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REVIEW ARTICLE

Current evidence for treatment with nusinersen for spinal muscular atrophy: a systematic review

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Abstract

Recent discovery of nusinersen, an antisense oligonucleotide drug, has provided encouragement for improving treatment of spinal muscular atrophy. No therapeutic options currently exist for this autosomal recessive motor neuron disorder. Nusinersen is developed for intrathecal use and binds to a specific sequence within the survival motor neuron 2 pre-messenger RNA, modifying the splicing process to promote expression of full-length survival motor neuron protein. We performed a MEDLINE and CENTRAL search to investigate the current evidence for treatment with nusinersen in patients with spinal muscular atrophy. Four papers were withheld, including two phase-3 randomized controlled trials, one phase-2 open-label clinical trial and one phase-1 open-label clinical trial. Outcome measures concerned improvement in motor function and milestones, as well as event-free survival and survival. Results of these trials are hopeful with significant and clinically meaningful improvement due to treatment with intrathecal nusinersen in patients with early- and later-onset spinal muscular atrophy, although this does not restore age-appropriate function. Intrathecal nusinersen has acceptable safety and tolerability. Further trials regarding long-term effects and safety aspects as well as trials including broader spinal muscular atrophy and age categories are required and ongoing.

Keywords Nusinersen · Intrathecal · Spinal muscular atrophy · Survival of motor neuron

Introduction

Spinal muscular atrophies (SMA) form a phenotypically heterogeneous spectrum and are progressive, hereditary, autosomal recessive disorders of anterior horn cells and selective motor cranial nerve nuclei [1]. Incidence is about 1/11,000 live births. The disease is caused by loss of function of both alleles of the survival of motor neuron (SMN) 1 gene resulting in decreased expression of SMN protein causing degeneration of motor neurons. In 95% of cases, a homozygous deletion is observed [2]. The SMN2 gene also encodes for SMN protein but differs by 11 nucleotides from SMN1 resulting in skipping of exon 7 in about 90% of the mature RNA transcripts and production of a truncated, non-functional protein [1–3]. The SMA phenotype is related to the copy number of the SMN2 gene [1]. Nusinersen, an antisense oligonucleotide drug, can be injected intrathecally in order to enhance expression of the SMN protein through targeting a heterogeneous nuclear ribonucleoprotein A1-dependent splicing silencer in intron 7 of the SMN pre-messenger RNA leading to increased synthesis of transcripts containing exon 7 [4]. Careful optimism concerning treatment for SMA exists. We wanted to verify the current evidence of efficacy concerning improvements in motor function, achieving motor milestones (MM) and survival of intrathecal administration of nusinersen in SMA patients versus standard medical care.

Materials and methods

Search strategy

The first author performed after determining the search protocol a MEDLINE and CENTRAL search on December 21,

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2018, respectively, via PubMed using search terms 'Muscular Atrophy, Spinal' as medical subject headings and 'nusinersen' or 'Spinraza' as text words and via the Cochrane Library using search terms 'spinal muscular atrophy' and 'nusinersen' as text words. The selected time period was unrestricted. The retrieved articles were examined for useful references. In order to update our search, a second search was performed on April 22, 2019, using the same protocol.

Selection

Only original articles evaluating the efficacy of intrathecal nusinersen in SMA patients were included. The interventions and outcome measures had to be clearly defined.

Outcome reporting

We intended to address outcome measurements concerning improvements in motor function, achieving MM and survival.

Evidence grading

The selected articles were assessed by the first author, and the findings of the studies were extracted and summarized. The quality of the studies was appraised according to the classification levels of evidence using the Evidence-Based Guideline Development (EBRO) classification of the Dutch Cochrane Centre [5]. Level of evidence was also considered based on the EBRO and Oxford 2009 [6] level of evidence criteria and the American Academy of Neurology (AAN) classification of evidence matrix [7]. Grade of recommendation was based on the Oxford 2009 criteria, and quality was interpreted using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) discriminatory instrument [8].

