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SPECIAL ARTICLE

Evidence in focus: Nusinersen use in spinal muscular atrophy

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Abstract

Objective

To identify the level of evidence for use of nusinersen to treat spinal muscular atrophy (SMA) and review clinical considerations regarding use.

Methods

The author panel systematically reviewed nusinersen clinical trials for patients with SMA and assigned level of evidence statements based on the American Academy of Neurology's 2017 therapeutic classification of evidence scheme. Safety information, regulatory decisions, and clinical context were also reviewed.

Results

Four published clinical trials were identified, 3 of which were rated above Class IV. There is Class III evidence that in infants with homozygous deletions or mutations of *SMN1*, nusinersen improves the probability of permanent ventilation-free survival at 24 months vs a well-defined historical cohort. There is Class I evidence that in term infants with SMA and 2 copies of *SMN2*, treatment with nusinersen started in individuals younger than 7 months results in a better motor milestone response and higher rates of event-free survival than sham control. There is Class I evidence that in children aged 2–12 years with SMA symptom onset after 6 months of age, nusinersen results in greater improvement in motor function at 15 months than sham control. Nusinersen was safe and well-tolerated.

Clinical context

Evidence of efficacy is currently highest for treatment of infantile- and childhood-onset SMA in the early and middle symptomatic phases. While approved indications for nusinersen use in North America and Europe are broad, payer coverage for populations outside those in clinical trials remain variable. Evidence, availability, cost, and patient preferences all influence decision-making regarding nusinersen use.

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Glossary

AAN = American Academy of Neurology; **AE** = adverse effect; **CADTH** = Canadian Agency for Drugs and Technologies in Health; **CHOP-INTEND** = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; **CI** = confidence interval; **COI** = conflict of interest; **FDA** = Food and Drug Administration; **GDDI** = Guideline Development, Dissemination, and Implementation; **HFMSE** = Hammersmith Functional Motor Scale Expanded; **HINE-2** = Hammersmith Infant Neurological Exam–part 2; **LP** = lumbar puncture; **mRNA** = messenger RNA; **QALY** = quality-adjusted life-year; **SMA** = spinal muscular atrophy; ***SMN1*** = survival motor neuron 1 gene; ***SMN2*** = survival motor neuron 2 gene.

Evidence in Focus is a pilot product of the American Academy of Neurology (AAN) Guideline Development, Dissemination, and Implementation (GDDI) Subcommittee (appendixes e-1 and e-2, links.lww.com/WNL/A737 [GDDI mission statement]) aiming to provide an evidence-based discussion of focused topics of timely relevance for neurologists and patients. This product is a systematic review that uses an abbreviated version of the AAN guideline methodology[1] to highlight the strength of evidence underlying new therapies, accompanied by a discussion to aid the practicing neurologist, other medical professionals, patients, and families.

This first Evidence in Focus examines the use of nusinersen, the first drug approved by the Food and Drug Administration (FDA) for the treatment of spinal muscular atrophy (SMA). Approval raises questions of when and how treatment should be used, with implications for clinicians, patients, families, and payers, whether private or governmental.

5q SMA is an autosomal recessive disorder caused by homozygous deletion or mutation involving exon 7 of survival motor neuron 1 gene (*SMN1*) and characterized by anterior horn cell degeneration. Nonmotor neuronal cells also may be involved.[2] Affected individuals have variable copy numbers of survival motor neuron 2 gene (*SMN2*), which differs meaningfully from *SMN1* at a single nucleotide that results in an exon splicing suppression sequence at exon 7. Consequently, exon 7 is excluded from most *SMN2* messenger RNA (mRNA), producing a truncated, rapidly degraded protein. Because *SMN2* produces some functional SMN protein when exon 7 is not spliced from the mRNA (10%–15%), a greater number of *SMN2* copies correlates with a milder SMA phenotype.[3]

