Analysis of Overall Survival (OS) in Patients with Acid Sphingomyelinase Deficiency Type B Using the Standardized Mortality Ratio Method

Venediktos Kapetanakis1, Pragya Shukla2, Marie Fournier3, Henri Folse4, Nancy el Hoyek5, Ruth Pulikottil-Jacob6
1Evidera, London, United Kingdom; 2Evidera, Montreal, Quebec, Canada; 3Sanofi Aventis, Longjumeau, France; 4Evidera, San Francisco, CA, United States; 5Sanofi Genzyme, Cambridge, MA, United States; 6Sanofi Genzyme, Reading, United Kingdom.

Introduction

- Acid sphingomyelinase deficiency (ASMD) is a rare, lysosomal storage disease caused by pathogenic variants in the SMPD1 gene that result in progressive cell and tissue damage, impairing the function of multiple organs.1–3
- ASMD presents with variable clinical features across a broad spectrum of disease severity, ranging from a severe, progressive neurodegenerative disease1–4 that leads to death by 3 years of age1,5,6 (ASMD type A), to a more variable, chronic non-neuronopathic form with survival into adulthood (ASMD type B).1,3
- Currently, there are no approved disease-specific treatments for patients with ASMD; however, several clinical trials in children/adults treated with olipudase alfa (Sanofi Genzyme) are complete (ASCEND Phase 1b, NCT01722526; ASCEND Pediatrics, NCT02292654) or ongoing (ASCEND Phase 2/3, NCT02004891; and a long-term study, NCT02004704). Olipudase alfa is generally well-tolerated and patients with ASMD experience improvements in clinical disease measures.5–10
- Given the rarity of ASMD, standard parametric survival analyses may not provide reliable mortality estimates due to the small number of patients that can be included and the high proportion of censoring that occurs during studies, therefore, alternative methods of estimating overall survival (OS) may be helpful.11
- A prospective, multicenter, multinational cross-sectional study (NCT02004704) collected natural history data (follow-up: 0.01–11.04 years) from 59 patients (adults, n=29; children, n=30) with ASMD type B.12,13
  - The shape of the observed OS was subject to high uncertainty due to nine recorded deaths within a small sample size and the high amount of censoring (85%).
  - A standardized mortality ratio (SMR) may be used to compare the mortality risk of the ASMD population against a standard population as an alternative approach for estimating OS.

Objective

- To describe the use of the SMR as a possible alternative approach in the analysis of OS in patients with ASMD type B.

Methods

Calculation of an SMR for the ASMD population

- The SMR for the ASMD type B population was calculated using published life tables from the United States (2017),14 as most patients recruited in the prospective study were from North America. The SMR was estimated using the formula:

  \[ SMR = \frac{Actual \ number \ of \ deaths}{Expected \ number \ of \ deaths} \times 100 \]

- The actual number of deaths and expected number of deaths, were based on the age-specific mortality rates in the general population, retrieved from the life tables (Table 1).
- Once the SMR was calculated, it was applied to the general population mortality data obtained from published life tables for the United Kingdom (2016–2018)15 to calculate adjusted survival probabilities for patients with ASMD. This allowed the SMR estimated OS to be relevant in multiple geographic regions.
  - The probability of dying between age x and x+1 for the ASMD population in the UK was calculated as:

    \[ q_x^{ASMD} = q_x \times SMR \]

    where \( q_x \) is the age-specific mortality rate in the UK.
  - General population mortality rates were used for patients aged 0–3 years.
  - SMR-adjusted mortality rates were used from age 3 years onwards (as mortality is so high in the first few years and reduces later, applying the SMR during 0–3 years would lead to a sharp drop in survival probability, which may not have been representative of the epidemiology of ASMD type B).
  - SMRs were calculated for the overall ASMD type B population and separately for the adult and pediatric populations.

Table 1
14TH INTERNATIONAL CONGRESS OF INBORN ERRORS OF METABOLISM
21-23 NOVEMBER 2021, SYDNEY, AUSTRALIA

Table 1 Representative table to demonstrate the calculation of SMR using OS data from the NCT02004704 trial and US life tables (2017)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Probability of dying between ages ( x ) and ( x + 1 ) (( q_x ))</th>
<th>At risk patients in NCT02004704 (( N_x ))</th>
<th>Expected deaths (( q_xN_x ))</th>
<th>Observed deaths (( d_x ))</th>
<th>Excess deaths (( d_x - q_xN_x ))</th>
<th>SMR (( \frac{\sum d_x}{\sum q_xN_x} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>0.00578</td>
<td>0</td>
<td>0</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>1–2</td>
<td>0.00038</td>
<td>0</td>
<td>0</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>16–17</td>
<td>0.00042</td>
<td>22</td>
<td>0.0093</td>
<td>1</td>
<td>0.9907</td>
<td>0.9907</td>
</tr>
<tr>
<td>17–18</td>
<td>0.00051</td>
<td>25</td>
<td>0.0127</td>
<td>1</td>
<td>0.9873</td>
<td>0.9873</td>
</tr>
<tr>
<td>18–19</td>
<td>0.00060</td>
<td>25</td>
<td>0.0151</td>
<td>1</td>
<td>0.9815</td>
<td>-0.0151</td>
</tr>
<tr>
<td>19–20</td>
<td>0.00070</td>
<td>26</td>
<td>0.0181</td>
<td>1</td>
<td>0.9818</td>
<td>-0.0181</td>
</tr>
<tr>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>98–99</td>
<td>0.29425</td>
<td>0</td>
<td>0</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>99–100</td>
<td>0.31646</td>
<td>0</td>
<td>0</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>≥100</td>
<td>1.00000</td>
<td>0</td>
<td>0</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Total</td>
<td>( \sum q_xN_x = 0.72 )</td>
<td>( \sum d_x = 9 )</td>
<td>( \sum (d_x - q_xN_x) = 8.28 )</td>
<td>12.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE (SMR)</td>
<td>4.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCI (SMR)</td>
<td>4.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCI (SMR)</td>
<td>20.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LCI, lower confidence interval; OS, overall survival; SE, standard error; SMR, standardized mortality ratio; UCI, upper confidence interval.