Results

An overview of the literature search is shown in Fig. 1. Twenty and 17 references were found via MEDLINE and CENTRAL, respectively, on December 21, 2018. Two trial registrations [9, 10], nine conference abstracts [11–19] and one conference review [20] were excluded. Three articles were found via MEDLINE and CENTRAL [1–3]. One reference concerned the same article [2]. Of the remaining, six reviews mentioned information on included papers [21–26] and ten articles were not focused on the predefined outcome measures [27–36], of which one also was found in both databases [36]. Finally, four studies remained, of which two had more than 120 subjects, both two phase-3 randomized controlled trials (RCTs) [1, 2] and two studies of 20–28 subjects, a phase-2 open-label clinical trial [3] and a phase-1 open-label clinical trial [4]. No additional papers were included after the second search, as shown in supplementary Fig. S1. A summary of the selected articles is given in Table 1, and baseline characteristics of the subjects are shown in supplementary table S1. Data on principal inclusion and exclusion criteria are given in supplementary table S2. No additional papers were identified through reference lists. A list of all screened, but excluded references is available in the supplementary appendix. Quality and evidence levels are depicted in Table 2, and throughout the text

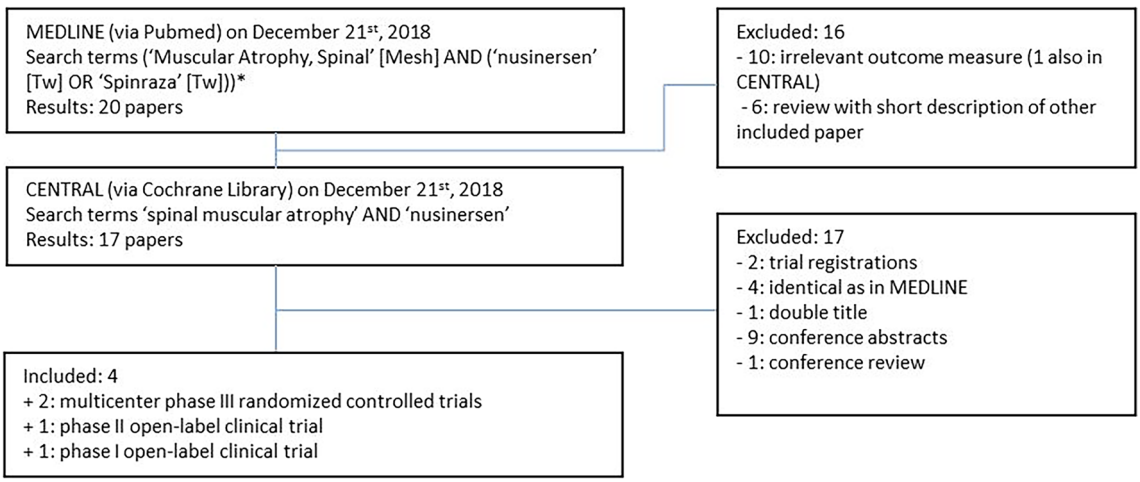

Fig. 1 Search strategy and outcome. *Additional filters: 1. Languages: English. 2. Article types: Case reports, Clinical Trial, Controlled Clinical Trial, Multicenter Study, Randomized Controlled Trial, Review and Systematic Reviews. *CENTRAL* Cochrane Central Register of Controlled Trials, *MEDLINE* Medical Literature Analysis and Retrieval System Online, *Mesh* medical subject headings, *Tw* text word

Table 1 Summary of trials [1–4]