SMA is clinically classified into 4 types based on the highest motor milestone attained (table 1). Type 1 SMA presents before 6 months of age with generalized weakness and progressive respiratory failure. It is the most severe form and accounts for 60% of incident cases.[4] Without supportive care or treatments, most children with type 1 SMA die before 2 years of age and are never able to sit independently. Children with SMA type 2 achieve the ability to stay seated independently, although some lose this ability and are never able to walk independently; scoliosis is common. With supportive care, individuals with type 2 SMA may live into adulthood. Individuals with types 3 and 4 may have normal lifespans and be able to walk independently, although some may lose this ability. SMA severity varies within subtypes, representing a continuum. Epidemiologic studies are limited and largely predate genetic testing. Estimated incidence is 1 per 10,000 live births, and prevalence is 1–2 per 100,000 persons.[4]

Nusinersen is an antisense oligonucleotide that modifies pre-mRNA splicing to promote exon 7 inclusion in *SMN2* mRNA transcripts, resulting in production of more full-length SMN protein.[5] It is administered using intrathecal injections via lumbar puncture (LP). Its mechanism of action is purely within the CNS. The manufacturer's recommended dosing schedule consists of 4 loading doses of 12 mg in the first 2 months of treatment, followed by doses every 4 months.

Description of the analytic process

In September 2017, the AAN GDDI subcommittee approved the Evidence in Focus pilot and appointed one content expert (E.C.), one GDDI member with content expertise (S.A.), one former GDDI member with content expertise (D.M.), a patient representative (E.L.), and a guideline methodologist (M.J.A.) to develop the first product. Subsequently guideline leadership approved the involvement of 2 additional GDDI members with content expertise to contribute content revisions representing a range of clinical experience (P.N., M.O.). Conflicts of interest (COI) were assessed and addressed as per GDDI Subcommittee policy.[1] Two of the 7 authors were determined to have COIs, which were judged to be not significant enough to preclude them from authorship (E.C., M.O.). All authors determined to have COIs were not permitted to review or rate the evidence. These individuals were used in an advisory capacity.

A pragmatic literature search for clinical trials of nusinersen use in patients with SMA was performed on September 28, 2017, and updated on November 20, 2017, and February 16, 2018 (appendix e-3, links.lww.com/WNL/A737). Conference abstracts were not included in the formal evidence review (figure). Clinicaltrials.gov was also searched. Two panel members independently reviewed titles and abstracts for inclusion. The 3 searches yielded a total of 15 titles (appendix e-4), of which 4 were relevant. Data were also reviewed from studies identified as "completed, has results" on clinicaltrials.

Supplemental Data
NPub.org/i6th9m

Table 1 Types of spinal muscular atrophy (SMA)

SMA type	Typical age at onset	Highest motor function without treatment	Typical age at death without ventilator/other support	Typical no. of *SMN2* copies
1	0–6 mo	Never sit independently	<2 y	1–2[a]
2	6–18 mo	Able to sit, never able to walk independently	Variable; many live to early adulthood	2, 3,[a] 4
3	≥18 mo	Able to walk independently	Can have normal lifespan	3[a]–4[a]
4	≥21 y	Able to walk independently	Normal lifespan	4,[a] 5,[a] 6–8[b]

Abbreviation: *SMN2* = survival motor neuron 2 gene.
[a] The most common copy numbers for each SMA type.
[b] Individuals with more than 6 copies of *SMN2* may be phenotypically normal.

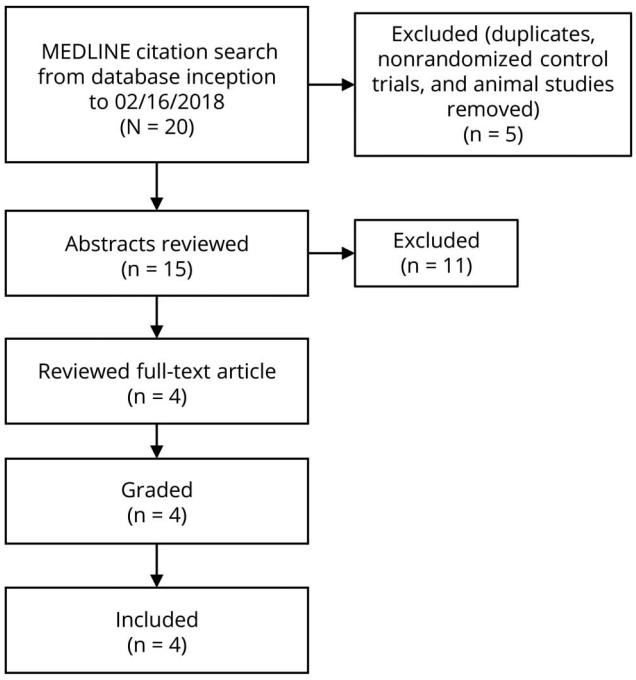
gov without associated publications to date. Selected articles were each classified by 2 independent raters (2017 AAN therapeutic classification scheme [appendix e-5]).[1] Level of evidence statements were developed according to the process used for *Neurology*® level of evidence reviews.

