Gene replacement therapy in spinal muscular atrophy: filling the data gaps

Tim Hagenacker[a,*] and Ulrike Schara-Schmidt[b]

[a]Department of Neurology, Center for Translational Neuro- and Behavioral Sciences (C-TNBS), University Hospital Essen, Hufelandstr. 55, Essen 45147, Germany
[b]Department of Pediatric Neurology, Center for Neuromuscular Disorders, Center for Translational Neuro- and Behavioral Sciences (C-TNBS), University Hospital Essen, Hufelandstr. 55, Essen 45147, Germany

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The genetically-based therapy of spinal muscular atrophy (5qSMA) has been a pioneer in the development of therapies for hereditary neuromuscular diseases. Within a few years, the *SMN2* splicing modifiers nusinersen and risdiplam and the gene replacement therapy (GRT) onasemnogene abeparvovec (OA), three different substances have been approved for treatment, leading to a revolution in the therapeutic landscape.[1] All therapies have proven to be highly effective in the treatment of SMA, comparative studies are not available at this time, so the choice of therapy is based on the label and practical considerations, which vary.

Clinical trials have examined very defined patient populations for all forms of therapy, but these do not reflect the phenotypic variance, duration of disease and patient age in the "real world". In Europe, the therapy is approved for SMA patients who have either been diagnosed with SMA type 1 (the most severe type) or have up to 3 SMN2 copies. For GRT with OA, the best evidence from randomised trials is for patients under 24 months with a body weight up to 15 kg.[2–5] However, initial real-world studies of OA also suggest efficacy in older and higher body weights in patients with type 1 SMA.[6]

In this issue of *The Lancet Regional Health–Europe*, Gowda and colleagues now report on the treatment results of the nationwide use of OA in the UK in patients older than 2 years and with body weights over 13.5 kg.[7] The data was collected as part of an observational study conducted at all centers authorized to treat SMA in the UK. Ninety-nine SMA (45 of which were treatment-naïve) were treated with OA (median age at treatment: 10 [range, 0.6–89] months; median weight: 7.86 [range, 3.2–20.2] kg; duration of follow-up: 3–22 months). After OA infusion, the mean change in CHOP-INTEND score was 11.0 ± 10.3 with an increase in score in 66/78 patients; patients aged <6 months had a 13.9-point increase in CHOP-INTEND score compared with patients ≥2 years (95% CI, 6.8–21.0; P < 0.001).

Thrombocytopenia and transaminase elevations (transaminitis) are among the typical side effects of gene replacement therapy with OA, which regularly require the use of corticosteroids at the start of therapy.[8] Asymptomatic thrombocytopenia was observed in 71/99, asymptomatic troponin I elevations in 30/89 and transaminitis in 87/99 patients. There were no cases of potentially life-threatening thrombocytopenic microangiopathy. The steroids used for side effect management were used for a mean of 97 (range, 28–548) days with dose doubling required in 35/99 patients. The risk of a transaminase increase >100 U/l was 22.5-fold higher (95% CI, 2.3–223.7; P = 0.008), and the risk of needing steroid doubling was 21.2-fold higher (95% CI, 2.2–209.2; P = 0.009) in patients ≥13.5 kg vs <8.5 kg. The duration of steroid therapy correlated with body weight at the time of therapy (r = 0.43; P < 0.001). Steroid-sparing immunosuppressants were used in 5 children to enable steroid withdrawal. Two deaths were reported that did not appear to be related to OA.

Limitations to the validity of the study include missing measurements in some patients, variable follow-up duration, and timing of post-infusion functional assessment. In pre-treated patients, the limited duration of follow-up makes it impossible to say whether the improvements in motor function and side effects were due to OA, the prior therapy, or a combination of both. The data from this study adds to the data gaps from the clinical trials and shows increasing evidence for the use of OA in older and more severe children with SMA type 1.

Gene therapeutics have the potential to treat previously incurable diseases causally, i.e., directly at the site of the genetic defect. The challenge for the application is that often only a small number of patients have received the novel therapy in studies up to the time of approval. Accordingly, there is little knowledge about the efficacy and, above all, the safety of the new drugs at the time of approval. Decisive findings on the safety profile and therapeutic potential of the drugs are only obtained in the first few years after approval, so-called real world data, as also reported in this manuscript from the UK. From the point of view of patients and users, a sustainable care model and structured data collection would be important to meet the high structural and financial demands placed on the new drugs. The undisputed potential of the new gene therapies could be exploited more sustainably in this way.

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*Corresponding author.
E-mail address: tim.hagenacker@uk-essen.de (T. Hagenacker).

Contributors
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