AGNETA MARKSTRÖM

Associate Professor, Astrid Lindgren Children's Hospital, Stockholm, Sweden

Agneta Markström is associate professor of anaesthesiology and intensive care at Uppsala University and senior consultant at Karolinska University Hospital, specialising in home mechanical ventilation and CPAP treatment in children. At Uppsala University Hospital Dr Markström supervises the sleep clinic, working as a senior consultant with children and adults with sleep disorders. Her research is focused on home mechanical ventilation in children and sleep disorders.

LISA BENGTSSON

Speech Language Pathologist, Mun-H-Center, Gothenburg, Sweden

Lisa Bengtsson works as a speech and language pathologist at Mun-H-Center, an orofacial resource centre for rare diseases within the Swedish Public Dental Service, located in Gothenburg in Sweden. Lisa has a particular interest in neuromuscular diseases, and is involved both in the clinical care of people with SMA and in research projects on orofacial function, speech and nutrition in SMA.

NINA OLSSON

Parent to a child with SMA, Uppsala, Sweden

Nina Olsson holds a Bachelor's degree in social work from Uppsala University. She is also the mother of Viggo, a 4-year-old boy who was diagnosed with SMA Type I at the age of 10 weeks. Together with fellow SMA mum Maja, Nina co-hosts the Swedish podcast "Sjukt Liv!" (editor's note: "Sick Life"), sharing frankly and passionately what life is like being a parent of a child with special needs and providing round-the-clock love and care for a terminally ill child.

ULRIKA KREICBERGS

Professor, Ersta Sköndal Bräcke University College, Stockholm, Sweden

Ulrika Kreicbergs is Professor of Palliative Care of Children and Adolescents within the Palliative Research Centre at Ersta Sköndal Bräcke University College in Stockholm. Professor Kreicbergs has a long-standing research interest in the experience of families of terminally ill children and uncovering how their experiences can be used to shape and improve palliative paediatric care.

MARIKA PANE

Professor, Catholic University and Policlinico Gemelli, Rome, Italy

Marika Pane is Professor of Paediatric Neurology at the Catholic University in Rome in Italy. Professor Pane is a leader in the field of neuromuscular disorders, with more than 100 peer-reviewed papers on topics related to this field. Professor Pane is involved in clinical studies in all neuromuscular disorders. She is currently caring for more than 100 SMA patients treated with nusinersen.

MÁR TULINIUS

Professor, Queen Silvia Children's Hospital, University of Gothenburg, Sweden

Már Tulinius is Professor of Paediatrics at the University of Gothenburg and senior consultant in paediatric neurology at the Queen Silvia Children's Hospital within Sahlgrenska University Hospital. Professor Tulinius' experience with nusinersen dates back to joining the ENDEAR and CHERISH studies as an investigator in 2015, and treating patients within an expanded access programme from the end of 2016.

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3rd edition

REPORT

"The Little Child"

LIS-N & LER-N

Educational meeting in SMA

December 5, 2019

Biogen

About spinal muscular atrophy

Spinal muscular atrophy (SMA) is characterised by degeneration and loss of motor neurons in the brain and spinal cord. The loss of functioning motor neurons leads to progressive muscle weakness and atrophy as muscles stop receiving signals from the central nervous system. SMA is caused by a mutation or deletion in the survival motor neuron 1 (*SMN1*) gene which encodes the survival motor neuron (SMN) protein. A second SMN gene (*SMN2*) produces a shortened and less functional SMN protein. SMA develops when the mutation or deletion is present on both copies of the *SMN1* gene, in which case there will be insufficient SMN protein levels for the motor neurons to survive.[1-3]

SMA with autosomal-recessive inheritance is classified into different subtypes according to age of onset and severity, with the most common subtypes being:[4-7]

- **SMA Type I**, the classic form of SMA also known as infantile-onset SMA or Werdnig-Hoffmann disease, typically manifests itself before the age of six months. SMA type I is the most severe form of SMA; if untreated, children with SMA Type I will never be able to sit and their life expectancy is less than two years.
- **SMA Type II** typically appears between six and 18 months of age and is a less severe form of SMA. Children with SMA Type II are able to sit independently but not walk; 70% of the patients are still alive at the age of 25.
- **SMA Type III**, or Kugelberg-Welander disease, develops in children older than 18 months. Children with SMA Type III are typically able to walk independently and have a normal life expectancy. However, although SMA III is a milder form of SMA, patients with SMA Type III may progressively deteriorate as they grow older.

A typical presentation of SMA type I is muscle weakness and hypotonia, known as the “floppy baby syndrome.” SMA is diagnosed based on the medical history and clinical presentation together with neurophysiological testing and DNA sequencing to confirm the *SMN1* gene mutation or deletion.[4,8]

Patients with SMA are treated with supportive interventions that focus on the quality of life, including physiotherapy, mobility assistance, and respiratory and nutritional support.[4,9-12] Until recently there was no effective drug treatment for SMA and the main focus was then on palliative interventions.

About Spinraza® (nusinersen)

Spinraza®(nusinersen) is the first medical treatment to be approved for the treatment of SMA. Nusinersen is an antisense oligonucleotide (ASO) that acts by modifying pre-mRNA splicing of the *SMN2* gene to produce functional, full-length SMN protein. Randomised sham-controlled clinical studies show that nusinersen treatment resulted in increased achievement of motor milestones and improved motor function, as well as prolonged survival and independence from permanent ventilation in patients with infantile-onset and later-onset SMA, as well as presymptomatic infants.[13-16] Nusinersen was approved by the FDA in December 2016 and by the EMA in May 2017 for the treatment of all types of 5q SMA. Nusinersen is administered by intrathecal injection with the aid of lumbar puncture. The recommended dose is 12mg, given initially as four loading doses on Days 0, 14, 28 and 63, and then as maintenance therapy every four months.

Precautions

Patients with profound hypotonia and respiratory failure at birth, a setting in which nusinersen has not been studied, may not experience a clinically meaningful benefit due to severe SMN protein deficiency. There is a risk of adverse reactions occurring as part of the lumbar puncture (such as headache, back pain, vomiting; see section 4.8 in the SmPC). Potential difficulties with the route of administration may be seen in very young patients and those with scoliosis.[17]

Thrombocytopenia and coagulation abnormalities including acute severe thrombocytopenia, as well as renal toxicity have been observed after administration of other subcutaneously or intravenously administered antisense oligonucleotides. If clinically indicated, laboratory testing of platelets, coagulation and urine protein is recommended prior to administration of nusinersen.[17]

There have been reports of communicating hydrocephalus. See section 4.4 in the SmPC for further details.[17]

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1. Lefebvre S, Burglen L, Reboullet S, *et al.* Identification and characterization of a spinal muscular atrophy-determining gene. Cell 1995;80:155-65. **2.** https://ghr.nlm.nih.gov/gene/SMN1. **3.** Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. Arch Neurol 2011;68:979-84. **4.** Mercuri E, Finkel RS, Muntoni F, *et al.* Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018;28:103-115. **5.** Markowitz JA, Singh P, Darras BT. Spinal muscular atrophy: a clinical and research update. Pediatr Neurol 2012;46:1-12. **6.** Lunn MR, Wang CH. Spinal muscular atrophy. Lancet 2008;371:2120-33. **7.** Moosa A, Dubowitz V. Motor nerve conduction velocity in spinal muscular atrophy of childhood. Archives of Disease in Childhood 1976;51:974-977. **8.** D'Amico A, Mercuri E, Tiziano FD, et al. Spinal muscular atrophy. Orphanet J Rare Dis 2011;6:71. **9.** Lemoine TJ, Swoboda KJ, Bratton SL, *et al.* Spinal muscular atrophy type 1: are proactive respiratory interventions associated with longer survival? Pediatr Crit Care Med 2012;13:e161-5. **10.** Iannaccone ST. Modern Management of Spinal Muscular Atrophy. Journal of Child Neurology 2007;22:974-978. **11.** Oskoui M, Levy G, Garland CJ, *et al.* The changing natural history of spinal muscular atrophy type 1. Neurology 2007;69:1931-6. **12.** Chatwin M, Bush A, Simonds AK. Outcome of goal-directed non-invasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. Archives of Disease in Childhood 2011;96:426-432. **13.** Finkel RS, Mercuri E, Darras BT, *et al.* Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med 2017;377:1723-1732. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29091570. **14.** Mercuri E, Darras BT, Chiriboga CA, *et al.* Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med 2018;378:625–635. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29443664. **15.** Vivo DC De, Bertini E, Swoboda KJ, *et al.* Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord 2019;29:842–856. Available at: https://doi.org/10.1016/j.nmd.2019.09.007. **16.** Castro D, Farrar MA, Finkel R, *et al.* Longer-term assessment of the safety and efficacy of nusinersen for the treatment of infantile-onset spinal muscular atrophy: An interim analysis of the SHINE study. Neurology 2018;90:e2183. **17.** Biogen. *Spinraza Summary of Product Characteristics.* Last updated 01/2020.