Evidence summary

Level of evidence

Level of evidence statements are provided in table 2. The first study was a Class IV, phase 1, open-label study of nusinersen administration to medically stable patients aged 2–14 years with types 2 and 3 SMA (NCT01494701; NCT01780246).[6] Four ascending single-dose levels (1, 3, 6, and 9 mg) were examined in 6–10 participant cohorts. The primary outcomes were safety and tolerability. The exploratory clinical assessment was the Hammersmith Functional Motor Scale Expanded (HFMSE), a 33-item scale that grades SMA-specific motor function (e.g., related to sitting, crawling, squatting, climbing stairs) on a 3-point (0–2) scale.[7] In the 1-, 3-, and 6-mg groups, there were no significant HFMSE score changes from baseline to day 29, day 85, or 9–14 months (mean changes in the 1-mg group: +1.0 points at day 29, −1.7 points at 9–14 months; the 3-mg group: +1.0 points at day 29, +0.5 points at 9–14 months; and the 6-mg group: +0.7 points at day 85, +2.5 at 9–14 months). The 9-mg group demonstrated improved HFMSE scores from baseline at day 85 (mean change +3.1 points, $p = 0.016$). After 9–14 months, the mean increase was 5.8 points (32.8%, $p = 0.008$).[6]

Figure Systematic evidence review flow diagram



A phase 2, open-label study investigated nusinersen doses of 6 mg or 12 mg dose equivalents in infants with SMA symptom onset between 3 weeks and 6 months of age, a *SMN1* homozygous gene deletion or mutation, and either 2 or 3 *SMN2* copies (NCT01839656) (table 2).[8] This study was rated Class III based on the use of a well-defined historical control cohort. Outcomes included event-free survival and change from baseline according to results from 2 motor function assessments: the motor milestones portion of the Hammersmith Infant Neurological Exam–Part 2 (HINE-2) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) motor function test. The HINE-2 motor milestones portion rates 8 items (from head control to walking) on a 5-point (0–4) scale in children younger than 2 years.[9] CHOP-INTEND includes 16 items relating to motor skills (capturing neck, trunk, and proximal and distal limb strength/function) rated on a 5-point (0–4) scale.[10] Participants receiving 6 mg equivalent loading doses on days 1, 15, and 85 were switched to 12-mg doses starting on day 253. The interim efficacy analysis included all participants who completed the loading doses and day 92 assessment; follow-up duration ranged from 2 to 32 months. Change in HINE-2 from baseline to last visit was significant for the 12-mg group and the 6- and 12-mg cohorts combined ($p < 0.001$, $p = 0.0002$, respectively; n = 19). CHOP-INTEND scores increased from baseline to last visit, with a mean increase of 11.5 points in the 6- and 12-mg cohorts combined ($p = 0.008$, n = 18) and 15.2 points in the 12-mg group ($p = 0.0013$). This contrasts with the natural history controls, who had a mean decline of 1.27 points

Table 2 Levels of evidence for published spinal muscular atrophy (SMA) nusinersen trials