Author, year	Design (x)	Patients (*N*)	Time-frame	Location	Intervention	Comparator	Length of follow-up	Outcome measures	Intervention group outcome	Control group outcome	Effect size
Mercuri et al. 2018 [1]	Multicenter, double-blind, sham-controlled phase-III RCT with 2:1 randomization (24)	126 (84:42)	11/2014–02/2017	Canada, France, Germany, Hong Kong, Italy, Japan, Republic of Korea, Spain, Sweden, USA	IT nusinersen 12 mg d1, 29, 85, 274	Sham-procedure	15 m (early termination of trial)	Primary EP A. Interim analysis: Change from baseline in HFMSE score (least-squares mean (95% CI)) B. Final analysis: Change from baseline in HFMSE score (least-squares mean (95% CI)) Secondary EP (final analysis) Children with change in HFMSE score of ≥ 3 points (%) (95% CI)) Children who achieved ≥ 1 new WHO motor milestone (% (95% CI)) Change from baseline in number of WHO motor milestones achieved (least-squares mean (95% CI)) Change from baseline in RULM score (least-squares mean (95% CI)) Children who achieved ability to stand alone (≥ 15 feet) (% (95% CI)) Children who achieved ability to walk with assistance (% (95% CI))	4.0 (2.9–5.1) 3.9 (3.0–4.9) 57 (46–68) 20 (11–31) 0.2 (0.1–0.3) 4.2 (3.4–5.0) 2 (0–8) 2 (0–8)	− 1.9 (− 3.8 to 0) − 1.0 (− 2.5 to 0.5) 26 (12–40) 6 (1–20) − 0.2 (− 0.4 to 0) 0.5 (− 0.6 to 1.6) 3 (0–15) 0 (0–10)	(Difference/*P* value) 5.9 (3.7–8.1)/*P* < 0.001 4.9 (3.1–6.7)/*P*– 30.5 (12.7–48.3)/*P* < 0.001 14 (− 7 to 34)/*P* = 0.08 0.4 (0.2–0.7)/*P*– 3.7 (2.3–5.0)/*P*– − 1 (− 22 to 19)/*P*– 2 (− 19 to 22)/*P*–
Finkel et al. 2017 [2]	Multicenter, double-blind, sham-controlled phase-III RCT with 2:1 randomization (31)	121 (80:41)	08/2014–11/2016	Australia, Belgium, Canada, France, Germany, Italy, Japan, Republic of Korea, Spain, Sweden, Turkey, UK, USA	IT nusinersen 12 mg EqD d1, 15, 29, 64, 183, 302	Sham-procedure	13 m (early termination of trial)	Primary EP A. Interim analysis Motor-milestone response (HINE-2)[a] (*n* (*n* %)) B. Final analysis Motor-milestone response (HINE-2) (*n* (*n* %)) No death or use of permanent assisted ventilation[b] (*n* (*n* %)) Secondary EP (final analysis) Children with change in CHOP-INTEND score of ≥ 4 points (*n* (*n* %)) No death (*n* (*n* %)) No permanent assisted ventilation (*n* (*n* %)) CMAP response (peroneal nerve—TA)[c] (*n* (*n* %)) No death or use of permanent assisted ventilation among those with disease duration ≤ 13.1w at screening (*n* (*n* %)) No death or use of permanent assisted ventilation among those with disease duration > 13.1w at screening (*n* (*n* %))	21 (41) 37 (51) 49 (61) 52 (71) 67 (84) 64 (78) 26 (36) 30 (77) 19 (46)	0 (0) 0 (0) 13 (32) 1 (3) 25 (61) 28 (68) 2 (5) 7 (33) 6 (30)	(Hazard Ratio (95% CI)/*P* value) –/< 0.001 –/– 0.53 (0.32–0.89)/0.005 –/< 0.001 0.37 (0.18–0.77)/0.004 0.66 (0.32–1.37)/0.13 –/– 0.24 (0.10–0.58)/– 0.84 (0.43–1.67)/–

Table 1 (continued)

Author, year	Design (x)	Patients (*N*)	Time-frame	Location	Intervention	Comparator	Length of follow-up	Outcome measures	Intervention group outcome	Control group outcome	Effect size
Finkel et al. 2016 [3]	Multicenter open-label, dose-escalation phase II clinical trial (4)	20	05/2013–07/2014	USA, Canada	IT nusinersen (EqD) 6-12 mg ($n=4$) (6 mg d1,15,85, 12 mg d253 and then every 4 m) 12 mg ($n=16$) (12 mg, same schedule)	–	6–12 mg 9–32 m 12 mg 2–27 m (early study closure, intended 45 m)	Change from baseline in HINE-2[d] (improvement (*n*, *n* %)) Change from baseline in CHOP-INTEND[e] (mean change in points/improvement (*n*, *n* %)) Change from baseline in CMAP Peroneal nerve—TA[f] (mean change (mV)/improvement (*n*, *n* %)) Ulnar nerve—ADM (mean change (mV)/improvement (*n* %)) Median age at death or use of permanent assisted ventilation[g] (=age at probability of permanent ventilation-free-survival 0.5)	Overall: 16, 84 12 mg: 15, 100 Overall: + 11.5/14, 78 12 mg: + 15.2/12, 86 12 mg: 1.56/15, 100 12 mg: 0.62/12, 80 Not reached	–	$P=0.0002$ $P<0.0001$ $P=0.0080$/– $P=0.0013$/– $P<0.0001$ $=0.0103$
Chiriboga et al. 2016 [4]	Multicenter open-label, single escalating-dose phase I clinical trial (4)	28	11/2011–01/2013	USA	IT nusinersen 1 mg ($n=6$) 3 mg ($n=6$) 6 mg ($n=6$) 9 mg ($n=10$)	–	9–14 m	Mean change from baseline in HFMSE score at 1 m/3 m/9-14 m 1 mg (points) 3 mg (points) 6 mg (points) 9 mg (points (and in %)) PedsQL Measurement 4.0 Generic Core Scales in 9 mg group at 3 m (mean % change) PedsQL 3.0 Neuromuscular Model 9 mg group at 3 m (mean % change)	+ 1.0/NM/− 1.7 + 1.0/NM/+ 0.5 NM/+ 0.7/+ 2.5 NM/+ 3.1 (+ 17.6%)/+ 5.8 (+ 32.8%) Improvement 9.8% (patient), 8.4% (parent) Improvement 17.7% (patient), 4.6% (parent)	–	Not significant Not significant Not significant –/($P=0.016$)/($P=0.008$) Not significant Not significant

