Defining the effect of medical treatment on respiratory needs in patients with Type 1 spinal muscular atrophy

To the Editor:

We read with interest the article by Sansone et al.[1] We would like to offer 2 comments on this timely and pertinent study.

First, among patients <7 months of age at baseline, none had improved respiratory function, 25% remained stable, 58% required further ventilatory assistance, and 17% died. These data are striking because they are not concordant with the data from motor function studies, which show a significant increase in survival and an overall improvement of motor function in patients treated with nusinersen compared with a sham procedure.[2] This finding implies that improved motor function is neither the surrogate of respiratory function on its own, nor the only reason for improved survival.

In the older groups, most children remained stable, but the majority were already assisted by some level of respiratory support. The authors argue that "being stable" from a respiratory perspective, points to an actual effect of the treatment. However, at baseline most children had already initiated respiratory assistance with a mechanical in-exsufflator. A comparison with and without a mechanical in-exsufflator is not possible. Natural history studies do not have detailed information about proactive respiratory care.[3,4] Thus, a comparison of the authors' data with these studies provides an incomplete view of respiratory prognosis. It is well-known that extubation and prolonged survival are possible with noninvasive interventions.[5,6]

Researchers may be unable to study this effect, because respiratory care by experienced specialists and proactive care have become standards of care and randomizing patients would be questioned from the ethics aspect.[7] Because the modality and hours of ventilation are highly dependent on proactive respiratory care, better surrogates for respiratory function should be studied in the future cohorts. Vital capacity can be a good surrogate since it correlates with disease severity and prognosis in spinal muscular atrophy.[8]

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Reply

To the Editor:

We are grateful to Yetimakman et al for their comment and the opportunity to clarify a few points related to our study reporting respiratory function in patients with spinal muscular atrophy (SMA) treated with nusinersen. Yetimakman et al rightly point out that none of the children in the younger age group (<7 months) improved. Three patients in this age group continued spontaneous breathing at 10 months, and one-quarter remained stable. Although we agree that respiratory data have a different pattern compared with motor function, which often improves, we believe that stabilization of respiratory function in this age group should not be underestimated. Natural history studies in young infants with SMA type 1 show a clear progressive decline in respiratory function, and stabilization over 12 months is unexpected. We appreciate, however, that this is a topic that should be addressed with families when discussing treatment options.

Yetimakman et al also draw attention to our interpretation of stability in older patients who were already ventilated and who were more likely to remain stable. We do acknowledge that the interpretation of these data is difficult, because natural history data reporting possible changes in hours or modalities of ventilation are scanty and often depend on compliance with standards of care, availability of resources, or, in the past, different approaches to proactive respiratory care. Although we agree completely that these data should be interpreted with caution, we have had feedback from the families that many older ventilated patients were not always stable and had to change parameters over time, often in the setting of infections. Infections or other adverse events often triggered an increased need for ventilation that often persisted after the infection subsided. Furthermore, from our personal experience during continuous interviews with parents and families, most parents report that stability represents one of their targets when choosing treatment for their children.

We also fully agree on the need for better surrogates for respiratory function in which proactive care and type and approach to ventilatory care should play a minor part. This may prove to be challenging in our children with type 1 SMA. Vital capacity, as suggested, is definitely a good measure, but not applicable to children younger than 6 years of age or in very weak older patients. More longitudinal data over longer periods will hopefully help to define what is the best measure to monitor ventilatory progression in the treated patients who are developing new phenotypes, compared with those classically identified in the different forms of SMA.

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E.M. and V.S. serve as scientific consultants in Biogen's Advisory Boards.

Reconsidering asymptomatic bacteriuria and contamination as causes of bacteriuria without pyuria

To the Editor:

Shaikh et al performed a meta-analysis to determine the prevalence of asymptomatic bacteriuria in children.[1] The clinical issue is whether a positive urine culture with a negative urinalysis represents a urinary tract infection (UTI) or asymptomatic bacteriuria. The authors calculate the rate of bacteriuria without pyuria (the working definition of asymptomatic bacteriuria) to be 0.18% in boys and 0.38% in girls. They compare these rates with the 5% rate of what they call "UTIs," determine the rate of asymptomatic bacteriuria to be "at least an order of magnitude less than the prevalence of UTI," and conclude that "the current definition of UTI should be revisited."[1] However, the majority of the 5% have both bacteriuria and pyuria and clearly have a UTI, not asymptomatic bacteriuria. It is the remainder of the 5%—the 5%-15% with bacteriuria without pyuria—that should be compared with the prevalence of asymptomatic bacteriuria. Because 5%-15% of 5% is 0.25-0.75%, the rate in febrile children is similar to the prevalence of asymptomatic bacteriuria calculated by Shaikh et al.

The authors not only dismiss asymptomatic bacteriuria as an explanation for bacteriuria without pyuria but contamination as well. There are ample data to refute their position, including specimens obtained by catheterization.[2-4]

Fortunately, the combination of bacteriuria without inflammation (positive culture-negative urinalysis) occurs in only about 0.5% of febrile infants. Accordingly, the rate of missed bacteriuria is low when screened by urinalysis; moreover, the significance of bacteriuria without inflammation is not clear because inflammation appears to be required to cause renal scars.[5] There is harm in presuming that bacteriuria without inflammation represents a UTI: treatment of asymptomatic bacteriuria increases the likelihood of a symptomatic UTI,[6] which would be mistaken as a recurrent UTI and trigger imaging, increasing cost, radiation, and discomfort.

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