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▼Spinraza «Biogen»

Middel mot spinal muskelatrofi. ATC-nr.: M09A X07

INJEKSJONSVÆSKE, oppløsning *12 mg:* *Hvert hetteglass inneh.:* Nusinersennatrium tilsv. nusinersen 12 mg, natriumdihydrogenfosfatdihydrat, dinatriumfosfat, natriumklorid, kaliumklorid, kalsiumkloridhydrat, magnesiumkloridheksahydrat, natriumhydroksid/saltsyre (til pH-justering), vann til injeksjonsvæsker.
Indikasjoner: Behandling av 5q spinal muskelatrofi. **Dosering:** Behandling skal kun startes av lege med erfaring i behandling av spinal muskelatrofi (SMA). Beslutning om behandling skal baseres på individuell nytte-/risikovurdering. Anbefalt dose 12 mg (5 ml) pr. administrering. Behandling bør starte tidligst mulig etter diagnostisering, med 4 ladningsdoser. 1 dose gis på dag 0, 14, 28 og 63. Deretter bør en vedlikeholdsdose gis 1 gang hver 4. måned. Ingen informasjon vedrørende langtidseffekt. Behov for videre behandling skal vurderes regelmessig og på grunnlag av klinisk tilstand og behandlingsrespons. ***Glemt dose:*** Glemt ladningsdose gis så snart som mulig, med ≥14 dager mellom dosene, og dosering fortsettes iht. plan. Glemt vedlikeholdsdose gis så snart som mulig, og dosering fortsettes hver 4. måned. ***Spesielle pasientgrupper:*** *Nedsatt leverfunksjon:* Ikke undersøkt. Behov for dosejustering lite sannsynlig. *Nedsatt nyrefunksjon:* Sikkerhet og effekt ikke fastslått, pasienten bør observeres nøye. ***Tilberedning/Håndtering:*** Se pakningsvedlegg. Kun til engangsbruk. ***Administrering:*** Gis intratekalt ved spinalpunksjon, som bolusinjeksjon i 1-3 minutter vha. kanyle til spinalanestesi. Skal gis av helsepersonell med erfaring i spinalpunksjon. Injeksjonen skal ikke settes i hudområder med tegn på infeksjon/inflammasjon. Cerebrospinalvæske (CSF) tilsvarende volumet som skal injiseres bør tas ut før administrering. Sedasjon kan være nødvendig. Se også Forsiktighetsregler. **Kontraindikasjoner:** Overfølsomhet for innholdsstoffene. **Forsiktighetsregler:** Bruk er ikke undersøkt hos pasienter med uttalt hypotoni og respirasjonssvikt ved fødselen, og pga. den alvorlige SMN-proteinmangelen vil ikke disse nødvendigvis ha klinisk signifikant nytte av behandlingen. *Spinalpunksjonsprosedyre:* Gir risiko for bivirkninger (f.eks. hodepine, ryggsmerter, oppkast, se Bivirkninger). Problemer med administreringsveien kan sees hos svært unge pasienter og ved skoliose. Bruk av ultralyd/andre bildeteknikker til hjelp ved administrering vurderes iht. skjønn. *Blod:* Koagulasjonsforstyrrelser og trombocytopeni, inkl. akutt alvorlig trombocytopeni, er sett for andre antisense-oligonukleotider gitt s.c. eller i.v. Laboratorietesting av blodplater og koagulasjon anbefales før administrering hvis klinisk indisert. *Nyrer:* Nyretoksisitet er sett for andre antisense-oligonukleotider gitt s.c. eller i.v. Måling av proteiner i urin (fortrinnsvis første morgenurin) anbefales hvis klinisk indisert. Ved vedvarende forhøyet protein i urin bør ytterligere utredning vurderes. *Hydrocefalus:* Kommuniserende hydrocefalus ikke relatert til meningitt eller blødning er rapportert, og skal vurderes som mulig årsak ved nedsatt bevissthet. Nytte/risiko ved behandling etter implantering av ventrikuloperitoneal shunt er ukjent, og fortsatt behandling må vurderes nøye. *Immunogenisitet:* Lav insidens av antistoffer mot legemidlet. **Interaksjoner:** FFor utfyllende informasjon om relevante interaksjoner, bruk interaksjonsanalyse. Ingen interaksjonsstudier er utført. In vitro-studier indikerer ingen induksjon/hemming av CYP450-mediert metabolisme, samt liten sannsynlighet for interaksjoner som skyldes hemming av transportproteiner eller konkurranse om binding til plasma-/transportproteiner. **Graviditet, amming og fertilitet:** *Graviditet:* Ingen/begrensede data. Dyrestudier indikerer ingen direkte eller indirekte skadelige effekter mht. reproduksjon. Bruk under graviditet bør unngås. *Amming:* Overgang i morsmelk er ukjent. Risiko for nyfødte/spedbarn kan ikke utelukkes. Det må tas en beslutning om amming skal opphøre eller behandling avstås fra, basert på nytte-/risikovurdering. *Fertilitet:* Ingen effekt er sett i dyrestudier. Humane data mangler. **Bivirkninger:** *Svært vanlige:* Gastrointestinale: Oppkast[1]. Muskel-skjelettsystemet: Ryggsmerter[1]. Nevrologiske: Hodepine[1]. *Ukjent frekvens:* Infeksiøse: Aseptisk meningitt[2]. Alvorlig infeksjon, som meningitt[2]. Nevrologiske: Kommuniserende hydrocefalus[2]. **Overdosering/Forgiftning:** Ingen rapporterte tilfeller. *Behandling:* Støttende medisinsk behandling, inkl. konsultasjon og nøye observasjon av klinisk status. Se Giftinformasjonens anbefalinger M09A X07 på www.felleskatalogen.no. **Egenskaper:** *Virkningsmekanisme:* Nusinersen er et antisense-oligonukleotid (ASO) som øker andelen av ekson 7-inklusjon i SMN2 (survival motor neuron 2)-mRNA-transkripter ved binding til et sete i intron 7 i SMN2 pre-mRNA. Denne bindingen fortrenger undertrykkende spleisefaktorer, og gir retensjon av ekson 7 i SMN2-mRNA. Når SMN2-mRNA dannes kan det dermed translateres til funksjonelt SMN-protein av full lengde. *Absorpsjon:* Gjennomsnittlig C_{min} i CSF før neste injeksjon akkumulerer ca. 1,4-3 ganger etter gjentatte ladnings- og vedlikeholdsdoser, og når steady state innen ca. 24 måneder. Etter intratekal administrering var C_{min} i plasma før neste injeksjon relativt lav sammenlignet med C_{min} i CSF. Median T_{max} i plasma: 1,7-6 timer. Gjennomsnittlig C_{max} og AUC i plasma økte ca. doseproporsjonalt. Ingen akkumulering i plasmaeksponering (C_{max} og AUC) etter gjentatt dosering. *Fordeling:* Omfattende distribusjon i CNS. Terapeutiske nivåer oppnås i målvev i ryggmargen. Nusinersen er også påvist i nevroner/andre celler i ryggmarg og hjerne, og i skjelettmuskulatur, lever og nyre. *Halveringstid:* Gjennomsnittlig terminal t1/2 i CSF: 135-177 dager. *Metabolisme:* Langsomt og primært ved eksonuklease (3'- og 5')-mediert hydrolyse. *Utskillelse:* Nusinersen/metabolitter utskilles primært via urin. **Oppbevaring og holdbarhet:** Oppbevares i kjøleskap (2-8°C), og i ytteremballasjen for å beskytte mot lys. Skal ikke fryses. Kan oppbevares ved ≤30°C i opptil 14 dager. Uåpnet hetteglass kan tas ut av/settes tilbake i kjøleskap ved behov. Dersom det tas ut av originalemballasjen skal samlet total tid utenfor kjøleskap være ≤30 timer ved ≤25°C. Skal brukes innen 6 timer etter at oppløsningen er trukket opp i sprøyten. **Pakninger og priser:** 5 ml (hettegl.) 458838.
Sist endret: 12.09.2019
Basert på SPC godkjent av SLV/EMA: 01/2020
[1]Anses å være forbundet med spinalpunksjonsprosedyren, som manifestasjoner av postspinalpunksjonssyndrom.
[2]Ved behandling ved spinalpunksjon.

Spinraza® (nusinersen) Rx, EF, ATC-kod: M09AX07
Injektionsvätska 12 mg

Baserad på SPC 01/2020

▼Detta läkemedel är föremål för utökad övervakning.