Study	Number enrolled	Population studied (key inclusion criteria)	Explanation of level of evidence	Level of evidence statement
Chiriboga et al., 2016[6] (NCT01494701; NCT01780246, CS1[a])	28	Male and female patients aged 2–14 years Symptomatic SMA and documented *SMN1* homozygous gene deletion; medically stable, with life expectancy >2 years; able to complete all study procedures	Class IV due to open-label design	This study provides Class IV evidence that in children with type 2 and type 3 SMA, intrathecal nusinersen is not associated with safety or tolerability concerns
Finkel et al., 2016[8] (CS3A,[a] NCT01839656)	20	Male and female patients aged 3 weeks–7 months Onset of SMA symptoms between 3 weeks and 6 months; *SMN1* homozygous gene deletion or mutation; body weight >5th percentile, gestational age 35–42 weeks, gestational body weight ≥2 kg, receiving adequate nutrition and hydration, not hypoxemic, receiving standard of care, expected to complete all study procedures	Class III due to open-label design with comparison to well-defined historical cohort	This study provides Class III evidence that in infants with *SMN1* homozygous gene deletions or mutations, nusinersen improves the probability of permanent ventilation-free survival at 24 months vs a well-defined historical cohort
Finkel et al., 2017[11] (CS3B,[a] NCT02193074, ENDEAR)	142 Screened, 122 randomized	Younger than 7 months at screening Homozygous deletion or mutation in the *SMN1* gene, with 2 copies of the *SMN2* gene; onset of SMA clinical symptoms at 6 months or earlier; body weight >3rd percentile, gestational age 37–42 weeks, receiving adequate nutrition and hydration, not hypoxemic, receiving standard of care, able to complete all study procedures, parent/guardian with adequate psychosocial support	NA, Class I	This study provides Class I evidence that in infants with a gestational age between 37 weeks and 42 weeks with SMA and an *SMN2* copy number of 2, treatment with nusinersen results in a better motor milestone response and higher event-free survival than the sham control (after at least 6 months of treatment)
Mercuri et al., 2018[12] (CS4,[a] NCT02292537, CHERISH)	126	Male and female patients aged 2–12 years Medically diagnosed with SMA, with sign and symptom onset later than 6 months of age;	NA, Class I	This study provides Class I evidence that in children aged 2–12 years with SMA symptom onset after 6 months of age, treatment with nusinersen results in greater improvement in motor function at 15 months than the sham control

Continued

Table 2 Levels of evidence for published spinal muscular atrophy (SMA) nusinersen trials *(continued)*

Study	Number enrolled	Population studied (key inclusion criteria)	Explanation of level of evidence	Level of evidence statement
		able to sit independently but never able to walk independently; HFMSE ≥10 and ≤54 at screening; able to complete all study procedures; estimated life expectancy >2 years; no respiratory insufficiency, medically required gastric feeding tube, severe contractures, or scoliosis		
CS2,[a] NCT01703988: an open-label safety, tolerability and dose-range finding study of multiple doses of nusinersen (ISIS 396443) in participants with SMA	34	Male and female patients aged 2–15 years Genetic documentation of 5q SMA (homozygous gene deletion or mutation); clinical signs of SMA; able to complete all study procedures; no respiratory insufficiency or medically required gastric feeding tube	Class IV due to open-label design	This study provides Class IV evidence that in children with 5q SMA (homozygous gene deletion or mutation), nusinersen is not associated with safety or tolerability concerns

Abbreviations: HFMSE = Hammersmith Functional Motor Scale Expanded; *SMN1* = survival motor neuron 1 gene; *SMN2* = survival motor neuron 2 gene.
[a] CS labels refer to the Food and Drug Administration review nomenclature identifying different studies.

annually (95% confidence interval [CI] 0.21–2.33). Study participants with 2 copies of *SMN2* (n = 17) had a higher probability of ventilation-free survival compared with natural history controls who had 2 copies of *SMN2* (n = 23) (log-rank test, $p = 0.0014$). Only 7 of the 20 total participants reached the endpoint of death or permanent ventilation prior to the interim analysis.[8] Final study results are not available.

