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Commentary

"The Times They Are a-Changin'." In reply to El-Zaidy et al.: AVXS-101 (Onasemnogene Abeparvovec) for SMA1: Comparative Study with a Prospective Natural History Cohort

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I was a newly-minted pediatrician when I had to disclose for the first time of my career a diagnosis of spinal muscular atrophy type 1 (SMA1). My supervisor gave me relevant advice just before I met with the family. "Do you have everything ready?" she asked. "You mean the appointment with the psychologist, the palliative care contact, the test for the parents?" I responded. "No, the bottle of vodka in the freezer for you tonight." Twelve years later, it was with a bottle of Belgian beer that we celebrated treating our first pre-symptomatic kid with the AVXS-101, a gene therapy that results in expression of a normal copy of the *SMN* gene in motor neurons, that is now marketed as Zolgensma.

The times they are a changin' indeed, and the work of Al-Zaidy, Mendell, and co-workers [1] has greatly contributed to this extraordinary change. But time remains an issue, as there are two time-related questions regarding treatment of infants diagnosed with SMA1: When and how long?

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When to treat is an easier question to answer, and the paper authored by Al-Zaidy and co-workers brings an important insight, yet it was not the primary objective of the study. The answer, which also comes from studies of nusinersen [2] and risdiplam [3], is clear: as soon as possible.

By carefully matching *a posteriori* the population of infants with SMA1 having received AVXS-101 at the therapeutic dose with untreated SMA1 patients and healthy controls, the authors clearly demonstrate that SMA1 patients treated with gene replacement therapy have a completely different 24-month outcome compared to untreated patients. This is not only illustrated by the 100% event-free survival, but also by the high proportion of sitters, which is a remarkable achievement. Matching with an historical cohort of SMA1 patients also clearly reveals how outstanding the two very young outliers in the gene replacement therapy study did. Each scored 50 on the CHOP-INTEND at baseline, 17 points above the best performers of the control cohort. Since we know from previous reports of the study that these two patients are the patients who are walking today [4], the results of Al-Zaidy and colleagues nicely reinforce what

most of clinicians already understood: Capturing patients post-symptom onset via the classical diagnosis pathways does not result in the best efficacy of these innovative therapies. Written between the lines of the article of Al-Zaidy et al. is a plea for newborn screening, which is currently being implemented in more and more countries [5]. Here is what I take away from this paper: "If you want your patient to achieve autonomous ambulation, do not wait that he or she is diagnosed by classical pathways and referred to you. Catch him or her at birth and treat at the best clinical condition, ideally before symptoms are evident."

The other time-related question is: "How long will the transgene be expressed, how long will these kids be off any other medication?" The paper of Al-Zaidy et al. reports no waning of motor function, ulnar CMAP peak area, or motor milestone achievements were observed in patients treated with a single dose of AVXS-101. This statement would have been stronger if it was noted how many patients in the cohort were also given nusinersen. The authors made the understandable choice not to discuss this issue. I assume that underlying this choice is the following: I do not have a single, post-symptomatic treated patient whose parents are not asking me to consider giving their child an additional therapy – whatever is the primary one. We must face the fact that no post-symptomatic treated patient is likely to be ever completely normal and so parents will always ask the physician to consider going the extra mile and then the mile after. It is thus very likely that our first time-sensitive question regarding the "when" will help answer the second related to "how long". In pre-symptomatic patients, the therapeutic objective is nothing less than normality. But it is also foreseeable that no one will be happy to expose (or to pay for exposing) a (near) normal kid to an additional medication.

Since direct and controlled comparisons between the new treatments for SMA will probably never be conducted and since baseline characteristics of the different studies are so different that making comparisons is at best tricky and at worst unfair, the truth will likely come from treatment of pre-symptomatic patients. How long these patients are asymptomatic when treated with the different available medications is going to be the most important question. This is likely to be a question that will not be answered for 10, 15, or even more years by the newly minted pediatricians of today. Fortunately, these pediatricians will never have to have vodka ready-for-use to drown their despair after disclosing a new SMA1 diagnosis, which shows, that indeed, the times they are a changin' . . . .and definitely for the better.

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