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: 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 information om kontraindikationer, varningar och försiktighet, biverkningar, dosering och förpackningar se www.fass.se

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▼Tähän lääkevalmisteeseen kohdistuu lisäseuranta.

Tällä tavalla voidaan havaita nopeasti turvallisuutta koskevaa uutta tietoa. Terveydenhuollon ammattilaisia pyydetään ilmoittamaan epäilyistä lääkkeen haittavaikutuksista.

Spinraza 12 mg injektioneste, liuos Yksi 5 ml:n injektiopullo sisältää nusinerseeninatriumia määrän, joka vastaa 12 mg:aa nusinerseeniä. Yksi ml sisältää 2,4 mg nusinerseeniä. **Käyttöaiheet:** Spinraza on tarkoitettu kromosomiin 5q liittyvän spinaalisen lihasatrofian hoitoon. **Ehto:** Spinraza-hoidon saa aloittaa vain lääkäri, joka on perehtynyt spinaalisen lihasatrofian (spinal muscular atrophy, SMA) hoitoon. Hoitoa saavat antaa vain lannepiston tekemiseen perehtyneet terveydenhuollon ammattilaiset. **Annostus ja antotapa:** Suositeltu annos on 12 mg (5 ml) antokertaa kohden. Spinraza-hoito pitää aloittaa mahdollisimman pian diagnoosin jälkeen neljällä latausannoksella päivinä 0, 14, 28 ja 63. Tämän jälkeen annetaan ylläpitoannos 4 kuukauden välein. Hoidon jatkamisen tarve on tarkistettava säännöllisesti ja arvioitava yksilöllisesti potilaan kliinisen tilan ja hoitovasteen mukaan. Spinraza annetaan lannepistolla spinaalinalaa käyttämällä 1–3 minuutin kestoisena bolusinjektiona selkäydinnesteeseen. Spinraza-valmisteen turvallisuutta ja tehoa munuaisten vajaatoimintaa sairastavien potilaiden hoidossa ei ole varmistettu. Munuaisten vajaatoimintaa sairastavia potilaita on seurattava huolellisesti Spinraza-hoidon aikana. Spinrazan käyttöä ei ole tutkittu potilailla, joilla on syntyessään vaikea hypotonia ja hengityksen vajaatoiminta, ja vaikean survival motor neuron (SMN) -proteiinin puutoksen vuoksi nämä potilaat eivät ehkä saa hoidosta kliinisesti merkittävää hyötyä. **Vasta-aiheet:** Yliherkkyys vaikuttavalle aineelle tai jollekin valmisteen apuaineelle. **Varoitukset ja käyttöön liittyvät varotoimet:** Lannepistotoimenpiteeseen liittyy haittavaikutusriski (esim. päänsärky, selkäkipu, oksentelu). Tähän antoreittiin saattaa liittyä vaikeuksia hyvin nuorilla potilailla ja skolioosipotilailla. Spinrazan intratekaalisen annon apuna voidaan käyttää lääkärin harkinnan mukaan ultraääntä tai muita kuvantamismenetelmiä. Muiden antisense-oligonukleotidien ihon alle tai laskimoon tapahtuneen annon jälkeen on havaittu veren hyytymiseen liittyviä poikkeavuuksia ja trombosytopeniaa, mukaan lukien akuuttia vaikea-asteista trombosytopeniaa, sekä munuaistoksisuutta. Ennen Spinrazan antoa suositellaan kliinisen tarpeen mukaan laboratoriokokeita veren trombosyyttipitoisuuden ja hyytymisen selvittämiseksi. Virtsan proteiinipitoisuus suositellaan tarkistamaan laboratoriokokeen avulla kliinisen tarpeen mukaan. Jos virtsan proteiinipitoisuus on jatkuvasti koholla, on harkittava lisätutkimuksia. Ahtaumattoman hydrokefaluksen tapauksia, jotka eivät liittyneet meningiittiin tai verenvuotoon, on markkinoille tulon jälkeisessä käytössä raportoitu nusinerseenihoitoa saaneilla potilailla. Potilaille, joiden tajunnan taso on alentunut, on harkittava tutkimuksia hydrokefaluksen poissulkemiseksi. **Yhteisvaikutukset:** Yhteisvaikutustutkimuksia ei ole tehty. *In vitro* –tutkimukset osoittivat, että nusinerseeni ei indusoi eikä estä CYP450-välitteistä metaboliaa. *In vitro* –tutkimukset osoittivat olevan epätodennäköistä, että kilpailu plasman proteiinehirin sitoutumisesta, kilpailu kuljettajaproteiinien kanssa tai kuljettajaproteiinien esto johtaisi yhteisvaikutuksiin nusinerseenin kanssa. **Raskaus ja imetys:** Varmuuden vuoksi Spinrazan käyttöä on suositeltavaa välttää raskauden aikana. On päätettävä, lopetetaanko rintaruokinta vai lopetetaanko Spinraza-hoito ottaen huomioon rintaruokinnasta aiheutuvat hyödyt lapselle ja hoidosta koituvat hyödyt äidille. **Vaikutus ajokykyyn ja koneiden käyttökykyyn:** Ei haittallista vaikutusta ajokykyyn ja koneiden käyttökykyyn. **Haittavaikutukset:** Yleisimmät Spinraza-valmisteen käytön yhteydessä raportoidut lannepistotoimenpiteeseen liittyvät haittavaikutukset olivat päänsärky, oksentelu ja selkäkipu. Myyntiluvan myöntämisen jälkeisessä käytössä Spinraza-hoitoa saaneilla potilailla on raportoitu vakavia infektioita, kuten meningiittiä, sekä ahtaumattoman hydrokefaluksen, aseptisen meningiitin ja yliherkkyyden tapauksia. Muut haittavaikutukset ks. valmisteyhteenveto. **Säilytys:** Säilytä jääkaapissa (2 °C - 8 °C). Ei saa jäätyä. Herkkä valolle. Huoneenlämpösäilytys ks. valmisteyhteenveto. **Pakkaukset ja hinnat:** Spinraza 12 mg (1 x 5 ml injektiopullo) tmh 83 328,00 €. **Korvattavuus:** Reseptilääke. Ei sv-korvattava. **Valmisteyhteenvetolyhennelmä 24.01.2020 perustuu 01/2020 päivättyyn valmisteyhteenvetoon.** Tutustu valmisteyhteenvetoon ennen lääkkeen määräämistä. **Lisätietoja:** Terveysportin tietokannat, Biogen Finland Oy, Bertel Jungin aukio 5 C 02600 Espoo, Puh. 020 7401 200, www.biogen.fi

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Biogen-50340 04/2020

Introduction

We are proud to share the 2019 LIS-N & LER-N report with you. This was the third LIS-N & LER-N meeting since the start of this initiative, and this year the focus was on “The Little Child”.

SMA is a rare disease for which there was no treatment until the approval of SPINRAZA® (nusinersen). The knowledge and experience of treating SMA varies between different countries and hospitals. The aim of the LIS-N & LER-N meeting is to provide a platform for healthcare professionals caring for patients with SMA in the Nordic countries to meet and interact across national borders, to share and promote knowledge and best practice with the ambition to improve the competence in SMA in the Nordic region. Following the approval in US in December 2016, and in Europe in May 2017, more than 10,000 patients with SMA have been treated with SPINRAZA® (nusinersen), which now is available in more than 40 countries around the globe.

The 2019 LIS-N & LER-N meeting contained a rich and varied programme of presentations by expert speakers, together with interactive question and answer sessions. The lectures and discussions were chaired by Professor Thomas Sejersen and covered a variety of topics, including pulmonary care in SMA with Professor Agneta Markström, and orofacial problems and communication with Lisa Bengtsson. Then followed a session, “Family life with SMA” in which Nina Olsson, the mother of a child with SMA Type I, presented the caregiver’s perspective on everyday life, living with a child with SMA Type I. Professor Ulrika Kreicbergs continued by sharing progress in studying the quality of life of parents to children with severe SMA. A specially invited guest speaker was Marika Pane, from the Catholic University of the Sacred Heart in Milan, Italy. Professor Pane presented the results of the NURTURE study, a recently published open-label study in which 25 pre-symptomatic infants with a genetic diagnosis of SMA were enrolled and initiated treatment with nusinersen at six weeks of age or younger. All 25 participants in NURTURE achieved the WHO motor milestone of ‘sitting without support’; 22 children (88%) achieved ‘walking with assistance’ and 17 of these 22* children (77%) achieved ‘walking alone’[1].

The results from the NURTURE study confirm the importance of early diagnosis and treatment of SMA and highlight the important work being done to include SMA in national newborn screening programmes, which was discussed by Professor Már Tulinius towards the end of the day. Biogen will continue to support this process by sharing knowledge and experience around SMA, until all children are diagnosed at birth. A key element in this commitment is the organisation and funding of the annual LIS-N & LER-N meeting.