Data not included in the article were searched at clinicaltrials.gov

ADM abductor digiti minimi muscle, *CHOP-INTEND* Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders score, *CI* confidence interval, *CMAP* compound muscle action potential, *d* day, *EP* endpoint, *EqD* equivalent dose, *HFMSE* Hammersmith Functional Motor Scale-Expanded, *HINE-2* Section 2 on Hammersmith Infant Neurological Examination, *IT* intrathecal, *m* month, *N* number of patients, *NM* not measured, *PedsQL* Pediatric Quality of Life Inventory, *RULM* Revised Upper Limb Module Test, *TA* tibialis anterior muscle, *UK* United Kingdom, *USA* United States of America, *WHO* World Health Organization, *x* number of centers

[a]Response was defined as response in at least one category (+ ≥ 1 point/category or + ≥ 2 points for kicking) and more categories with improvement than worsening. The category 'voluntary grasp' was not taken into account

[b]Permanent ventilation was defined as the need for ≥ 16 h ventilation/day continuously for > 21 days in the absence of an acute reversible event OR tracheostomy

[c]Response was defined as an increase in the peroneal CMAP amplitude to at least 1 mV or maintenance of an amplitude ≥ 1 mV at the end-of-trial visit

[d]Improvement was defined as an increase from baseline of two milestones or more in category 'voluntary grasp' or 'ability to kick' or the achievement of pincer grasp or of touching toes or an increase in one milestone in any of the other 6 categories

[e]Improvement was defined as at least a four-point increase from baseline

[f]Improvement in peroneal nerve CMAP was defined as an increase of 0.5 mV in amplitude

[g]Permanent ventilation support was defined as the need for ≥ 16 h ventilation/day continuously for at least 14 days in the absence of an acute reversible illness OR tracheostomy

