TreatSMA
Treat Spinal Muscular Atrophy

TreatSMA comments on the draft Managed Access Agreement on nusinersen

TreatSMA welcomes both the draft NICE guidance on nusinersen and the draft Managed Access Agreement.

We are yet to thoroughly analyse the **NICE draft guidance**, however our early view is that the document is well balanced and has properly used all the available evidence. It also appears to reflect the internationally accepted usage of nusinersen as a treatment across the spectrum of spinal muscular atrophy.

In our understanding, the primary objective of an **NHS managed access agreement** is to ensure that the entire population in whom NICE has appraised the technology as safe, effective and cost-effective is able to access it in a structured, monitored manner. Therefore, we will expect that, specifically, the eligibility (entry) and discontinuation (exit) criteria for nusinersen MAA shall reflect those contained in the NICE guidance.

Unfortunately, the current draft MAA diverges from the draft NICE guidance in a few important aspects or otherwise raises concerns. This is particularly evident in the section on entry criteria, on which we are focusing our response.

General comments

There is a general problem with the idea of relying on the few available functional scales as sole determinants of treatment efficacy in spinal muscular atrophy. Spinal muscular atrophy is a whole-system disease;[1] effects of pharmacological treatment can be observed in various body systems. Patients report improvements in, for example, muscle function, fine motor skills, swallowing, respiration, head control, metabolism, endurance, and stamina. While simple functional scores and the binary option of using/not using respiratory support can be useful for

[1] Parks, R.J., et al. "Spinal Muscular Atrophy: More than a Disease of Motor Neurons?" *Curr Mol Med.* 2016;16(9):779-792; Corti, S., et al. "Is Spinal Muscular Atrophy a disease of the motor neurons only: pathogenesis and therapeutic implications?" *Cell Mol Life Sci.* 2016 Mar; 73(5): 1003–1020; Lorson, Ch.L., et al. "Spinal muscular atrophy: a motor neuron disorder or a multi-organ disease?" *J Anat.* 2014 Jan; 224(1): 15–28.

clinicians to roughly estimate disease course, any deterioration on either should not be construed as a proof of treatment inefficacy when the treatment might be improving other abilities.

Another general problem with MAA is that what was intended to form discontinuation criteria, has been sometimes turned into entry criteria.

Specific points

Below we review the proposed entry criteria in the draft Managed Access Agreement.

> ***No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/tracheostomy requirement at baseline;***

This will negatively affect a fairly small number of patients (estimated 5), almost all being adolescents or young adults with weak type 2 who are now using permanent ventilation to help with breathing.

While a deterioration to the point of requiring permanent ventilation is a valid discontinuation criterion, in our view it should not form an entry criterion. Even in ventilated patients, nusinersen treatment is very likely to bring about stabilisation of the disease course and clinically meaningful improvements. In accounts coming from global clinical practice, continuous improvements in fine motor skills and endurance allow treated patients to be more independent in life, for instance when using modern technology.

Image 1. This young lady with SMA type 2 has recently published a book which she had typed with one finger. Despite her tracheostomy, nusinersen treatment is likely to bring about measurable improvement in her fine motor skills, making it much easier for her to write further books and thus fulfil her dreams. Photo: "Women of Success" event, 2018. Poland.

TreatSMA recalls that this criterion has been proposed by a neuromuscular consultant as a method to control possible immigration of weak SMA1 patients to the UK (sic!).

TreatSMA suggests that lack of permanent respiratory support is removed as an eligibility criterion and maintained as a discontinuation criterion. If immigration is of concern, then we suggest this criterion starts being implemented after all the current UK-based patients commence treatment.

> ***Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated;***
>
> ***Must not have received spinal fusion surgery following a diagnosis of scoliosis which prohibits safe administration of nusinersen;***

We agree in principle with these two criteria, however the feasibility should be put in the context of what is available nationwide rather than the skills and facilities in a particular hospital.