We hope you will enjoy reading this report and that it will help you in your daily practice.

Peps Bengtsson, Biogen

* 3 patients were aged <15 months (WHO-defined window for expected age of achievement).

References:
1. Biogen. *Spinraza Summary of Product Characteristics.* Last updated 01/2020.

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AGNETA MARKSTRÖM

Associate Professor, Astrid Lindgren Children's Hospital, Stockholm, Sweden

Pulmonary care in spinal muscular atrophy

Respiratory support, with mobilisation of secretions and use of non-invasive ventilation, plays an important role in the management of children with SMA, to prevent chest infections and promote thoracic development and compliance. Dr Agneta Markström from the Astrid Lindgren Children's Hospital in Stockholm presented an overview of the respiratory impact of SMA and how sleep studies can be used to assess the pulmonary function of infants with SMA, to allow interventions if needed.

When a healthy person breathes normally, the performance of the respiratory muscles relative to the respiratory load are carefully balanced through lung, airway and chest wall biomechanics. For patients with neuromuscular disorders including SMA, the respiratory muscles are weakened due to the illness and the respiratory load quickly exceeds the muscle performance, resulting in a significantly higher work of breathing with doubling or even trebling the level of oxygen consumption – Dr Markström compared it to having to run a marathon every day. This weakness of the respiratory muscles has a number of mechanical disadvantages. In adult patients the chest wall will become stiffer and increase the load on the costovertebral joints and tendons, whereas in infants and young children the chest wall is highly compliant, and the neuromuscular weakness in conditions such as SMA will cause the thoracic cage to distort and assume a characteristic bell shape which can impair normal growth and development of the lungs. Respiratory defects in infants with SMA include decreased total lung capacity (TLC), low tidal volumes, and increased residual volumes due to dysfunction of expiratory muscles which will lead to decreased vital capacity (VC) and inspiratory capacity. One of the more serious respiratory consequences of SMA is poor clearance of secretions in the airways which increases the risk of severe complications such as atelectasis and lower respiratory infections, and ultimately ventilatory failure.

The neuromuscular weakness of the chest wall in SMA patients may also impact on a number of other important body functions. The increased work of breathing can result in increased energy expenditure and caloric requirements which can cause undernourishment and malnutrition. Inability to swallow safely may lead to aspiration, the first signs of could be affecting mainly the upper right lobe of the lungs. Also, patients with SMA Type I often develop symptoms of bulbar dysfunction including difficulties speaking. A particular challenge is the use of nasogastric tubes – many infants with SMA rely on a nasogastric tube at least for some time in their lives. However, while this is an effective solution for nutrition, having a nasogastric tube will make breathing even more difficult, and the biofilm that forms on the tube will further increase the risk of developing upper airway infections.

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Respiratory evaluation – the role of sleep studies in SMA

Ventilatory failure is a common cause of death in SMA, and respiratory evaluation is an essential part of the clinical management of these patients. Infants and young children cannot perform conventional pulmonary function tests such as spirometry; instead, sleep studies provide a means of assessing respiratory parameters in these patients. During sleep, tidal volumes will decrease and the chest muscles relax – conditions which will enhance any breathing problems that may exist. Sleep studies combine EEG and ventilation variables to highlight disordered breathing during REM and non-REM sleep. In an infant with SMA, paradoxical breathing and the resulting increase in CO_2 and decrease in oxygen saturation provides a strong indication for initiating non-invasive ventilation. Recently updated standard of care recommendations for the diagnosis and management of SMA include sleep studies as part of a respiratory clinical algorithm for pulmonary management of SMA patients.[1] This algorithm comprises assessments of chest wall abnormalities, breathing frequency, feeding and bulbar function, together with chest radiology and sleep studies. Prevention in the form of vaccinations against influenza and pneumococcal infections is a key step in the algorithm. The recommended interventions include physiotherapy and use of a cough assist device for all children with SMA Type I. In patients with a chest infection and/or swallowing dysfunction, the recommended intervention is non-invasive ventilation with cough assist and percutaneous gastrostomy feeding.[1]

The standard of care recommendations for SMA state that non-invasive ventilation should be used in all symptomatic infants, to minimise the risk of respiratory failure and the distortion of the chest wall, and palliate dyspnoea.[1] In terms of the mode of non-invasive ventilation, the recommended mode of ventilation is bi-level positive airway pressure (BiPAP) which operates with a inspiratory positive airway pressure (IPAP) and a lower expiratory positive airway pressure (EPAP), where the EPAP helps to maintain the end-expiratory lung volume and prevent the lungs from closing.[2] BiPAP ventilation can be either spontaneous (S) or timed (T); the most common form is a combination of the two modes. The recommendations state that continuous positive airway pressure (CPAP) should not be used due to the risk of fatigue from breathing against an increased resistance.

Complications of non-invasive ventilation

Non-invasive ventilation is not without complications, some of which can be potentially serious. There is a risk of the skin breaking on the bridge of the nose if the mask is fastened too tightly; if this occurs, the patient cannot be ventilated again until the wound has healed. The fastening of the mask to the face is not intended to hold the mask in place but to create an airtight seal, and it is important not to use too much force when doing this. Another potentially severe complication of prolonged use of non-invasive ventilation is the development of mid-face hypoplasia; this can be prevented by minimising the airway pressure used. Mid-face hypoplasia can be a cause of breathing problems itself, and in severe cases surgery may be required to correct it later in life. If possible, limiting the time the child spends being ventilated may prevent severe mid-face hypoplasia from developing.

Mobilisation of secretions is vitally important for all children with SMA Type I with or without non-invasive ventilation, to reduce the risk of infections and to ensure adequate saturation. Secretions will prevent the blood/gas exchange and render BiPAP treatment suboptimal. Specialised physiotherapists play a key role for teaching parents to perform mobilisation of secretions both using manual techniques and with the help of a cough assist device. At Dr Markström's centre at the Astrid Lindgren Children's Hospital in Stockholm, the preferred mucolytic for nebulisation is isotonic saline, although some patients may require a hypertonic solution of 3% saline. The antimuscarinic agent glycopyrronium should be used with caution as there is a risk it may create secretion plugs in the airways. For children with SMA the cough assist device should be used daily, ideally two or three times a day in the absence of infection, to ensure that the parents have the skills to to use the machine when the child develops an

> *"For children with SMA the cough assist device should be used daily, ideally two or three times a day, to ensure that the parents are proficient in its use for when the child develops an upper respiratory tract infection."*

upper respiratory tract infection, and to maintain the mobility of the thorax. During an infection, the cough assist may be used 6-10 times a day.

Non-invasive ventilation has been associated with an increase in survival in neuromuscular disorders such as SMA. A retrospective cohort study published in 2018 reported the outcomes for nearly 500 children at the Royal Brompton Hospital in London who initiated home-based non-invasive ventilation from 1993 to 2011.[3] More than half of the children (56%) had neuromuscular disease. In total, 40% of the children transitioned into adult care within the study period, and 9% were able to discontinue ventilatory support. An observational study of 122 patients carried out in Italy found that among patients with SMA Type I, survival beyond the age of two years was linked to having gastrostomy and either a tracheostomy or being on non-invasive ventilation for more than 16 hours per day, whereas patients with less severe phenotypes who achieved head control did not require ventilatory or nutritional support.[4] Dr Markström stressed the importance of not only relying on the genotype when making treatment decisions about SMA patients, but to aim for personalising the therapy based on each patient's individual presentation.

At the Astrid Lindgren Children's Hospital children with SMA are referred to the Paediatric Respiratory Centre by the paediatric neurologist. The children are seen in the clinic every three months, using sleep studies and assessments of blood gases and oxygen saturation while awake. An important focus at Dr Markström's centre is to provide parents with as much information as possible to equip them for managing respiratory events at home, including individualised care plans, techniques for airway clearance, information on nutrition and hydration, and a prescription for antibiotics in case of respiratory infections. The individualised care plan includes criteria and thresholds for when to seek emergency care. Children who have to be admitted to hospital, for example due to an infection, should be managed with optimised BiPAP and augmented secretion clearance prior to oxygen supplementation. Fasting should be avoided; care should be taken to avoid aspiration in weak children who are fed orally. For patients with pneumonia where BiPAP ventilation is insufficient for maintaining optimal blood gases, endotracheal intubation should be considered, although this can be a challenging procedure in children with SMA due to mandibular contractures, limited neck mobility and other positioning restrictions. The cough assist device should be used during intubation to reduce secretions, and after extubation to prevent secretion plugs. Overall, when an SMA patient on non-invasive ventilation is admitted for emergency care, the parents will have done everything they know how to do at home to improve the situation, and therefore it is vitally important that the child can be admitted to intensive care and treated without unnecessary duplication of interventions and/or delay.

