Survival estimates for Type 2 spinal muscular atrophy (SMA)

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Introduction

• Spinal muscular atrophy (SMA) is a rare, severe, inherited neuromuscular disease resulting in progressive muscle weakness, paralysis and premature death.
• The recent development of targeted agents for this indication has highlighted the importance of robust survival data to inform cost-effectiveness assessments.
• The aim of the current analysis was to generate a robust estimate of survival in patients with Type 2 SMA.
• Type 2 SMA is evident between 7–18 months of age; patients may have a reduced life expectancy but can survive into adulthood.1

Methods

• A systematic literature review (SLR) was conducted in August 2019 to identify studies reporting survival curves in Type 2 SMA.
• Pseudo individual patient data (IPD) were generated by digitising the survival curves from eligible studies and applying a published algorithm1 using the R statistical software to provide estimates of x and y coordinates.
• The Guyot algorithm relies upon inverting the coordinates obtained from the digitization process, along with the number at risk at time t.2
• The output from the algorithm applied to each study Kaplan–Meier (KM) curve includes a dataset which comprises recreated survival data including time and event status (1 represents an event and 0 represents censored status).
• Following recreation of the pseudo IPD, data files for each study were pooled to create one dataset (i.e. no distinction between studies).

Results

• The SLR identified seven eligible publications published between 1997 and 2018 conducted in Australia, China, Europe and the US reporting Type 2 SMA survival curves (– Table 1).
• The number of patients enrolled ranged from 13 to 635 (total cohort, N=1,073) and the mean onset of disease was between 8.7 and 22.1 months.
• Where patient characteristics were reported, the mean age of onset of SMA was generally comparable across the study populations.
• The survival data presented from the CureSMA membership database in the US represents the largest body of evidence identified (n=435).3
• This is followed by Zerres, 19979 which presents a survival analysis based on a collaborative database using data from German and Polish hospitals (n=240) which has been cited as a source of survival data for Type 2 SMA in previous cost-effectiveness models.4
• There was limited reporting of the patient characteristics and loss of follow-up across the studies, so it was not feasible to conduct a robust assessment of the comparability of the patient populations.
• Furthermore, there is currently a lack of published data exploring potential prognostic factors for survival in Type 2 SMA.
• Patient gender was variable, with the percentage of female patients ranging from 52%–69% within studies.
• A key assumption of the analysis is that the survival probabilities reported by age and disease duration across different studies are comparable.

Table 1: Summary of the studies reporting survival curves for patients with Type 2 SMA

<table>
<thead>
<tr>
<th>Publication</th>
<th>Data source, territory</th>
<th>N</th>
<th>Patient characteristics</th>
<th>Approximate follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belter, 20188</td>
<td>CureSMA database, US</td>
<td>635</td>
<td>• Female, 298 (41%) • Mean age at diagnosis (SD), 22.1 (28.6) months</td>
<td>37.7 years (age)</td>
</tr>
<tr>
<td>Chung, 20043</td>
<td>Neuromuscular clinic, Hong Kong</td>
<td>26</td>
<td>• Female, 17 (65%) • Mean age at onset (SD), 11.5 (7.0) months</td>
<td>38 years (disease duration)</td>
</tr>
<tr>
<td>Farrar, 20135</td>
<td>Specialized neuromuscular clinic, Australia</td>
<td>31</td>
<td>• Female, 15 (48%) • Mean age at onset (SD), 11.7 (4.3) months</td>
<td>58 years (age)</td>
</tr>
<tr>
<td>Ga, 20126</td>
<td>Pediatric Institute, China</td>
<td>105</td>
<td>• Female, 43 (41%) • Mean age at onset (SD), 8.7 (3.8) months • Mean age at first visit (SD), 11.8 (11.0) months • Mean age at diagnosis (SD), 21.0 (15.0) months</td>
<td>9.17 years (age)</td>
</tr>
<tr>
<td>Mannaa, 20097</td>
<td>Cincinnati Children’s Hospital Medical Center, US</td>
<td>13</td>
<td>• Female, 8 (62%)</td>
<td>15 years (disease duration)</td>
</tr>
<tr>
<td>Petit, 20118</td>
<td>Lille and Toulose University Hospitals, France</td>
<td>23</td>
<td>• Mean age at onset, 11.0 months • Brainstem involvement, (57%)</td>
<td>42.5 years (disease duration)</td>
</tr>
<tr>
<td>Zerres, 19979</td>
<td>German/Polish hospitals (collaborative database)</td>
<td>240</td>
<td>• Female, 122 (51%)</td>
<td>50 years (age)</td>
</tr>
</tbody>
</table>

1. *As indicated by the survival curves.

Conclusions

• The current analysis provides the most comprehensive synthesis of published survival curves for patients with Type 2 SMA to date, highlighting the heterogeneity of survival estimates (median 43.1 years) from data captured over time and, in addition, reflecting potential regional differences in the standard of care for Type 2 SMA.
• Longer-term follow-up data from the CureSMA database and other global, regional, and/or local data collection platforms and disease registry networks (including SMArt-CARE, the Treat NMD Alliance, and the International SMA Registry) will help provide an accurate estimate of the long-term survival of patients with Type 2 SMA in the current treatment landscape.

| Figure 1: KM curves based on recreated IPD by study |

- The survival curves recreated from each publication are presented in Figure 1.
- Although there is broad agreement across the studies in the survival estimates up to 15 years (>80% in all studies), there is a paucity of longer-term (>30 years) follow-up which demonstrates a dramatic decrease in survival.
- The longer-term survival data are driven by studies with inherent weaknesses. Examples include: – Farrar, 20135 which enrolled a small number of patients (n=31) – Zerres, 19979 which does not reflect recent improvements in supportive care or availability of targeted treatments.
- The KM curve based on recreated data pooled across all studies is presented in Figure 2.

| Figure 2: KM curve based on recreated IPD pooled across all studies |

- The median survival of patients with Type 2 SMA, based on the pooled dataset, is estimated to be 43.1 (95% CI: 43.1–43.1) years.

Acknowledgments

The study was funded by F. Hoffmann-La Roche AG, Basel, Switzerland. Writing and editorial assistance was provided by MediTech Media, UK, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

References
