the ongoing long term follow-up study of OAX-treated patients (the START clinical trial [18-20]), which included 10 patients who received OAX for SMA Type1. These patients were <6 months of age at the time of infusion; their follow-up lasted up to 17 months. More recently, the results of this trial have been updated by including a longer follow-up [20].

The cohorts given no specific treatment were drawn from the control groups of the studies on nusinersen and OAX. Further details on these four cohorts can be found in the original studies [15-21].

To ensure comparability, the two curves of the comparison of nusinersen vs controls were truncated at \( t^* = 33 \) months, while the two curves of the comparison OAX vs controls were truncated at \( t^* = 57 \) months. In the indirect comparison between nusinersen and OAX, the milestone was set at 39 months.

3.2 Statistical analysis.

The values of restricted RMST were determined from the 4 time-to-event curves of the cohorts included in our study. Table 1 shows the values RMST along with the survival gain for three
pertinent (direct and indirect) comparisons. The graphs of the 4 fitted curves are shown in Figure 1. Performing the pairwise statistical comparisons was hampered by the lack of variance for the curve of OAX.

4. Discussion

Event-free survival is an appropriate end-point for quantifying the outcomes in patients with SMA; this is also confirmed by the homogeneous choice of this end-point in the original studies examined herein. Despite the use of a common end-point, comparing the outcomes across patients with SMA given different treatments (or no treatment) is complex for these data-sets mainly because the active treatments are recent, and consequently the lengths of follow-up are short. The median can be an exhaustive parameter to measure outcomes in untreated patients, but fortunately this parameter is unsuitable for patients who respond to the treatment received and consequently prolong their survival to a large extent; this makes the median not computable because cumulative survival remains greater than 50%.

Information on untreated patients presently relies on a longer follow-up [17-20,23] than that of treated patients. In this complex clinical and methodological context, the model-independent RMST provides an important advantage because its applicability is unlimited provided that an adequate t* is chosen.

The Kaplan-Meier curves of untreated patients have been followed-up for long enough to reach a quite low residual survival (<20%); this makes the information on controls adequate for the comparison with patients given a new treatment. As a result, as regards nusinersen and OAX, whatever milestone is chosen (or will be chosen in the future) to truncate the curve and to
calculate the RMST, an adequate control for untreated patients will always be available from the information published thus far [17-20,23].

The RMST is already useful to quantify the outcomes presently available for treated patients, but its importance will grow with time as the follow-up of these patients increases. The main objective of the between-treatment comparisons is to quantitatively estimate the incremental benefit (i.e. the survival gain) that innovative treatments determine in comparison with no treatment. The extent of this incremental benefit (i.e. the survival gain), which is important in pharmacoeconomic terms, is expected to increase strikingly with time, and so the analyses described herein (showing a gain around 1 year per patient for nusinersen and around 3 years per patient for OAX) will require an update in the next future. In other words, in interpreting these preliminary results caution should be exercised, while waiting for future evaluations based on a longer follow-up.

From a strictly clinical point of view, the results of our study are worthwhile also because a unit of measure (“months lived alive and with no need for ventilatory assistance”) has been identified that adequately determines the benefit. On the other hand, apart from issues of strictly methodological nature, the overall picture, presented herein, of the effectiveness of these two treatments is essentially the same as that reported in a recent Cochrane review [16]. Likewise, the outcomes found in the no-treatment cohorts of the two randomised trials were close to those reported in the observational study by Finkel et al [16].

One important limitation of our study is that the RMST was applied to two studies with a limited number of cases (17 versus 10) and with different follow up (see Table 1). Furthermore, the two populations, apparently similar for age at recruitment, were not completely comparable for age at onset of the disease, functional status, and comorbidities, which are variables with potential influence on survival.
Another point of controversy regards the ethical implications. For example, it is difficult to decide how dying at 6 months compares with dying at 12 months since newborns with a severe disease are not likely to reach childhood. This question, however, goes beyond the purposes of the present study.

In cost-effectiveness analysis, a threshold of acceptability is currently set at around 5,000 EUR per month gained. Although orphan drugs are recognised to deserve a cost-effectiveness ratio exceeding this threshold to some extent [24], the degree to which nusinersen, and probably also OAX, fail to meet the threshold might be considered unacceptable. At least, this is the conclusion reported by the main pharmacoeconomic studies published thus far [24-27].

In contrast, the pharmacoeconomic findings emerging from our analysis, though premature, indicate that the gains of 10 to 50 months per patient could be associated to an “acceptable” cost per patient from 50,000 up to 250,000 EUR; no further comments on this issue can be made at the present stage of the evidence because a much longer follow-up of treated patients would be needed permit to make reliable pharmacoeconomic decisions. Anyhow, while OAX is known to be the most expensive drug in the world [28], the drug has the advantage of being a one-shot treatment, and so the determination of its cost-effectiveness ratio is relatively easy. In contrast, determining the cost-effectiveness of nusinersen is more complex owing to its repeated dosing scheme.