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LISA BENGTSSON

Speech Language Pathologist,
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Orofacial function and communication – the role of the speech language pathologist in the examination and treatment of children with spinal muscular atrophy

In patients with SMA, the neuromuscular weakness affects basic vital functions including the ability to feed, talk and swallow. As a speech language pathologist specialising in helping patients with SMA overcome problems related to orofacial dysfunction, Lisa Bengtsson from specialist dental referral centre Mun-H-Center in Gothenburg works in a multidisciplinary setting with dentists and orthodontists to minimise the impact of these problems for SMA patients irrespective of type.

Orofacial function covers our ability to eat, control saliva, and communicate with speech and facial expressions. Common problems that affect orofacial function include trismus (limited range of motion in the jaw) and malocclusion (misalignment of the upper and lower teeth when closing the jaw), both of which can make feeding and communication difficult. Another challenging form of orofacial dysfunction is dysphagia. From a physiological point of view, swallowing is a complex mechanism which serves the primary purpose of stopping food and saliva from intruding into the lungs. Swallowing, or deglutition, occurs in three stages: an oral stage in which the food is gathered in the mouth, masticated and fragmented into a bolus; a pharyngeal stage where the bolus is propelled from the base of the tongue to the opening of the oesophagus; and the oesophageal stage in which the bolus progresses along the oesophagus to the stomach with the help of peristaltic waves. Impaired swallowing associated with neuromuscular disease can occur in the form of residues where the bolus stops in the throat or accumulates in the pharynx after swallowing; penetration, where the bolus enters into the airways; or aspiration where the bolus passes the vocal folds and moves into the lungs.[1]

Orofacial dysfunction in SMA Type II and III

The main body of evidence relating to orofacial dysfunction in patients with SMA comprises patients who have not received any medical treatment. In SMA Type II and III, orofacial function is well preserved in relation to other motor skills; however, eating and swallowing difficulties are common and around half of the patients rely on artificial nutrition to a greater or lesser extent. Common problems include malocclusion – typically overjet or open bite – and restricted jaw opening, which not only makes eating and chewing more difficult but can also affect oral hygiene in that it complicates brushing one's teeth and having dental examinations and treatments, and may also make it difficult to intubate the patient if required. Studies have shown that patients with SMA Type II can have difficulties at all three stages of swallowing, including chewing difficulties in the oral stage, problems with residues in the vallecula and upper oesophageal sphincter during the pharyngeal stage which may be exacerbated by the body and head position, and also problems with residues in the upper oesophageal sphincter at the oesophageal stage after swallowing.[2-5] Patients with SMA Type III may have chewing difficulties and problems with dysphagia and choking due to impaired neck stability in the oral and pharyngeal stages, but no problems have been reported in the oesophageal stage for these patients. Lisa Bengtsson stressed the importance of timing respiratory interventions in relation to food intake to minimise the risk of problems. "If a patient has problems with residuals after swallowing, it is very important to avoid using the cough machine immediately after eating as this can push food into the airways," she cautioned.

> *"If a patient has problems with residuals after swallowing, it is very important to avoid using the cough machine immediately after eating as this can push food into the airways."*

In children, the way the mouth is used affects its growth, and the way the mouth grows affects how it can be used. In SMA Type II and III, neuromuscular weakness together with factors such as wearing a breathing mask for prolonged periods of time can impair the growth and development of the jaw and face. Typical facial features in SMA Type II and III include increased mandibular angle or posterior rotation of the mandible. Asking about eating and swallowing difficulties is an important part of caring for these patients. In Lisa Bengtsson's practice, many patients are able to compensate quite well for any difficulties they may be having by changing the texture and consistency of what they eat and/or adjusting their body posture. However, in Lisa's opinion this makes it even more important to ask, as not every patient will be able to cope successfully. Evaluating the patient's swallowing function is important, not only to be able to diagnose problems but also as a guide for therapeutic interventions. The main goal of any intervention should be to preserve orofacial function as far as possible, which includes performing jaw stretching to maintain full movement of the jaw. This can be achieved with jaw stretching exercises with or without a training device such as the TheraBite®, which is available for adults and children down to the age of five years. To preserve and maintain the ability to eat, the best exercise is to keep eating by mouth, with adjustments of food consistency and/or body posture as needed. Patients who are unable to speak intelligibly due to orofacial dysfunction may require Augmentative and Alternative Communication (AAC) aids with technology for supplementing or replacing speech, such as pictures on a screen or a speech synthesiser.

Patients with SMA Type II and III should be seen regularly by an orthodontist, to monitor facial growth and any malocclusions. Lisa Bengtsson stressed the importance of adopting a preventive approach for patients with SMA. "Unlike other neuromuscular disorders such as Duchenne muscular dystrophy, where the recommendation is to monitor the jaw opening function and initiate stretching exercises if it shows signs of declining, jaw stretching in SMA should be performed as prevention since restricted jaw opening is very difficult to reverse." If a jaw stretching device is recommended, this should be fitted in a multidisciplinary setting by the dentist and speech language pathologist. To be effective, jaw stretching exercises should not only involve moving the jaw up and down but also laterally, since chewing is essentially a rotating movement of the jaw.

> *"SMA patients should do jaw stretching as prevention since restricted jaw opening is very difficult to reverse."*

Orofacial dysfunction in SMA Type I

To date, the medical literature on orofacial dysfunction and dysphagia among children with

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SMA Type I treated with nusinersen is very limited. In SMA Type I, cranial nerve dysfunction causes bulbar symptoms which in turn cause difficulties at all stages of eating and swallowing due to a range of physiological and disease-related factors. While silent aspiration is believed to be common in SMA Type I, the impact of tongue fasciculations is unknown. Children with SMA 1 display restricted jaw opening from a very young age – making preventive treatment to preserve orofacial function difficult – and impaired anterior and posterior saliva control. There is no known association between SMA Type I and cognition, but weak facial expressions and various degrees of dysarthria will affect the patient's ability to communicate to a greater or lesser extent. Video fluoroscopic swallowing examination (VFSS) is an important tool for diagnosing and monitoring patients with SMA Type I. Typical features seen on VFSS in SMA Type I include reduced laryngeal elevation, pharyngeal and vallecular residues, laryngeal penetration and aspiration.

As in other types of SMA, managing problems with eating and swallowing plays a significant role in the clinical care of children with SMA Type I. Most children with SMA Type I that are seen at the Mun-H-Center in Gothenburg will be fed at least partially with artificial nutrition. A number of children have been given a 'nil by mouth' recommendation, which is a concern for Lisa Bengtsson and her colleagues since not eating by mouth is known to have an adverse impact on oral and respiratory health. Children who never learn to eat by mouth can develop hypersensitivity in the oral region and may display defensive behaviour in relation to the mouth. This makes it difficult to brush the teeth and maintain oral hygiene, which in turn will alter the bacterial flora over time – something which will affect respiratory health through aspiration.

In Lisa Bengtsson's opinion, eating should be encouraged if at all possible. "Eating is the 'gold standard' of eating," she said. "If we expect children with SMA Type I to get better at eating, we must not stop them from eating." That said, there will always be children who will not be able to eat by mouth. For these children it will be important to compensate for the lack of eating, to activate the mouth and experience the sensation of food in

> *"Eating is the 'gold standard' of eating - if we expect children with SMA Type I to get better at eating, we must not stop them from eating."*

the mouth, and to counteract the development of defensive behaviour around the mouth and face. This can be achieved with the help of devices such as safe feeders or an electric tooth brush, or by massaging the face and mouth. Jaw stretching is also recommended for patients with SMA Type I.

Lisa Bengtsson finished her presentation by describing the project she is about to embark on for her doctoral thesis. Lisa will be focussing on studying orofacial function and development in children with SMA who receive treatment for their condition. "We do not know yet how the new phenotype of SMA patients will develop in terms of speaking and feeding – most of what we know today is based on patients who have not received treatment, but we think this picture is going to change."

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NINA OLSSON

Parent to a child with SMA, Uppsala, Sweden

Family life with spinal muscular atrophy

“Since SMA came into our lives, we have been feeling as though we are trying to cross through a landscape full of rock faces and sheer drops, on a dark and foggy night and blindfolded!” Nina Olsson from Uppsala in Sweden is the mother of a four-year-old son, Viggo, who was diagnosed with SMA Type I at the age of ten weeks. Nina co-hosts a podcast about life as a parent of a child with special needs. At Lis-n & Ler-n Nina talked about the journey she and her family have made since Viggo was diagnosed with SMA, and living with the burden of carrying the future of a vulnerable child on your shoulders.

