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LETTER

The need for evidence-based treatment decisions in spinal muscular atrophy type 0

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Dear Prof. Dr. Kessler,

Tiberi et al.[1] published a report of a patient with prenatal 5q spinal muscular atrophy (hereafter referred to as SMA type 0) who was treated with nusinersen but passed away at the age of 5 months. We thank the authors for their contribution, and take the opportunity to add a patient perspective to this topic.

As the authors note, today it is not clear which SMA type 0 patients may benefit from treatment. Importantly, as with other SMA types, within the SMA type 0 subpopulation there is evidence of heterogeneity in both disease severity and responsiveness to treatment. To illustrate this, in Table 1, we summarize three cases of SMA type 0 children who responded favorably to treatment, the oldest of whom is currently 30 months old.

While treatment options for SMA are evolving rapidly, empirical evidence regarding treatment effects for different subpopulations, including SMA type 0, is still missing. Questions on whether different treatments have different outcomes for individuals, or whether dual therapies may be more beneficial for some, and in particular individuals with SMA type 0 (see Table 1) remain unanswered. In order to close this knowledge gap, we formulate the following action points:

1 We ask clinicians to publish their experience with treatment of patients with SMA type 0.

Table 1. Summary of the characteristics of three children with SMA type 0 who responded favorably to treatment.

Patient	A	P	G
Gender	Male	Female	Male
Number of SMN2 copies	1	1	1
Current age	23 months	34 months	34 months
Respiratory status at birth	Intubated	NIV followed by intubation	Intubated
Current respiratory status	Invasive ventilation	Invasive ventilation	Invasive ventilation
CHOP-INTEND before treatment	2	14	0
Latest CHOP-INTEND	35	45	21
Description of current motor abilities	Moves and holds arms and legs against gravity, good head control	Moves and holds arms and legs against gravity, good head control, rolls from one side to the other	Antigravity movement from elbows down, wobbly head control
Type of treatment	Nusinersen at 16 days; onasemnogene abeparvovec at 4 months (nusinersen discontinued); risdiplam at 13 months	Nusinersen at 14 days; onasemnogene abeparvovec at 4 months (nusinersen continued)	Nusinersen at 17 days; onasemnogene abeparvovec at 7 weeks (nusinersen discontinued); risdiplam at 24 months

2 We ask clinicians and the pharmaceutical industry to *systematically* evaluate treatment effects in this population through disease registries.
3 We ask countries to not exclude patients with a single SMN2-copy (which is often the case in SMA type 0) from treatment reimbursement. While there is currently no empirical evidence that treatment is beneficial for this subpopulation, there is also no evidence that treatment is *not* beneficial. A priori excluding these patients from treatment will maintain this knowledge gap.
4 Finally, in-line with Glascock et al.,[2] we recommend that treatment decisions are made at the individual level, together with the involved families, and with full transparency. We strongly believe that an informed and shared decision will result in the highest level of efficacy and acceptance for the parents, allowing them to cope better with the outcome, whatever it will be.

We hope other stakeholders will follow the example of Tiberi and colleagues so that in the near future, treatment decisions for SMA type 0 patients will be evidence-based.

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Conflict of Interest

N.G. is an advisor and lecturer for Biogen, Novartis, Novartis Gene Therapies (AveXis) and Roche.

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