Table 2 Statements, recommendations, evidence and quality appraisal

Author, year	Quality of study EBRO	Classification of evidence AAN (Class)	Level of evidence of conclusion EBRO	Level of evidence Oxford (2009)	Grade of recommendation Oxford (2009)	Quality of evidence GRADE
A. Statements per article						
Motor function and motor-milestone development						
1. There is a significant and meaningful change from baseline in HFMSE score with improvement in children with later-onset SMA treated with intrathecal nusinersen 12 mg						
Mercuri et al. 2018 [1]	A2	I	2	1b	–	Moderate
2. There is a significant increase in the amount of children with later-onset SMA, treated with intrathecal nusinersen 12 mg, who have an improvement of ≥ 3 points in HFMSE score						
Mercuri et al. 2018 [1]	A2	I	2	1b	–	Moderate
3. There is no significant increase in the amount of children with later-onset SMA, treated with intrathecal nusinersen 12 mg, who achieve ≥ 1 new WHO motor milestone						
Mercuri et al. 2018 [1]	A2	II[b]	2	1b^{-}	–	Moderate
4. There is a significant increase in the amount of infants with early-onset SMA treated with intrathecal nusinersen 12 mg EqD, who have a motor-milestone response according to HINE-2						
Finkel et al. 2017 [2]	A2	I	2	1b$^{?}$	–	High
5. There is a significant increase in the amount of infants with early-onset SMA treated with intrathecal nusinersen 12 mg EqD, who have an improvement of ≥ 4 points on CHOP-INTEND score						
Finkel et al. 2017 [2]	A2	I	2	1b$^{?}$	–	Moderate
6. There is a significant change in the amount of infants with early-onset SMA, treated with intrathecal nusinersen 12 mg EqD or the combination of infants treated with 6-12 mg EqD and 12 mg nusinersen EqD, with improvement in HINE-2 score						
Finkel et al. 2016 [3]	B	III	3	3b	–	Very low
7. There is a significant increase in CHOP-INTEND score in infants with early-onset SMA, treated with intrathecal nusinersen 12 mg EqD or the combination of infants treated with 6-12 mg EqD and 12 mg nusinersen EqD						
Finkel et al. 2016 [3]	B	III	3	3b	–	Very low
8. There is a significant improvement in HFMSE score in children with later-onset SMA treated with a single dose of intrathecal nusinersen 9 mg						
Chiriboga et al. 2016 [4]	C	IV	3	4	–	Very low
Survival						
9. There is a significant increase in event-free survival in the amount of infants with early-onset SMA treated with intrathecal nusinersen						
Finkel et al. 2017 [2]	A2	I	2	1b^{-}	–	Moderate
10. There is a significant increase in survival in the amount of infants with early-onset SMA treated with intrathecal nusinersen						
Finkel et al. 2017 [2]	A2	I	2	1b^{-}	–	Moderate
11. There is no significant increase in the amount of infants with early-onset SMA treated with intrathecal nusinersen who have no permanent assisted ventilation						
Finkel et al. 2017 [2]	A2	I	2	1b^{-}	–	Moderate
12. Compared to a historical cohort [37], in infants with early-onset SMA, there is a significant increase in median age at death or permanent ventilation favoring treatment with intrathecal nusinersen (combination of infants treated wiht 6-12 mg EqD and 12 mg EqD)						
Finkel et al. 2016 [3]	B	III	3	3b	–	Very low
B. Overall statements						
Motor function and motor-milestone development						
1. Significant and meaningful improvement in motor function and achievement of development of motor milestones are seen in infants with SMA type 1 treated with intrathecal nusinersen 12 mg EqD						
Finkel et al. 2017 [2] Finkel et al. 2016 [3]	A2 C	I	2	1b$^{?}$	NA[a]	High
2. Significant and meaningful improvement in motor function and achievement of development of motor milestones is seen in children with later-onset SMA treated with intrathecal nusinersen 12 mg						
Mercuri et al. 2018 [1] Chiriboga et al. 2016 [4]	A2 C	I	2	1b	NA[a]	Moderate
Survival						
3. Survival and event-free survival are significantly increased in infants with SMA type 1 treated with intrathecal nusinersen 12 mg EqD						
Finkel et al. 2017 [2] Finkel et al. 2016 [3]	A2 C	I	2	1b^{-}	NA[a]	Moderate

Table 2 (continued)

AAN American Academy of Neurology, *CHOP-INTEND* Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders score, *EBRO* Evidence-Based Guideline Development, *GRADE* Grading of Recommendations Assessment, Development and Evaluation, *EqD* equivalent dose, *HFMSE* Hammersmith Functional Motor Scale-Expanded, *HINE-2* Section 2 on Hammersmith Infant Neurological Examination, *m* month, *NA* not applicable, *SMA* spinal muscular atrophy, *WHO* World Health Organization

$1b^{-}$: randomized controlled trial with wide confidence interval for the result

$1b^{?}$: no confidence interval given in the randomized controlled trial for the result

[a]Because only single studies of the same evidence level were found, measuring the grade of recommendation was not applicable

[b]Results of < 80% of patients

we show them together with the results as (AAN level of evidence, quality of evidence). Considerations for rating evidence along the GRADE tool are shown in supplementary table S3. All papers reported to receive funding for the conducted study and stated as conflicts of interest, for example, that the authors received grants, personal fees, held stock, were employees of the sponsor, but none of these are judged to be a major confounder.

Trial design

CHERISH TRIAL [1]—is a multicenter randomized, double-blind, sham-procedure-controlled phase-3 study that tested the clinical efficacy, safety, tolerability and pharmacokinetics of intrathecal nusinersen over 15 months in patients with later-onset SMA. There was actually a quadruple masking of the participants, care providers, investigator and outcome assessor. Sham kits for performing lumbar puncture by an unblinded dedicated personnel, who did otherwise not participate in the trial, were provided. Only patients with documented SMN1 mutations with onset of symptoms above the age of 6 months old, age 2–12 years old at screening, who could sit independently but had never reached the ability to walk independently and Hammersmith Functional Motor Scale-Expanded (HFMSE) ranging 10–54, were included. Patients were randomized in a 2:1 ratio to receive a dose of 12 mg intrathecal nusinersen or a sham-procedure four times over 15 months. Randomization was stratified according to age at screening (< 6 years vs. ≥ 6 years). A total of 126 patients were randomized, 84 in the intervention group, 42 in the control group.