A Class I, phase 3, randomized, double-blind, sham-controlled study investigated the use of nusinersen in symptomatic patients with infantile-onset SMA (NCT02193074, ENDEAR).[11] The study was terminated early after a positive interim analysis. Eighty-one infants were randomized to nusinersen treatment (12-mg dose equivalent) and 41 to the sham control. The primary endpoints were a motor milestone response (defined as improvement in at least 1 category or improvement in more categories than worsening on the HINE-2) and event-free survival (time to death or use of permanent assisted ventilation). In both the interim and final analyses (performed using last visit data in patients enrolled for at least 6 months), more infants in the nusinersen group had a motor milestone response (interim: 41% vs 0%, $p < 0.001$; final: 51% vs 0%, significance not tested). Event-free survival was higher in the nusinersen group than the control group by the final analysis cutoff date (61% vs 32%, $p = 0.005$; hazard ratio 0.53, 95% CI 0.32–0.89). Several secondary endpoints also demonstrated treatment benefits.[11]

A Class I, phase 3, randomized, double-blind, sham-controlled study investigated the use of nusinersen in children with SMA who had symptom onset after 6 months of age (NCT02292537, CHERISH).[12] Eighty-four patients were randomized to nusinersen (12 mg) and 42 patients received the sham control. The study was terminated after a positive interim analysis. The primary endpoint was the least-squares mean change in the total HFMSE score from baseline to month 15. In both the interim and final analyses, change in HFMSE scores at 15 months were significantly greater in the nusinersen group vs the control group (interim analysis: 4.0 vs −1.9, mean difference 5.9, 95% CI 3.7–8.1; final analysis: 3.9 vs −1.0, mean difference 4.9, 95% CI 3.1–6.7). In addition, more children receiving nusinersen than the sham procedure had a 3-point or greater increase in their HFMSE score at 15 months (57% vs 26%, $p < 0.001$).[12]

A Class IV, open-label, phase 1/2 study in children aged 2–15 years with later-onset SMA assigned 8–9 patients to each of 4 cohorts receiving 3-, 6-, 9-, or 12-mg doses of nusinersen (NCT01703988) (table 2). Safety and tolerability results are available only on clinicaltrials.gov.

Additional studies are underway (table 3). As demonstrated above, the regimen for loading and maintenance nusinersen dosing has evolved from varied dose ranges in phase 1 and 2 studies to focusing on 12-mg equivalent dosing in phase 3 studies.

Safety

Most information regarding possible adverse effects (AEs) is derived from clinical trial data presented to the FDA (<200 patients).[13] No serious AEs were classified as definitely treatment-related. Several AEs were more common in nusinersen-treated patients, including proteinuria, decreased platelet counts, atelectasis, lower and upper respiratory tract infections, and constipation. The FDA recommended that clinicians regularly monitor patients receiving nusinersen for coagulopathy, thrombocytopenia, and proteinuria. The incidence of clinically significant thrombocytopenia, platelet dysfunction, or nephrotoxicity across trials with similarly modified antisense oligonucleotides was very small,[11,14,15] but one patient treated with an antisense oligonucleotide (inotersen) in a study of individuals with familial amyloid polyneuropathy died due to thrombocytopenia-related intracranial hemorrhage.[16] Transient AEs related to intrathecal administration, including headache, vomiting, back pain, and post-LP syndrome, were reported in 40%–50% of patients. One rare but serious AE, communicating hydrocephalus, has been observed outside of clinical trials in five treated patients as of July 2018.[17]

Regulatory decisions

The FDA approved the indication "Spinraza® (nusinersen) injection for the treatment of spinal muscular atrophy in

Table 3 In-process studies of nusinersen in spinal muscular atrophy (SMA)[a]

Study (NCT number)	Title	Target enrollment	Population studied (key inclusion criteria)	Status (per clinicaltrials.gov, November 27, 2017)
NCT02386553 (NURTURE)	A study of multiple doses of nusinersen (ISIS 396443) delivered to infants with genetically diagnosed and presymptomatic spinal muscular atrophy	25	Gestational age of 37–42 weeks for singleton births (34–42 weeks for twins) Age ≤6 weeks at first dose 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation 2 or 3 copies of *SMN2* Baseline ulnar compound muscle action potential ≥1 mV No hypoxemia or clinical signs or symptoms of SMA prior to first dose	Active, not recruiting (no results)
NCT02462759 (EMBRACE)	A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B[b] or ISIS 396443-CS4[b]	21	5q SMA homozygous gene deletion or mutation or compound heterozygous mutation Onset of clinical signs and symptoms consistent with SMA at ≤6 months and have 3 *SMN2* copies or onset of clinical signs and symptoms consistent with SMA at ≤6 months, are >7 months at screening, and have 2 *SMN2* copies or onset of clinical signs and symptoms consistent with SMA at >6 months, are ≤18 months at screening, and have 2 or 3 *SMN2* copies Signs or symptoms of SMA not present at birth or within first week after birth No ventilation for 16 hours per day continuously for >21 days at screening or permanent tracheostomy	Active, not recruiting (no results)

