Spinal Muscular Atrophy and Spinraza(TM) (nusinersen)

Treatment at diagnosis, Regardless of the Presence of Symptoms (1)

References
1. Spinraza (nusinersen) SmPC 01/2022.

Biogen

There are currently three approved treatments for patients with spinal muscular atrophy (SMA) 5q, a rare genetic disease (incidence: ~1/6,000 to 1/10,000) (4) resulting in severe neuromuscular damage. Spinraza (nusinersen) was the first to be approved. This antisense oligonucleotide increases the production of the functional survival motor neuron (SMN) protein by acting on the splicing of the SMN2 gene and can be administered as soon as SMA is diagnosed, before symptoms occur. This already recorded indication is further supported by the interim analysis of the NURTURE study, which demonstrated that presymptomatic treatment of the paediatric form of SMA results in near-normal motor development.

SMA is a progressive neuromuscular disease of genetic origin, characterized by motor neuron degeneration resulting in severe muscle atrophy and weakness (1). In 95% of cases, it results from homozygous mutations or deletions of the SMN1 gene on the 5q chromosome, resulting in a decrease in the production of the SMN protein (2). The deficiency of this protein is responsible for the degeneration of motor neurons and atrophy of targeted muscles, which can lead to progressive muscle weakness in the limbs and affect, among other things, breathing, swallowing, walking and head maintenance (3). The functional SMN proteins produced by the SMN2 gene are insufficient for the maintenance and normal functioning of motor neurons (4). Lower copy number of the SMN2 gene is correlated with more severe types of SMA (4).

There are five types of SMA, depending on the age at which the first symptoms occur and the motor stage reached by patients, ranging from the most severe type 0, to type 4. Life expectancy varies from a few weeks after birth (type 0) to a normal life expectancy (types 3 & 4) (4).

Treatment

Spinraza (nusinersen) is an antisense oligonucleotide that modifies the splicing of SMN2 pre-messenger RNA in order to increase the production of functional SMN protein. This product can be administered intrathecally, from the time of diagnosis (5). More than 11,000 patients with SMA are currently being treated with this medicinal product, which is available in more than forty countries (6).

NURTURE: Results! [5]

NURTURE is an open-label study conducted in 25 pre-symptomatic infants with a genetic diagnosis of SMA, who were enrolled at six weeks of age or younger. These patients were considered to be at high risk of developing type 1 or 2 SMA (2 copies of the SMN2 gene, n = 15; 3 copies, n = 10). Their median age at the time of the first dose was 22 days.

At the time of the latest interim analysis (data cut 15 February 2021), which was conducted when the median duration of patient participation reached 4.8 years and their median age at the last visit was 4.9 year, all the patients were alive and without permanent ventilation. The life expectancy of type 1 patients is <2 years without treatment and respiratory support (7).

Patients reached motor stages never seen before with type 1 or 2 SMA and which were very similar to those of normal development. At the time of the interim analysis, all the 25 study patients were able to sit without help, 24 patients (96%) were able to walk with assistance, and 23 patients (92%) were able to walk independently.

During the study, the safety profile of Spinraza remained unchanged. No side effects led to the discontinuation of treatment.

ESSENTIAL POINTS

Pre-symptomatic treatment of the paediatric form of SMA in 25 children resulted in close to normal motor development:
- 100% of children sit without support;
- 96% of children walk with assistance;
- 92% of children walk without assistance.

References
1. Wang C, et al. J Child Neurol 2007;22(8):1027-49.
2. Sugarman E, et al. Eur J Hum Genet 2012;20(1):27-32.
3. Lunn M, Wang C. Lancet 2008;371(9630):2120-33.
4. Kolb S, Kissel J. Arch Neurol 2011;68(8):979-84.
5. Spinraza (nusinersen) SmPC 01/2022.
6. Biogen Q4 and Full Year 2021 Financial Results and Business Update. February 3, 2022.
7. Crawford TO et al. Poster 071. MDA. March 2022.