ENDEAR TRIAL [2]—is a multicenter randomized, double-blind, sham-procedure-controlled phase-3 study that tested clinical efficacy, safety, tolerability and pharmacokinetics of intrathecal nusinersen over 13 months in patients with infantile-onset SMA. As in the CHERISH trial, there was a quadruple masking and a similar sham-procedure was used. Only patients with genetic documentation of SMA and SMN2 copy number of 2 with onset of symptoms after 1 week, but before 6 months and age less than 7 months at screening were included. Patients were randomized in a 2:1 ratio to receive an equivalent dose (EqD) of 12 mg intrathecal nusinersen or a sham-procedure six times. Randomization was stratified according to disease duration (≤ 12 weeks vs. > 12 weeks). A total of 121 patients were randomized, 80 in the intervention group, 41 in the control group.

Finkel et al. TRIAL [3]—is a multicenter open-label, dose-escalation phase-2 trial that tested the clinical efficacy of multiple doses of nusinersen (6 mg and 12 mg dose equivalents), safety, tolerability and pharmacokinetics of intrathecal nusinersen in patients with infantile-onset SMA. Only patients with genetic documentation of SMA with onset of symptoms between 3 weeks and 6 months were included. Twenty patients were selected. Four patients received an EqD of 6 mg intrathecal each three times over a 3-month 'loading dose' period and further in the maintenance dose period an EqD of 12 mg intrathecal every 4 months starting from about 8 months. Sixteen patients received an EqD of 12 mg intrathecal each time following the same schedule. Interim results were reported in the study which was about 18 months since the last subject was enrolled with follow-up ranging 9–32 months and 2–27 months in, respectively, the 6–12 mg group and 12 mg group. The intended follow-up stated in the trial protocol was about 45 months. Some reported outcomes were compared to subjects from a historical cohort [37].

Chiriboga et al. (2016) TRIAL [4]—is a multicenter open-label ascending single-dose phase-1 trial that tested the preliminary clinical efficacy, safety, tolerability and pharmacokinetics of intrathecal nusinersen in patients with later-onset SMA. Data included in the report are baseline evaluations for a follow-up study. Only patients with genetic documentation of SMA with age at screening between 2 and 14 years old were included. Twenty-eight patients were selected. Nusinersen 1 mg, 3 mg and 6 mg was administrated to six patients each time, and ten patients received nusinersen 9 mg.

Motor function and motor milestones

All of the reports evaluated the achievement of motor function and MM development [1–4]. Two of these studies could be classified as methodological quality level A2 [1, 2].

In the CHERISH trial, a pre-specified interim analysis of the primary endpoint was conducted when all children had

been enrolled for at least 6 months and at least 39 children had completed their 15-month assessment with the use of a multiple-imputation method to account for missing data. In this interim analysis, concerning 54 subjects with observed data, 35 and 19 in the intervention and control group, respectively, and 72 children with imputed data, respectively, 49 and 23, there was a least-squares mean increase from baseline in HFMSE in the intervention group (+4.0 points) and a least-squares mean decrease in the control group (−1.9 points). The significant between-group difference favoring nusinersen (least-squares mean difference in change 5.9 points; 95% confidence interval (CI) 3.7–8.1; $P<0.001$) prompted early termination of the trial (I, moderate). In the final analysis, also a significant difference in the proportion of subjects who achieved a 3-point or greater increase from baseline in HFMSE was shown (I, moderate). More than half of the patients in the treatment group had a clinically meaningful increase in HFMSE score of at least three points with greatest improvements in younger children and those who received treatment early. There was a non-significant difference in the achievement of new World Health Organization (WHO) MM (II, moderate) [1].

In the ENDEAR trial, a pre-specified interim analysis of the primary endpoint 'MM response' according to Section 2 on Hammersmith Infant Neurological Examination (HINE-2) score was conducted when approximately 80 infants had been enrolled for at least 6 months. In this analysis, concerning 78 subjects, 51 and 27 in the intervention and control group, respectively, a significantly higher percentage of infants in the nusinersen group had a MM response (41% vs. 0%, $P<0.001$) (I, high) which prompted early termination of the trial. In the final analysis, one secondary endpoint significantly favored nusinersen, namely response on Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score (71% vs. 3%, $P<0.001$) (I, moderate) [2].