Abbreviation: *SMN2* = survival motor neuron 2 gene.
[a] Studies that are open-label follow-ups of prior study cohorts (NCT02052791 complete without available results; NCT02594124 [SHINE], enrolling by invitation) or expanded access programs (NCT02865109; available) are not included.
[b] CS labels refer to the Food and Drug Administration review nomenclature identifying different studies.

pediatric and adult patients" in December 2016.[13] Marketing authorization was granted by the European Medicines Agency in May 2017, with an indication "for the treatment of 5q spinal muscular atrophy."[18] Health Canada issued a Notice of Compliance for nusinersen for the treatment of 5q SMA in July 2017.[19] In Japan, nusinersen was approved to treat infantile-onset SMA.[20] Regulatory approvals are in process in other countries. Authorization for use is distinct from coverage decisions made by individual countries' health authorities and insurance providers.

Clinical context

Nusinersen's approval enabled physicians to offer more than symptomatic treatment for the most common genetic cause of mortality in infants and toddlers.[5] There is understandable optimism among families affected by all SMA subtypes but also uncertainty that requires further research.[21]

Populations for use

The phase 3 nusinersen trials (NCT02193074/ENDEAR,[11] NCT02292537/CHERISH[12]) enrolled children with SMA subtypes I and II who were in the early and middle symptomatic phases without significant scoliosis or contractures that would limit the potential for measured functional improvement on selected outcome scales (table 2). In these populations, nusinersen appears to be beneficial and to pose little risk, resulting in proposals to incorporate nusinersen into standards of care.[22] Less is known about how nusinersen affects a wider range of patients, such as those with milder SMA forms or those who are already severely disabled with muscle atrophy and fixed contractures. It is believed that nusinersen may be most effective when started as soon as possible after diagnosis (genetic or clinical), but NURTURE results and future research are needed. Preliminary NURTURE findings suggest that nusinersen use in presymptomatic infants with 2 or 3 copies of *SMN2* may allow for the greatest improvements on the HINE-2 motor milestones,[23] but results are open-label and preliminary. All nusinersen trials are of relatively short duration; long-term implications of treatment (safety, efficacy, and long-term prognosis in the context of treatment) remain to be established. Older patients with later-onset type III and type IV SMA may prove responsive to nusinersen as they carry more *SMN2* copies, but the cost–benefit ratio is different in these populations. Monitoring through nusinersen expanded access programs will inform some of these ongoing questions (e.g., results of real-world use, open-label efficacy in populations such as adults, and long-term effects/risks) but will reflect Class IV data.

Patients with more advanced disability, severe muscle atrophy, joint contractures, and skeletal deformities likely have less potential for functional improvement with nusinersen. These patients may still desire treatment if there is reasonable hope for stabilization and maintenance of an ability that is crucial to independence and quality of life, such as controlling the joystick of a power wheelchair or making communicative gestures. Such patients also face the greatest practical challenges to LP because of severe neuromuscular scoliosis and complex hardware from prior spinal fusion and instrumentation. Joint contractures make LP positioning more challenging and put patients at greater risk of injury. Advanced respiratory insufficiency or ventilator dependence may make interventionists unwilling to perform procedures with less than full anesthesia team support and general anesthesia use. In some children, use of spinal ultrasonography, fluoroscopy, conical CT guidance, and a transforaminal approach increases rates of successful intrathecal access.[24,25] In rare cases, laminectomies and intraspinal catheter and subcutaneous reservoir placements are performed by orthopedic surgeons to facilitate treatment. In patients in whom lumbar access is impossible, nusinersen delivery has been accomplished via fluoroscopic-guided lateral cervical puncture at the C1–2 interspace. These alternative administration routes have not been evaluated for drug delivery effects and are associated with additional procedural risks.