Már Tulinius
Professor of pediatrics, Gothenburg University,
Queen Silvia Children´s Hospital

Which clinical implications will this data have?

What we have learnt from the NURTURE study is the importance of early diagnosis and to start treatment before onset of symptoms. Now we know that if you start to treat newborn babies with SMA with nusinersen before six weeks of age, they seem to develop normally. The majority of the children in the study could sit and walk after two years of treatment.

Before this new treatment they usually died one to two years after birth. The main clinical lesson from recent data is that genetic testing and very early treatment seems to keep very similar motor stages as for those with normal development and gives these children a chance to grow up.

What does this data mean for all the doctors in contact with newborns?

If you work in neonatal care and suspect that a child could have SMA it´s very important to immediately contact a pediatric neuromuscular specialist for guidance. In Sweden only two hospitals are certified to initiate SMA treatment. We have to raise awareness about the symptoms and spread information about the importance of treating these babies as early as possible.

Data from the NURTURE study clearly indicates that a general SMA screening program for newborns would be beneficial, but in The Nordic countries, unlike countries like Belgium, Germany and some states in the US, we are not there yet. There are many ethical aspects to consider and the authorities here are still quite restrictive about allowing DNA-tests. For example, is it good or bad to find out that you are a carrier of a genetic disease, especially if you haven't asked for this information?

One of the main challenges with screening is that the results could be interpreted as stigmatising for many people. But to be able to treat children with SMA successfully we need to diagnose them early through genetic testing, and start treatment before the onset of symptoms, so we are hopeful that this DNA screening that we have applied for will be implemented also in Sweden as soon as possible.

Which importance does treatment have for older SMA-patients?

We have also older patients with SMA who have had the disease for many years before starting treatment. In Sweden we reimburse treatment up to 18 years of age but recent research clearly shows that continued treatment can slow down the progress of the disease. Older children or adults with SMA type 2 or 3 who receive treatment with nusinersen report better endurance and strength and their motor skills improve (1, 2).

Due to the fact that SMA patients live so much longer today with their complex disease it´s necessary to work in multidisciplinary teams to meet all their needs. A functional team should consist of doctors, nurses, physiotherapists, dieticians, speech- and occupational therapists. It´s also important to have good access to X-rays and support from orthopedic surgeons, pulmonologists etc. We work in such teams in Gothenburg with good results.

References
1. Darras BT, et al. Neurology 2019;92(21):e2492-e2506
2. Coratti G, et al. Orphanet J. Rare Dis. 2021;16(1):430.

Spinraza(TM) (nusinersen), Rx, ATC-kod: M09AX07
Injektionsvätska, lösning 12 mg, EF ej förmån.

Baserad på SPC 01/2022

Indikation: För behandling av spinal muskelatrofi av typ 5q.

Dosering: Spinraza administreras intratekalt genom lumbalpunktion. Den rekommenderade dosen av Spinraza är 12 mg (5 ml) per administrering. Behandlingsschemat är 4 laddningsdoser på dag 0, 14, 28 och 63 följt av en underhållsdos en gång var 4:e månad.
Biverkningar: De vanligaste biverkningarna i samband med administrering av Spinraza är huvudvärk, kräkningar och ryggsmärta. Fall av allvarlig infektion, såsom meningit, har observerats. Det har även förekommit rapporter om kommunicerande hydrocefalus, aseptisk meningit och överkänslighet (t.ex. angioödem, urtikaria och hudutslag).
Kontraindikationer: Överkänslighet mot den aktiva substansen eller mot något hjälpämne.

För ytterligare information om dosering, kontraindikationer, varningar och försiktighet, biverkningar och förpackningar se www.fass.se. Biogen-154864 februari 2022

Biogen-100041 May 2022

Biogen
Kanalvägen 10A | 194 61 Upplands Väsby
Tel 08-594 113 60 | www.biogen.se