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Editorial Commentary

Gene therapy for spinal muscular atrophy: Solomon's consensus in Covid times

The paper by Kirschner et al. appearing in the current issue of European Journal of Pediatric Neurology [1]: "European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy", is trying to set some initial general principles in the chaos of the new therapeutic era for spinal muscular atrophy (SMA).

Patients with SMA were somehow "blessed" in recent years compared to other orphan rare diseases, since medical treatment of SMA has been revolutionised by the availability of multiple disease-modifying therapies-first nusinersen (Spinranza) and then onasemnogene abeparvovec (Zolgensma), with risdiplam and other agents in the pipeline-, changing dramatically the life expectancy and the quality of life of patients with SMA.

There are many reasons why this ad-hoc consensus statement regarding the role of onasemnogene abeparvovec in SMA is of major importance. Apart from the fact that existing trial data cover only a proportion of potentially eligible subjects, there are major concerns worldwide and especially in the EU regarding efficacy, side-effects and cost of the above therapy, especially in older patients.

A million dollar therapy in a time of crisis

Cost is perhaps the strongest argument for the development of national and international guidelines for the treatment of patients with SMA. With onasemnogene abeparvovec single-dose cost estimated around 2 million Euros and nusinersen first year therapy cost around 750.000 Euros (with additional yearly cost for subsequent injections) and risdiplam cost not yet defined, one can easily understand that in terms of cost and subsequent reimbursement of those life-changing new therapies the sky is the limit … And all that taking place in a EU not in its best financial situation and struck (as the rest of the globe) by Covid-19.

Time to apply: how soon is now?

It is clear enough that, especially in presymptomatic patients, the younger age of initiation of therapy (ideally age 0), the better the outcome [2,3]. In the vast majority of patients but not exclusively, and especially the presymptomatic setting, SMN2 copy number is indeed the most important predictor of clinical severity (the more the better). There is accumulating evidence from preclinical studies, suggesting a specific time-frame in neuromuscular development when the effect of increasing SMN levels is on the highest level. On the other hand, there are data on record in patients with later-onset type 2 SMA demonstrating significant motor improvement after treatment with nusinersen [4], thus questioning the above time-frame hypothesis.

The crucial factor to consider: weight or age?

Available data from clinical trials cover only patients during the first six months of life with a weight below 8.4 kg. Thus, very little is known about the safety and efficacy of onasemnogene abeparvovec in older or heavier patients. One should of course take into account that an effective and safe treatment, nusinersen, is already widely available in this patient population. Additional data of patients up to 2 years and weighting up to 13.5 kg have been reported in congresses. These are mainly non-systematic US data, where onasemnogene abeparvovec is approved by the FDA up to the age of 2 years. In the EU the EMA approval is broad enough by not defining any age or weight limit, thus leading to a large number of possibly eligible patients who fulfil the criterion SMA with up to 3 SMN2 copies. Since the applied dose is proportional to the patient's body weight, treatment of heavier patients implies a significantly higher total dose than previously used in clinical trials. As Kirschner et al. [1] correctly point out, it is possible that advanced disease stage and higher total dose have a negative impact on the risk-benefit ratio.

Combined therapy?

Apart from a few single case-reports [5], there is no solid evidence that combination of the two disease-modifying therapies (usually gene therapy followed by nusinersen) is better than any single therapy alone, after demonstrating lack of efficacy. The reason for this is the irreversible degeneration of motor neurons and muscle, which are the most important factors for rescue of the phenotype regardless of the amount of SMN protein available from any treatment [6].

Epilogue

SMA patients and caregivers, accredited genetic laboratories and excellence centers with expertise in SMA (applying both the standards of care and new therapeutic modalities, as well as distributing any new data in an academic way), industry, national health-care systems and patient associations will play a crucial role in redefining the role of current and new disease-modifying therapies in the near future.

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