Patient preferences

While many patients and families are pursuing nusinersen treatment outside the clinical trial populations, some patients and families decline nusinersen even when insurance coverage is likely. Reasons to defer treatment include lack of sufficient information with which to weigh treatment risks and benefits, caution about using a medication with a novel mechanism of action, lack of long-term safety data, risks related to repeated LPs, desire to participate in other clinical trials, and cumulative radiation and anesthesia exposure risks. Families also may be discouraged by financial and logistical burdens directly or indirectly related to treatment, such as taking time off from work or having to travel to distant administration sites. Weight placed on these considerations varies according to phenotypic severity and individual circumstances and values.

Infrastructure for use

Nusinersen administration requires a collaborative approach among neurologists, pharmacists, anesthesiologists, interventional radiologists, therapists, patients, and families. Prescribing neurologists must be comfortable with patient selection and counseling. In addition to discussing potential benefits and risks, physicians should explain that nusinersen is not a cure. Successful treatment will improve disease trajectory, but patients and families will still face life with a chronic disease. Repeated (e.g., every 6 months) time-consuming evaluations of motor function by physical therapists familiar with the scales used in SMA are required to monitor therapy response and maintain insurance approval for continued therapy. These evaluations require expertise and equipment that are not universally available and often require visits to specialized multidisciplinary clinics. Individuals receiving nusinersen also require laboratory access for AE monitoring.

Coverage considerations

In the United States, nusinersen's list price is $125,000 per injection, equaling approximately $750,000 for drug administration during the first year and $375,000 annually in subsequent years, not including physician, therapist, or facility fees associated with drug administration[26] or indirect costs for patients and families (e.g., travel and lost wages). The high per-treatment and lifetime costs mean that US patients face significant hurdles in getting treatment approved by insurers, although processes are becoming more streamlined. Some patients, particularly those with SMA forms not included in the phase 3 trials, face persistent difficulties if not denials from insurers. After initial approval, some insurers ask physicians to submit the results of therapy assessments/motor function tests used in the phase 3 trials to justify ongoing treatment.[22,27] Insurers may also require evidence that patients' conditions have not deteriorated to a point of requiring permanent ventilator support.[27] Even when coverage is approved, patients and families face billing challenges related to in-network and out-of-network costs, as nusinersen administration and related assessments are often only available at select centers.

Several US insurers have declined requests to cover nusinersen in patients with later-onset type III and IV SMA, classifying the treatment as experimental. There are concerns that high treatment costs are not justified by the clinical benefit in this population. Variations in how physicians and insurers are weighing the uncertainties about the quality of life and value to society provided by nusinersen use in different patient groups has led to discrepancies in treatment availability in different clinics and states.[28] Some patients choose to travel out of state or to change insurance providers to obtain treatment.

In December 2017, the Canadian Agency for Drugs and Technologies in Health (CADTH) recommended nusinersen reimbursement for the treatment of 5q SMA in infants symptomatic before 7 months of age, based on ENDEAR evidence.[11,29] Similar to US insurers, treatment discontinuation is recommended if there is no demonstrated improvement or maintenance of function as assessed by the HINE-2 or if permanent invasive ventilation is required. The coverage decision is conditional on SMA specialist care, a substantial reduction in treatment price, and collection of "real-world evidence" on nusinersen use.[29]

Cost-effectiveness

No US nusinersen cost-effectiveness analyses are published. A technical brief for the Institute for Clinical and Economic Review Orphan Drug Assessment & Pricing Summit noted that high nusinersen costs "are likely to result in cost-effectiveness estimates that exceed commonly cited thresholds in the US (i.e., $50,000–$150,000 per quality-adjusted life-year [QALY] gained), even if substantial cost offsets from reduced supportive care needs are realized."[26] A CADTH reanalysis of the manufacturer cost–utility model found that nusinersen was unlikely to be cost-effective in Canada at the submitted price, with costs per QALY of $9.2 million for SMA type I, $24.4 million for SMA type II, and $7.4 million per QALY for SMA type III (with different levels of certainty). CADTH noted that even in the scenario of a 95% price reduction, incremental cost–utility ratios would still exceed $400,000 per QALY.[29]

Using traditional cost-effectiveness thresholds for treatments of rare conditions is controversial, with challenges including small populations on which to base judgments, novel therapeutic mechanisms of action, clinical trial feasibility, quality of life assessments in diseases affecting infants and young children, incorporation of the effect of quality of life factors on families and caregivers, assessment of both quality and extension of life, and the distribution of high costs across a small population.[26] At societal and clinician levels, there remain unanswered questions about the balance of improving the lives of individual patients vs the societal responsibility to control health care costs and maximize benefits for all.