Finally, in the analysis of the outcomes of OAX vs nusinersen, the need to develop more efficient methodological tools for survival analysis has been addressed by Dabbous et al [30] who proposed to apply the number needed to treat (NNT) to this comparison. Their result was that the NNT to prevent one more death with OXA instead of nusinersen is 6.2. However, this methodological proposal has been criticised because, in general, the NNT is not designed to be applied the way described by Dabbous et al (the so-called “unanchored” NNT). Sandrock & Farwell [31] have
explicitly emphasised the poor reliability of this “unanchored” NNT approach mainly because no adjustment was made for differences in patient characteristics and study design. As regards study design, the length of the follow-up is, in our view, a factor that cannot be left out from any analysis.

5. Conclusions
In conclusion, the current scenario of treatments for SMA is rapidly evolving. Our paper has pursued the objective to summarise the present evidence, to identify an appropriate metric for quantifying effectiveness and, finally, to lay the foundations for repeating these assessments of effectiveness and cost-effectiveness when the clinical data on these two treatments become more mature.

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Authors’ contribution
The two authors contributed equally to this study.

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Declaration of interests
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6. References

Papers of special note have been highlighted as: * of interest, ** of considerable interest


5. **Messori A. Eight major international journals have recently published a paper to highlight the methodological advantages of the restricted mean survival time, published 13 July 2020, Open Science Framework, https://osf.io/3gj96/ DOI 10.17605/OSF.IO/DY3UH

This preprint highlights the methodological endorsement that these 8 major journals have unanimously given to the RMST in the past months. These papers contain an excellent

This preprint describes the large amount of methodological literature published on the RMST in 2019 and 2020.


   This phase-2 study has been the source of information for determining the outcomes over time of patients treated with nusinersen.


   This observational study has been the source of information for comparing the outcomes of the no-treatment cohorts in the two randomised trials vs observational studies.


This reference has been the source of information for determining the outcomes over time of patients treated with onasemnogene abeparvovec.


23. Youtube. “Find the area under a curve in Excel”.
https://www.youtube.com/watch?v=U6EWnEsdR5A accessed 6 May 2020


27. Pharmacoeconomic Review Report: Nusinersen (Spinraza): (Biogen Canada Inc.):


Table 1. Characteristics of the three cohorts and values of RMST estimated from the time-to-event curves.

<table>
<thead>
<tr>
<th>Data-set</th>
<th>No. of patients</th>
<th>RMST (months) with 95% confidence interval</th>
<th>Gain (months)</th>
<th>Statistical significance (P value)</th>
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<tbody>
<tr>
<td>1) Comparison of nusinersen vs no treatment</td>
<td></td>
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<td></td>
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<tr>
<td>Nusinersen (t*=33 mos)</td>
<td>17</td>
<td>24.33 (23.12 to 25.53)</td>
<td>11.57</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Untreated patients (t*=33 mos)</td>
<td>23</td>
<td>12.76 (11.62 to 13.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Comparison of OAX vs no treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAX (t*=57 mos)†</td>
<td>10</td>
<td>57.00 (not computable)</td>
<td>38.68</td>
<td>NC‡</td>
</tr>
<tr>
<td>Untreated patients (t*=57 mos)</td>
<td>23</td>
<td>18.32 (16.89 to 19.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Comparison of nusinersen vs OAX</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nusinersen (t*=39 mos)</td>
<td>17</td>
<td>28.65 (27.34 to 29.96)</td>
<td>13.95</td>
<td>NC‡</td>
</tr>
<tr>
<td>OAX (t*=39 mos)†</td>
<td>10</td>
<td>39.00 (not computable)</td>
<td></td>
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<tr>
<td>4) Single-curve analyses at the maximum length of follow-up</td>
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<tr>
<td>Nusinersen (t*=39 mos)</td>
<td>17</td>
<td>28.65 (27.34 to 29.96)</td>
<td>Not computed due to the different length of the follow-up</td>
<td>NC‡</td>
</tr>
<tr>
<td>OAX (t*=57 mos)†</td>
<td>10</td>
<td>57.00 (not computable)</td>
<td></td>
<td></td>
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</tbody>
</table>

†100% event-free at t*
‡ NC, not computable; the p-value could not be computed because one of the values of RMST had no variance.

Abbreviations: RMST, restricted mean survival time; OAX, onasemnogene abeparvovec; t*, milestone
Legends for figures

**Figure 1.** Four Kaplan-Meier curves were included in our analysis. The curve (denoted with red circles) that has been digitised and then subjected to the RMST analysis is that of nusinersen (Panel A), controls of the nusinersen trial (Panel B), OAX (Panel C), and controls of OAX trial (Panel D). In each curve, the AUC represents the RMST. The graphical results of each fitting procedure are represented by the series of small red circles that are superimposed to the original curve.
Figure 1: Kaplan-Meier survival curves for patients with different diagnoses.

A: Probability of permanent ventilation-free survival vs. age (months) for patients with Diagnoses X and Y. (Diagnosis X: blue line, Diagnosis Y: red line.)

B: Similar to A but for a different subset of patients.

C: Graph showing a constant survival rate for patients with Diagnosis Z.

D: Graph showing a constant survival rate for patients with Diagnosis W.

Legend:
- Diagnosis X: Blue line
- Diagnosis Y: Red line
- Diagnosis Z: Green line
- Diagnosis W: Black line

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