In Finkel et al., a significant change in HINE-2 score for both cohorts combined and in the 12 mg group was described, $P=0.0002$ and $P<0.0001$, respectively (III, very low). CHOP-INTEND score showed a mean increase of 11.5 points (III, very low) [3]. The historical cohort [37] revealed a mean decline of 1.27 points per year from baseline (95% CI 0.21–2.33; $P=0.02$) [3].

In Chiriboga et al. (2016), a significant improvement in HFMSE in the 9 mg group at 85 days and at 9–14 months was noticed with mean increase in HFMSE +3.1 points or +17.6% ($P=0.016$) and +5.8 points or +32.8% ($P=0.008$) (IV, very low) [4].

Survival

Two studies assessed survival outcome measurements [2, 3], one of which was classified as methodological quality level A2 [2].

In the ENDEAR TRIAL, in the final analysis the primary endpoint 'event-free survival' was significantly better for the intervention group [61% vs. 32%; Hazard Ratio 0.53 (95% CI) 0.32–0.89; $P=0.005$] (I, moderate). This was most pronounced among infants with a disease duration at screening no longer than the median duration of 13.1 weeks, and a significantly lower percentage of infants in the treatment group had died. The secondary endpoint 'survival' was also significantly favoring nusinersen [84% vs. 61%; Hazard ratio 0.37 (95% CI) 0.18–0.77; $P=0.004$] (I, moderate). The secondary endpoint 'permanent ventilation' was not significantly different among patients treated with nusinersen and the control group (I, moderate) [2].

In Finkel et al., median age at death or to permanent ventilation was not reached. A differentiation in age at death or permanent ventilation was calculated by comparing infants with two copies of SMN2 ($n=17$) to infants with two copies from the historical cohort [37] and was significant ($P=0.0014$) (III, very low) [3].

Safety

The two RCTs conducted safety analysis in all patients who had been randomized and underwent at least one study procedure. None of the RCTs reported new safety concerns. The

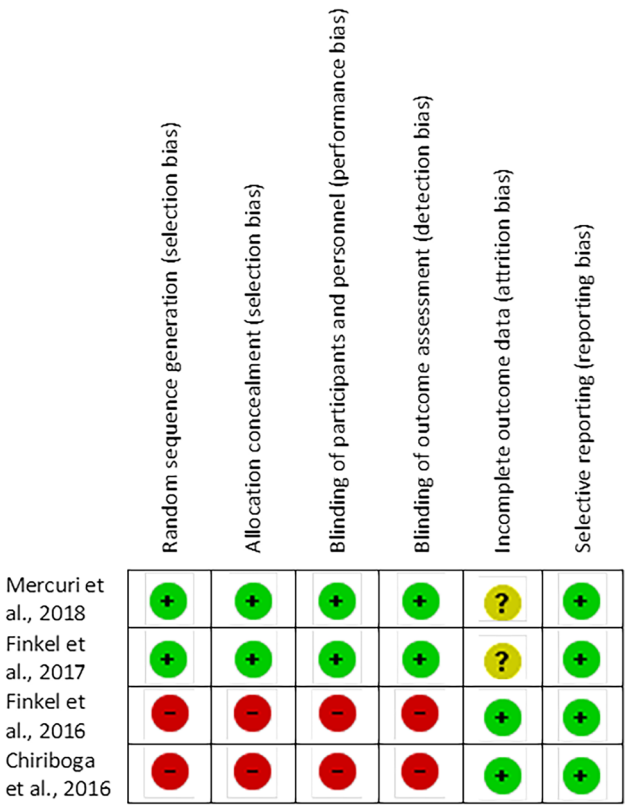

Fig. 2 Risk of bias summary

overall incidence of adverse events (AEs) and type of AEs were similar in the treatment and control group. The majority of AEs were deemed unlikely or not related to study treatment and could be explained by another cause such as SMA or concomitant therapy for another disorder [1, 2]. In the CHERISH trial, back pain and headache occurred in up to one-third of children who underwent lumbar puncture, consistent with the incidence reported in literature. Serious AEs occurred in 17% of the patients treated with nusinersen and in 29% in the control group. No child discontinued treatment or was withdrawn from the trial because of an AE [1]. In the ENDEAR trial, serious AEs occurred in 76% vs. 95% of, respectively, the intervention and control group. Sixteen percent of subjects treated with nusinersen vs. 39% of patients who underwent the sham-procedure had an AE leading to discontinuation of the trial, and all these AEs had fatal outcomes. The most common AE with fatal outcome was a respiratory disorder, plausibly linked to SMA [2]. The Finkel et al. and Chiriboga et al. trials reported good tolerability and no safety concerns [3, 4]. Overall, the most commonly reported AEs were possibly related to the lumbar puncture, namely backache, headache and vomiting [2, 4].