Before Nina began telling us about how Viggo was diagnosed with SMA and how she and Viggo’s dad embarked on their journey as parents of a severely disabled child, she made a point of introducing us to Viggo the person – a small boy who has just celebrated his fourth birthday; who is happy and playful and who loves trains, and music, and having a swing, and going to the pictures. Because in Nina’s experience, within the healthcare services young children with severe illnesses tend get overshadowed by their diagnosis. These children tend to be seen and referred to as “sick”, or “disabled” with everyone’s focus being on the condition rather than the person – somehow people manage to overlook that a sick or disabled child is still a child, albeit on its own special terms.

The shock of the diagnosis

Nina and her partner had no inkling that anything might be wrong with Viggo back then, when he was 10 weeks old and his mum and dad took him to their local child healthcare centre for a check-up. Viggo had been disinclined to hold his head up and Nina had been thinking to herself that perhaps he had a streak of idleness in him, already at that tender age. But the doctor who examined Viggo immediately noticed that something was not as it should be, and instead of physiotherapy sessions, Viggo and his parents were issued with an emergency referral to the paediatric neurology department at Uppsala University Hospital. Within a week, Viggo had been diagnosed with SMA Type I. “My partner and I had never heard of this diagnosis,” said Nina. “It came as a shock to us; we were angry and heartbroken. We began grieving for something we had never had, but that we had been taking for granted we would have – but all of a sudden seemed very uncertain.”

In the initial phase after Viggo had been diagnosed, Nina remembers being seized with feelings of powerlessness and uncertainty, and above all fear – fear of the deadly disease, but also of the lack of knowledge she encountered, both within the healthcare services and in society as a whole. “This is a rare disease, and the initial prognosis was not very encouraging,” she said. And paradoxically, once Viggo began receiving treatment, the uncertainty grew even worse – now the family were really entering unchartered territory! The sense of powerlessness arose from being sucked into the healthcare “machine” – from having to accept that as parents, Nina and her partner were no longer in charge, they were not the ones making the decisions about Viggo anymore. Now that Viggo was a patient, things had to be done a certain way and in a certain order, amid limited resources and strict priorities. “As a parent, it is very difficult to accept that your own child cannot always be at the top of the queue,” said Nina. “The doctors and nurses have to consider all the other children as well, and we have to accept that we are part of a big machine. This sense of losing control is frightening.”

Things took a turn for the worse when Viggo suddenly stopped breathing one day, due to a mucus plug that developed while using the cough machine. “We had no idea what to do,” recalls Nina. “It was sheer luck we were able to get him breathing again while we were waiting for the ambulance.” This episode became the first of many, as Viggo developed recurring breathing and mucus problems. Nina and her family ended up moving into the paediatric neurology ward in Uppsala and remaining there for several months, shuttling in and out of the paediatric intensive care unit (PICU) whenever Viggo stopped breathing. Nina and her partner completed something she calls the “PICU school” in Uppsala where they were taught to become “PICU parents” and be able to care for Viggo’s airways to prevent mucus plugs from forming and perform acute cardiopulmonary resuscitation when needed. “I remember thinking that the PICU training may be useful, but that we weren’t really going to need it – Viggo was just a bit poorly, he was going to get better and we wouldn’t ever need to do these procedures,” said Nina. But instead, relying on daily ventilation and breathing management was to become Viggo’s new normal.

> ***“I remember thinking that the PICU training may be useful, but that we weren’t really going to need it – Viggo was just a bit poorly, he was going to get better and we wouldn’t ever need to do these procedures.”***

Returning home as PICU parents

After three weeks in the PICU and many months in hospital, it was time for Viggo and his parents to move back home. A slow process, as Nina recalls, and scary. “As long as we remained in the hospital, I felt safe – Viggo’s life and well-being was in their hands, the PICU was just around the corner and we only had to press a button for a doctor to come.” The PICU training had given Nina and her partner back some sense of control – they would be able to continue with the daily respiratory management routines and medications, and they felt confident they could cope if an acute situation arose. “However, we soon realised we had returned home, only to continue doing the same thing we had been doing in the hospital,” she said. “Viggo would be lying in his bed and his two parents would be surrounding him on all sides with his cough machine, BiPAP, feeding pump and all the rest of it – the only difference was that we were in our kitchen rather than in the hospital!” Nina and her partner realised this situation was not sustainable – they had come home to give Viggo a chance to develop and thrive, to be a child and not merely a patient. “We had to ‘gear up’,” she said. “Initially it was just about trying to move into another room with Viggo, but over time we were able to leave the flat, and try things like sitting up, having a bath, going on the swings, and all the time being able to cope. We simply had to become even better PICU parents – quicker, more efficient, and bolder.”

A big step in the initial “gearing up” was for each parent to be alone with Viggo. “This really spooked me,” said Nina. “One of us had to be able to leave the flat, to go to the shops or go out to work or whatever – but I was terrified of being alone with the responsibility if something was to happen, I just could not face it. But somehow, along the way I must have managed it – and now I can barely remember how we got to where we are today.”

Another part of the “gearing up” process for Nina and her partner was getting to grips with the formalities of applying for the various disability benefits that Viggo is entitled to by law in Sweden, such as personal care assistants and travel allowances. However, this process proved a devastating experience for Nina who, as a trained social worker, ended up

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shouldering the lion share of this task. “In everyday life, in the midst of the chaos of coping and learning to take control, I was able to somehow tell myself that this was a normal situation – I expect it’s a sort of defence mechanism that the mind develops. But having to sit down and compile long lists, in black and white, of everything Viggo was unable to do and needed help with – that was a hard thing to do. Those lists ended up very long,” she said.

Finding the way to a “normal” life

Viggo and his parents have now reached what Nina suspects will be their “top” gear, where they will hopefully remain for the rest of Viggo’s life. As a family they have achieved some important goals. Viggo now goes to nursery school a couple of days a week, something he enjoys a great deal. And Nina and her partner have been able to go back to work, at least part-time. “As parents we have to be able to go to work – for the sake of our finances, and for our mental health!” she said. Together they continue to strive towards living a “normal” life, where Viggo has a chance to not only survive but to thrive, and where Nina and her partner can have friends and hobbies and achieve some balance in their lives. “It is extremely hard, knowing that everything depends on us finding the strength to continue moving forward, to solve each new problem, battle the benefits bureaucracy, hire and train personal care assistants and hope they will remain long enough to be able to relieve us of some of the day-to-day responsibility. As parents we have to be in the driving seat all the time.”

Nina is often seized with feelings of guilt and inadequacy. No matter how hard she and her partner struggle to give Viggo the best possible chance to thrive and develop like other children, there is always the sense that something could have been done better, or sooner. “Viggo will never be able to improve beyond the opportunities we provide him with,” she said. “I sometimes see other children with SMA making great progress on social media or other networks and I ask myself – could that have been Viggo, had we only been more proactive and more committed? But you cannot keep thinking like that – it doesn’t go anywhere; you have to keep moving forward.” But Nina often wishes there was just a bit more help and support to be had from the healthcare system, so that she and her partner would not be quite so alone with the burden of Viggo’s care all the time.

> *“I sometimes see other children with SMA making great progress on social media or other networks and I ask myself – could that have been Viggo, had we only been more proactive and more committed? But you cannot keep thinking like that – it doesn’t go anywhere; you have to keep moving forward.”*

But Nina is hopeful for the future, for herself and for her family. At a recent event for families with disabled children, she was asked by another parent “how ill is your son, really?” and surprised herself by responding “not ill at all!” Nina thinks she may have come to terms with the situation to such an extent that she no longer sees Viggo as a sick child. “What I said simply isn’t true,” she said. “Viggo cannot sit upright, he cannot speak, and he cannot eat, and he needs help to breathe every day. But for us, those are Viggo’s terms and for us this is now normality – Viggo has never known anything else, and we have forgotten what life was like before!” Nina finished by telling us that the sense of powerlessness and uncertainty she felt when Viggo was first diagnosed is still there and will probably always be there. “But I’m not as frightened anymore, and I’m not as frightened as often. I’ve got back some sense of control in our lives.”

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ULRIKA KREICBERGS

Professor, Ersta Sköndal Bräcke University College, Stockholm, Sweden

Families' experiences of having a child with spinal muscular atrophy

Caring for a child with a life-limiting and life-threatening condition such as SMA can have a profound impact on families – not only parents but also on siblings – and healthcare professionals have an important role to play in terms of providing support and involving families in the clinical decision-making. Professor Ulrika Kreicbergs from the Palliative Research Centre at Ersta Sköndal Bräcke University College in Stockholm summarised previous studies involving families of children with SMA, and outlined an ongoing study which will capture parents' and healthcare professionals' experiences and help to develop consensus recommendations.