Changing approach

The discovery and approval of nusinersen is fundamentally altering the landscape of SMA diagnosis and treatment. With emerging treatments that prevent disease manifestations and improve function, systems for early diagnosis are needed to maximize potential benefits. The Cure SMA advocacy group lobbied the US Congress to include SMA in the Recommended Uniformed Screening Panel for newborn screening, with several states initiating pilot programs in 2018. If NURTURE shows nusinersen efficacy in preventing or lessening clinical manifestations in presymptomatic infants, early diagnosis and treatment will be further emphasized. Caution is needed in interpreting genetic testing results in presymptomatic individuals, however. *SMN2* copy number is correlated with SMA subtype but is not completely predictive,[30] partly related to phenotypic modifiers.[31]

Nusinersen will redefine the natural history of SMA. No evidence is currently available to counsel patients and families about what to expect for long-term prognosis and function after nusinersen treatment, a critical gap that will be addressed in part by ongoing open-label follow-up studies. Historical treatment protocols developed for guiding optimal SMA care will need revision as approaches and natural history are redefined.

Other novel SMA treatments also are under investigation. Targets for therapeutic intervention include increasing SMN protein production either through alternative *SMN2* splicing (nusinersen, RG7916, branaplam) or gene replacement of *SMN1* (AVXS-101), preventing motor neuron death by maintaining neuronal mitochondrial integrity (olesoxime), or increasing muscle endurance through a fast skeletal muscle troponin activator that amplifies muscle response (CK-2127107). These investigations need to explore the therapeutic effect beyond the motor neuron alone, as research suggests that low SMN levels affect muscle, afferent sensory

nerves, brain, heart, blood vessels, liver, pancreas, bone, lungs, and intestines, with implications for treatment timing and therapeutic targets.[2,32]

Suggestions for future research

Additional outcome data from randomized controlled trials in infants (NCT02462759/EMBRACE) and the open-label study of infants with presymptomatic type I and II disease (NCT02386553/NURTURE) are pending (table 3) and will provide important insights into populations for use and expected benefits. Open-label follow-up studies will provide needed long-term safety and prognostic data. Efficacy outcomes should compare patients continuing vs discontinuing treatment to determine whether there is a time at which nusinersen can safely be stopped without substantial risk of resumed disease progression. Studies are needed to determine whether intrauterine treatment is feasible and safe and whether it offers benefits beyond those seen with postnatal treatment. Studies of children with more advanced disease and adults with type III and IV SMA are needed to provide safety data and establish the expected response. It is likely that future studies, particularly if enrolling infants with type 1 SMA, will require a nusinersen control group instead of placebo. Asking infants with type 1 SMA to forego nusinersen treatment to enroll in a placebo-controlled study is both ethically problematic and limiting in terms of recruitment potential. Future research should investigate optimal administration strategies, including the risks and benefits of sedation options, positioning, needle use, and imaging guidance to establish best practices for performing spinal infusions, particularly for patients with advanced and surgically repaired scoliosis.

Considerations for nusinersen use may benefit from cost–benefit analyses for different SMA subtypes and stages. Such analyses should include the costs associated with multidisciplinary drug administration in addition to drug costs and expectations of reduced supportive care. Ethical dilemmas, such as how to objectively assign monetary value to improved quality of life, should be addressed transparently and in close collaboration with patients, families, physicians, and ethicists in addition to private and governmental payers.

Author contributions

Dr. Michelson: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Ashwal: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Ciafaloni: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. E. Lewis: acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Narayanaswami: drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Oskoui: drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Armstrong: study concept and design, acquisition, analysis, and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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