Fitting parametric survival distributions to the life table probabilities
- Parametric survival analyses were conducted using six survival distributions (exponential, Weibull, Gompertz, log-logistic, log-normal and generalized gamma), which were fitted to the age-specific survival probabilities.

Linking the SMR with spleen volume
- After estimating the mortality curve for the overall ASMD type B population, the overall SMR was further expressed as a weighted average of two SMRs: SMR₁ for patients without severe splenomegaly at baseline (<15 MN) and SMR₂ for patients with severe splenomegaly (≥15 multiples of normal [MN]).
  - The overall SMR was expressed as:
    \[
    SMR = (1 - p) \times SMR_1 + p \times SMR_2
    \]
    where \( p \) was the proportion of patients with severe splenomegaly at baseline.
  - A Cox proportional hazards model was used to evaluate the association between OS and spleen volume in NCT02004704, by estimating a hazard ratio (HR) for OS for patients with versus without severe splenomegaly at baseline.
  - The HR for OS was created by rearranging the following equation (patients with splenomegaly divided by patients without severe splenomegaly):
    \[
    SMR_2 = HR \times SMR_1
    \]
    SMR₁ and SMR₂ were then applied to UK lifetables and parametric distributions were fitted.
  - STATA® Version 15 and R version 4.0.0 was used for all the analyses.

Results
- An SMR of 12.50 [95% CI: 4.33; 20.67] was generated for the ASMD type B population; the wide confidence interval reflected the small sample size.
- The SMR of the adult population was 6.88 [95% CI: 0.14; 13.61] compared with 36.23 [95% CI: 4.47; 67.98] for the pediatric population.

Fitting survival distributions to the adjusted survival probabilities
- The estimated SMR of 12.50 was applied to the mortality rates of the UK population as a multiplier to calculate adjusted survival probabilities as shown in Figure 1.

Figure 1 Adjusted survival probabilities for patients with ASMD compared with the general population

ASMD, acid sphingomyelinase deficiency; SMR, standardized mortality ratio. The general mortality rate was used for patients aged 0–3 years and the SMR-adjusted mortality rate from age 3 years onwards, for patients with ASMD type B.
Linking the OS SMR with spleen volume

- Among patients with intact spleens, 21% of patients had severe splenomegaly and 79% of patients were without severe splenomegaly.
- The HR for OS comparing patients with spleen volume ≥15 MN (patients with severe splenomegaly) versus <15 MN (without severe splenomegaly) was 9.99 (95% CI: 1.03; 97.14).
- This suggested a significant impact of spleen volume on ASMD mortality and led to the following result:
  - The SMRs for patients with ASMD with and without severe splenomegaly were 43.05 and 4.33, respectively. The observed survival probability curves for patients with and without severe splenomegaly are shown in Figure 3.
  - A previous similar analysis also identified splenectomy as a risk factor for mortality in the same patient population [NCT02004704].

Figure 3 Observed survival probability curves for patients with ASMD type B with and without severe splenomegaly

Graphs are generated using information from the UK lifetables and therefore general UK population. ASMD, acid sphingomyelinase deficiency.

Conclusion

- The calculated overall SMR in ASMD was 12.50 [95% CI: 4.33; 20.67]. This indicates there were 12.5 more excess deaths in ASMD compared to the age-specific mortality rates in a general population.
- This study extends our knowledge on the elevated risk of mortality in patients with ASMD, and could to estimate ASMD mortality.
- Spleen volume (≥15 MN) was demonstrated to have a substantial impact on OS.
- Under the assumption that the SMR is independent of geographic region, this method can be used to estimate OS in patients with ASMD in different countries by using country-specific life tables.
- The SMR approach was able to provide a reasonably robust estimate of OS, in rare conditions such as ASMD, where standard parametric survival analyses may not be appropriate.

References


Disclosures

NRF and RP-J are employees of Sanofi–Genzyme and may hold shares and/or stock options in the company. NH was employed by Sanofi–Genzyme while the study was conducted and is currently affiliated with Exact Sciences. McDermot, United States, VK, PS and IF are employees of Evidera, which received financial support from Sanofi–Genzyme for this study.

Acknowledgments

Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Emily Duven, of Ashfield MedComms, an Ashfield Health company, and funded by Sanofi–Genzyme in accordance with Good Publication Practice guidelines.

Funding

The study is sponsored by Sanofi–Genzyme.