The introduction of nusinersen has helped to spark interest in the parental perspective in SMA as a field of research. In 2016 Professor Kreicbergs and her team published a Swedish nationwide survey of parents who had lost a child to SMA type I or II regarding their experience of communicating with healthcare professionals about life expectancy and wishes at the end of life.[1] The results of this survey showed that parents who had had a dialogue with the clinical team regarding their child's end-of-life care were more likely to report that their wishes had been realised. "The dialogue with parents regarding their child's end-of-life care is very important," said Professor Kreicbergs. "If we as healthcare professionals are successful in our communication, this can help bereaved parents through the long-term grieving process."

> *"If we as healthcare professionals are successful in our communication, this can help bereaved parents through the long-term grieving process."*

Other issues that emerged in the Swedish survey was the lack of support for siblings of children with SMA, and parents looking to healthcare professionals for high levels of disease-specific and treatment-specific knowledge and information, especially at the time of diagnosis.[2] Parents also asked for more practical support and coordination of care.

The results of the Swedish survey were consistent with those of a similar study in Denmark.[3] Importantly, both the Swedish and the Danish study confirmed that no treatment decisions regarding children with SMA had been taken without informing the parents. A contrast between the countries was that bereaved parents in Sweden were more likely to be satisfied with the information they received than non-bereaved parents, whereas in Denmark the opposite was the case – Professor Kreicbergs attributed this to the work done by Muskelsvindfonden (Muscular Dystrophy Foundation) on raising awareness and providing support and resources for families affected by SMA. "This suggests the Swedish SMA community would do well to learn from the Danish example and work with these matters in a similar way," suggested Professor Kreicbergs.

Ongoing study of medical opportunities for children with SMA

Professor Kreicbergs and colleagues, including Camilla Udo and Professor Thomas Sejersen, have recently begun collaborating with teams at the Children's National Hospital in Washington DC and the University of Nebraska Medical Center in the US on a survey study into the concerns and considerations of families and healthcare professionals in relation to novel medical opportunities for children with SMA. The study is enrolling families of children with SMA aged up to 18 years who are asked to complete web-based questionnaires on each family member's quality of life, and healthcare professionals who are interviewed in person about their experience of caring for children with SMA and their families in the era of nusinersen. The overall aim of the study is to evaluate how families are affected by a treatment that can mitigate the symptoms of SMA and what expectations they have, to enable healthcare professionals to provide the best possible care for children with SMA and their families. An additional objective is to use the findings to develop consensus-based recommendations based on families' needs and wishes.

Enrolment has so far been slower than anticipated, with only five families included to date. To address this issue, the investigators have obtained ethical approval to approach Swedish families with SMA children under 18 years directly, in addition to recruiting patients via an ad on the national SMA patient organisation website. Despite this, the study team has already made some notable observations. "It is interesting to note that none of the parents in the study were informed about the availability of nusinersen by a healthcare professional," said Professor Kreicbergs. "They encountered it online or found out about it through other parents, but not through the healthcare system." Another interesting finding so far is that parents tend to rate their child's quality of life as rather high – they also rate their own quality of life as high, but not as high as that of the child. In the survey, parents ask that healthcare professionals should have a high level of knowledge and keep up to date on the latest findings in the field of SMA, especially to be aware of new treatments that may be on the horizon. But for Professor Kreicbergs, the main learning from the study has been about the administrative challenges with involving parents in studies, despite the fact that the high response rates on surveys show that this is something parents of severely ill children often appreciate, as it can make them feel less alone with their burden and gives them a sense of being seen and listened to. "The difficulties we have had so far in recruiting families to this study is not only a failure for us as researchers, but it is also a failure for a society where data protection and privacy regulations have become restrictive to the point of becoming overprotective," she concluded.

> *"The difficulties we have had so far in recruiting families to this study is not only a failure for us as researchers, but it is also a failure for a society where data protection and privacy regulations have become restrictive to the point of becoming overprotective."*

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MARIKA PANE

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Treatment of pre-symptomatic spinal muscular atrophy – the NURTURE study

November 2019 saw the publication of interim results from the important NURTURE study, which show that early treatment with nusinersen in presymptomatic infants with a genetic diagnosis of SMA is associated with substantial clinical benefit and a favourable benefit-risk profile.[1] At LIS-N & LER-N 2019, the interim results from NURTURE were presented by Professor Marika Pane from the Department of Paediatric Neurology at the Catholic University in Rome, where currently 154 SMA patients are receiving treatment with nusinersen.

The NURTURE study is an ongoing, phase-2, open-label, single-arm study that is currently running in 15 sites in seven countries, with the aim of evaluating the long-term efficacy and safety of treatment with nusinersen prior to the onset of clinical signs of SMA. Eligible for inclusion in NURTURE are infants who receive their first dose at or before the age of six weeks, and have a genetic diagnosis of 5q SMA and are clinically presymptomatic, with two or three *SMN2* copies and a baseline compound muscle action potential (CMAP) amplitude of at least 1 mV. Under the study protocol, participants in the study receive nusinersen as intrathecal injection at a dose of 12mg, administered as four loading doses on Days 1, 15, 29 and 64 and then a maintenance dose every 119 days for a treatment period of five years. The primary endpoint in NURTURE is time to death or respiratory intervention, defined as six or more hours per day of invasive or non-invasive ventilation for a minimum of seven consecutive days, or tracheostomy. Secondary endpoints reported in the interim analysis included attainment of motor milestones as assessed by WHO criteria and section 2 of the Hammersmith Infant Neurologic Examination (HINE-2), respectively; and change from baseline in CHOP INTEND scores.

Clinical efficacy results in NURTURE

The interim analysis comprised a total of 25 infants who fulfilled the eligibility criteria and were enrolled between May 2015 and February 2017. Fifteen of the enrolled infants had two *SMN2* copies and ten infants had three *SMN2* copies. At the time of the data cut-off in March 2019, the enrolled infants had been in the study for a median of 33.9 months (range 25.3–45.1 months) and their median age at the last visit was 34.8 months (range 25.7–45.4 months). All infants received nusinersen as per the study protocol; there were no discontinuations of treatment or withdrawals from the study. The median age at first dose was 22 days overall (19 days among infants with two *SMN2* copies and 23 days among those with three *SMN2* copies). Further, in the group with two *SMN2* copies, the median CHOP INTEND total score at baseline was 45 and the median ulnar CMAP amplitude 2.30mV; the corresponding baseline values in the group with three *SMN2* copies were 53.5 and 2.90mV, and for the study population as a whole 50 and 2.65mV, respectively. In terms of the primary endpoint, all infants in the study were alive, and four infants (16%) who all had two copies of the *SMN2* gene required respiratory intervention for six or more hours per day for a minimum of seven consecutive days, all during episodes of acute reversible illness. Importantly, none of the infants required permanent ventilation (defined as 16 or more hours' ventilation per day for more than 21 consecutive days) at the time of the interim analysis. In her presentation at LIS-N & LER-N 2019, Professor Pane contrasted this result – that all infants were alive and not in need of permanent ventilation at the age of nearly three years – with findings from a prospective observational cohort study of the natural course of SMA type I prior to the introduction of nusinersen, in which the infants had either died or required ventilation support for a minimum of 16 hours per day for more than 14 consecutive days at a median age of 13.5 months.[2,3]

> *"At the time of the interim analysis, all infants in the study were alive and none required permanent ventilation."*

The secondary endpoints showed that participants in the NURTURE study achieved motor development milestones at a rate that was incongruent with the natural course of SMA type I and II, and in many cases within the timeframes established for healthy children. All 25 participants in NURTURE achieved the WHO motor milestone of 'sitting without support'; 22 children (88%) achieved 'walking with assistance' and 17 of these 22* children (77%) achieved 'walking alone'.[1,4] The HINE-2 total scores increased over time for all participants regardless of the number of *SMN2* copies, with an increase in the mean total score of 21.2 from baseline until the last visit. There was also a steady increase from baseline in the CHOP INTEND score, with a majority (two-thirds of infants with two *SMN2* copies and all infants with three *SMN2* copies) achieving the maximum CHOP INTEND score of 64.

Safety and tolerability

Nusinersen and the lumbar puncture procedure were generally well tolerated in the NURTURE study; no new safety concerns were identified during the follow-up period of the interim analysis. The most frequently reported adverse events that were considered possibly related to nusinersen included two cases of proteinuria, and single cases of muscular weakness, pyrexia, and rash, respectively. There were no serious adverse events considered related to nusinersen. However, as part of the safety summary Professor Pane reminded the audience that the summary of product characteristics for nusinersen states that cases of serious infection, such as meningitis, have been observed, and also that there have been reports of communicating hydrocephalus, aseptic meningitis and hypersensitivity reactions such as angioedema, urticaria and skin rash.[4]

> *"Participants in the NURTURE study achieved motor development milestones at a rate that was incongruent with the natural course of SMA type I and II, and that was in many cases within the timeframes established for healthy children."*

Professor Pane concluded her presentation by emphasising the role of continued collaboration to improve treatment options and outcomes in SMA, and cautioned that in the pursuit of a cure for this condition, there is a risk of overlooking the importance of a high standard of care.