Based on international experience, we foresee that a proportion of adolescent and adult patients will require nusinersen administration using CT-guided injections.[2] In lack of such equipment or a trained team, the patient should be eligible to be referred for treatment in a different hospital.

Additionally, some patients with spinal fusion may decide to undergo a surgical procedure in the spine to create an opening for lumbar puncture, as it is a practice in some countries. Such patients should be allowed to be re-evaluated for nusinersen treatment.

> ***Must not have severe contractures which in the opinion of the clinician prohibits measurement of motor milestones;***

This NHS criterion is arbitrary and not consistent with draft NICE guidance. In our view, it is a misunderstanding to expect that nusinersen-treated patients will attain milestones (in fact, only a minority of nusinersen treated patients do).

In accordance with treatment discontinuation criteria, the clinician is only expected to detect deterioration on specific scales. Non-attainment of milestones is currently not a discontinuation criterion, given that the stabilisation of the disease course is already a major therapeutic achievement.[3]

---

[2] Wurster, C.D., "Intrathecal administration of nusinersen in adolescent and adult SMA type 2 and 3 patients" *J Neurol.* 2019;266(1):183-194. Oldenburg, D., "Radiation exposure of image-guided intrathecal administration of nusinersen to adult patients with spinal muscular atrophy" *Neuroradiology*. 2019;61(5):565-574. Monroe, E.J., "Transforaminal intrathecal delivery of nusinersen using cone-beam computed tomography for children with spinal muscular atrophy…" *Pediatr Radiol*. 2018;48(3):392-397.

[3] Rouault, F., et al. „Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients" *Neuromuscul Disord.* 2017;27(5):428-438

Therefore, we believe that patients should not be routinely barred from accessing nusinersen treatment simply because the clinician fears that they will not be able to measure future milestone attainments.

> ***If gained independent ambulation prior to initiation of therapy must still be independently ambulant. Independent ambulation is defined as per the WHO definition: patient takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object;***

This NHS criterion is arbitrary and not consistent with draft NICE guidance. TreatSMA considers it as mistaken. Patients' eligibility for treatment must be evaluated on the basis of their status at baseline; not by how they fared many years earlier. There is no justification for differentiating, for the purpose of therapy, between patients of identical abilities and functional score solely on the grounds that one patient was able to make a few steps in early childhood and the other was not. In our view – as also confirmed by NICE committee based on RCT data – both these categories of patients should be equally eligible to receive nusinersen therapy.

Adopting this arbitrary criterion will result in an unfounded and unfair exclusion of hundreds of UK children and adults from accessing the only effective treatment for their disease. TreatSMA objects adopting this criterion in the strongest possible terms.

Image 2. Should this 3-years-old girl be left untreated? A few months before taking this photo she lost independent ambulation. The proposed MAA will thus exclude her. Left untreated, she will lose her ability to crawl.

Must not be type IV SMA patient i.e. must not have symptom onset at or after 19 years of age.

TreatSMA proposes to append the following sentence: "*unless in the opinion of the treating clinician the patient is on the verge of losing independent ambulation or another important function*." This modification will allow clinicians to exercise their best judgment in borderline cases.

Must not be type 0 SMA patient.

This in our view requires more precision, since "type 0" is not clearly defined in literature – the term is loosely used to denote either patients with prenatal onset of symptoms or patients with a single copy of the *SMN2* gene (and typically a very severe disease course).

TreatSMA accepts that children with a single *SMN2* copy do not have a positive prognosis even with nusinersen treatment.

As to the second definition, generalised hypotonia in neonates with two *SMN2* copies requires careful consideration to exclude other possible factors, even of unknown aetiology. For instance, we have seen a case of a child with genetically confirmed SMA (two copies of *SMN2* gene) and a neonate-onset severe hypotonia and respiratory insufficiency requiring intubation, consistent with SMA type 0. However, respiratory insufficiency and much of hypotonia subsided spontaneously within 2 weeks and afterwards the child developed like a typical type 1 child. Children like this one should be eligible for nusinersen treatment and the wording of this criterion should reflect this.