* In NURTURE, genetically diagnosed patients who received nusinersen before the onset of SMA symptoms achieved age-appropriate motor milestones at the planned interim analysis[4]

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Early nusinersen treatment may allow for age-appropriate development[1]

Nusinersen-treated children at Day 778 in NURTURE[1]

Survival and ventilation	Nusinersen-treated patients who survived (IES) n=25	Nusinersen-treated patients who survived (%)
Alive and free from permanent ventilation	25 of 25 patients	100%
Motor development milestones (expected age of attainment in healthy infants)	**Nusinersen-treated patients who achieved the milestones (IES) n=25**	**Nusinersen-treated patients who achieved the milestones (%)**
Sitting without support (assessed if ≥7 months)	25 of 25 patients	100%
Walking with assistance (assessed if ≥11 months)	22 of 25 patients	88%
Walking alone (assessed if ≥15 months)	17 of 22* patients	77%

- In NURTURE, genetically diagnosed patients who received nusinersen before the onset of SMA symptoms achieved age-appropriate motor milestones at the planned interim analysis[2]

IES=interim efficacy set.
*3 patients were aged <15 months (WHO-defined window for expected age of achievement).

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MÁR TULINIUS

Professor, Queen Silvia Children's Hospital, University of Gothenburg, Sweden

Newborn screening – why do we want it? What does the process look like?

Newborn screening for SMA is now available in a number of countries, including Germany, Belgium, and several states in the US. In Sweden, an application has recently been submitted to extend the newborn screening programme to include SMA. Professor Már Tulinius from Queen Silvia Children's Hospital at the University of Gothenburg in Sweden summarised the evidence supporting newborn screening for SMA and moderated an update on the status of newborn screening in the Nordic countries.

There is accumulating evidence that early treatment of SMA is associated with better outcomes. For nusinersen, the SHINE open-label extension programme of the phase-3 studies CHERISH and ENDEAR found that the only factor associated with improved event-free survival was the time between first symptoms and first dose.[1] In extended access programmes for nusinersen in Germany, Italy and France, early treatment was associated with greater improvement in motor function for patients with SMA type I as assessed by the CHOP INTEND score.[2–4] This experience is also reflected at Professor Tulinius' own centre in Gothenburg, where children with SMA type I and two copies of the *SMN2* gene who initiated nusinersen treatment early achieved significant improvements in CHOP INTEND score together with normalisation of the levels of neurofilament light chain (NFL), a biomarker of axonal damage.[5] Reflecting on the Gothenburg experience, Professor Tulinius pointed out that while starting treatment early is preferable, later treatment is still worthwhile. "The CHOP INTEND score does not tell us everything about a patient's life," said Professor Tulinius. "We should still treat all patients, as long as we do not expect to achieve the same result as with early treatment if we begin late."

> *"The CHOP INTEND score does not tell us everything about a patient's life. We should still treat all patients, as long as we do not expect to achieve the same result as with early treatment if we begin late."*

More recently, the NURTURE study has demonstrated normal or near-normal motor development in infants with SMA receiving pre-symptomatic treatment with nusinersen,[6] and the CHERISH study in children with SMA type II found that age and disease duration were the only significant prognostic factors for treatment response to nusinersen.[7] The benefit of early treatment in SMA type I has also been demonstrated for other treatments than nusinersen – a phase 1 study of *SMN1* gene replacement therapy showed a trend towards better functional improvement in patients treated early compared with late, consistent with preclinical study results.[8]

Newborn screening for SMA in Sweden

In Sweden, neonatal screening for hereditary metabolic diseases was introduced in 1965, and now includes a total of 24 metabolic conditions. Recently, screening for severe combined immune deficiency (SCID) was included in the programme, which is the first test to involve DNA rather than protein screening. The actual screening test is done on a dry blood spot from a neonatal heel prick sample, a so-called Guthrie test, which is analysed at the Centre for Inherited Metabolic Diseases at Karolinska University Hospital in Stockholm. DNA testing, as in the case of screening for SMA, brings with it some particular challenges. There are questions around the clinical relevance of carrying a single working copy of the *SMN1* gene and how to handle any carriers that may be found, not least from an ethical point of view. Other questions are around the predictive value of different numbers of *SMN2* gene copies and how to treat these. The latter issue has been addressed recently with the publication of a treatment algorithm for infants diagnosed with SMA during newborn screening, under which patients with SMA type 0 with a single copy of the *SMN2* gene are only treated if presymptomatic treatment is possible and at the physician's discretion; patients with two or three copies of the *SMN2* gene are treated, and patients with four copies are monitored and treated at the onset of symptoms.[9] "We now have a good algorithm for when to treat if we find these patients on screening," said Professor Tulinius.

An application to begin newborn screening for SMA was submitted to the Swedish National Board of Health and Welfare (Socialstyrelsen) in April 2019 by Dr Sofia Botella, who is a consultant neurologist at Karolinska University Hospital. The Swedish National Board of Health and Welfare evaluates national screening programmes based on a model of 15 criteria which must be met, including that the screened condition is an important health problem with a known natural history and an asymptomatic phase, that a treatment is available, and that the screening procedure is feasible and acceptable

> *"We cannot be sure what would have happened if we had waited for the National Board of Health and Welfare to initiate this process themselves. Now at least the application has been put in and the wheels have been set in motion."*

– all of which criteria would be fulfilled by SMA screening, according to Dr Botella. The process of expert review and approval is expected to take around two years, although it is hoped that the fact that the application has come from a clinician may help to speed up the process. "We cannot be sure what would have happened if we had waited for the National Board of Health and Welfare to initiate this process themselves," Professor Tulinius pointed out. "Now at least the application has been put in and the wheels have been set in motion."

Newborn screening for SMA is being discussed in the other Nordic countries as well, and applications have been submitted in Norway and Denmark. Screening for SCID has been implemented recently in Norway and Finland and will begin in Denmark on 1 February 2020. All three countries are hopeful that newborn screening for SMA will soon follow suit.

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Take-home summaries

Pulmonary care in spinal muscular atrophy
Agneta Markström, Associate Professor, Astrid Lindgren Children's Hospital, Stockholm, Sweden

Serious respiratory consequences of SMA include increased work of breathing and poor clearance of secretions in the airways, which increase the risk of severe complications such as atelectasis and lower respiratory infections, and ultimately ventilatory failure. Sleep studies with monitoring for paradoxical breathing, decreased oxygen saturation and increase in CO_2 is the gold standard for evaluating respiratory function in infants and small children with SMA.

Orofacial function and communication – the role of the speech language pathologist in the examination and treatment of children with spinal muscular atrophy
Lisa Bengtsson, Speech Language Pathologist, Mun-H-Center, Gothenburg, Sweden

Orofacial dysfunction is a common challenge for patients with SMA irrespective of type. While speech language pathologists specialising in helping SMA patients overcome difficulties with eating, swallowing and speaking are rare in the paediatric neurology setting, they play a key role in the multidisciplinary team.

Family life with spinal muscular atrophy
Nina Olsson, Parent to a child with SMA, Uppsala, Sweden

"It is extremely hard, knowing that everything depends on us finding the strength to continue moving forward and to solve each new problem. As parents we have to be in the driving seat all the time; I often wish there was just a bit more help and support to be had so that we would not be quite so alone."

Families' experiences of having a child with spinal muscular atrophy
Ulrika Kreicbergs, Professor, Ersta Sköndal Bräcke University College, Stockholm, Sweden

Studies in Sweden and Denmark have shown that empowering parents of children with SMA through communication and dialogue with healthcare professionals can help them cope with the burden of end-of-life care and bereavement. In the era of nusinersen it will be important to evaluate how families are affected by this novel treatment and what their expectations are, to enable healthcare professionals to provide the best possible care.

Treatment of pre-symptomatic spinal muscular atrophy – the NURTURE study
Marika Pane, Professor, Catholic University and Policlinico Gemelli, Rome, Italy

Interim results from the NURTURE study show that early treatment with nusinersen in pre-symtomatic infants deemed likely to develop SMA type I or II is associated with substantial clinical benefit and a favourable benefit-risk profile. To date, the participants in the NURTURE study have achieved survival, ventilation and motor development outcomes that would not be expected in the natural history of SMA.

Newborn screening – why do we want it? What does the process look like?
Már Tulinius, Professor, Queen Silvia Children's Hospital, University of Gothenburg, Sweden

The availability of effective treatment provides a strong rationale for including SMA in the national newborn screening programme. An application to begin newborn screening for SMA has been submitted to the Swedish National Board of Health and Welfare, and the process of expert review and approval is expected to take around two years. Applications have also been submitted in Norway and Denmark.

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