Discussion

Recent discovery of nusinersen provides hope for optimizing treatment in patients with SMA. So far, the literature on efficacy is scarce. In this review four papers were witheld, including two RCTs. Because of heterogeneity in design, population and outcome measures, no meta-analysis could be performed. Due to different definitions of response, this also hinders comparison of outcomes between trials. For example, the ENDEAR trial [2] did not include voluntary grasp in the HINE-2 assessment because none of the incremental changes in this motor function require movement against gravity and voluntary grasp is more developmentally based. This category was included in the assessment of HINE-2 in Finkel et al. [3].

Risk of bias analysis is shown in Fig. 2. Inherent to the open-label design there is high risk for selection, performance and detection bias in the open-label trials [3, 4]. There is an unclear risk of attrition bias in the RCTs because of early termination of these trials [1, 2]. In Finkel et al., results from an interim analysis are given with no important missing data at the time of this analysis [3].

Significant and meaningful improvement in motor function and achievement of development of MM are seen in infants with SMA type 1 treated with intrathecal nusinersen 12 mg EqD (I, high). Significant and meaningful improvement in motor function and achievement of development of MM are seen in children with later-onset SMA treated with intrathecal nusinersen 12 mg (I, moderate). Though most of information came from an RCT [2], quality of recommendation was judged to be moderate because of imprecision due to appreciable benefit that warranted downgrading because of relative risk increase greater than 25% (Tables S3.2, S3.3, S3.14) and a CI containing no meaningful effect (Table S3.1). Survival and event-free survival are significantly increased in infants with SMA type 1 treated with intrathecal nusinersen 12 mg EqD (I, moderate). Though most of information came from an RCT [2], quality of recommendation was judged to be moderate because of imprecision due to appreciable benefit that warranted downgrading because of relative risk increase greater than 25% (Tables S3.9, S3.10, S3.15) and a CI containing inconsistent effects (Table S3.11). Evidence from the included non-RCTs [3, 4] was judged to be of very low quality and this because of imprecision due to the low number of participants.

A similar search was also performed by the Brazilian Medical Association [28]. By grading the level of evidence, they considered major inconsistency in the CHERISH trial because of conflicting results with improvement in the motor function in HFMSE and Revised Upper Limb Module Test (RULM) scores, but no differences in new WHO milestones. RULM and HFMSE are broader scales with different grades per item, and RULM is used to investigate upper limb function. For example, a maximal gain in rolling from prone to supine and/or lifting the head from prone leads to a significant improvement in HFMSE, but does not alter development of WHO MM. The same consideration can be made for the RULM scale. Both scales are validated for their use in SMA outcome measurement, whereas development of WHO MM not [38–41]. For this reason, we did not consider it an inconsistent finding, but it stipulates the need for the use of validated and similar outcome measurements in different trials, also with the use of the same definitions of 'response.'

Limitations

Although several statements are level I recommendations, we think these findings should be scrutinized. Both RCTs were terminated early because the primary endpoint at the pre-specified interim analysis was reached and found statistically significant. A multiple-imputation method to account for missing data was used and included 54 (35:19) patients in the CHERISH trial. In the CHERISH trial, a sample size of 117 patients was estimated to give the trial at least 90% power to detect a mean difference of three points in HFMSE score. In the final analysis, complete observational data were available for 100 patients. The data imputation method was used to include 126 patients in total. Because of the lack of observational data, the real effect size of treatment is unclear. Based on statistical considerations, significance of the primary endpoints was not evaluated in the final analysis in both trials, and using a hierarchical strategy no significance

analyses were performed on all secondary endpoints [1, 2]. Because of strict inclusion criteria, the investigated population might be younger and more homogenous and therefore not representative for the overall group of SMA patients [1]. Limitations of the non-RCTs [3, 4] are, besides the study design, the small number of included patients and relatively short duration of follow-up [3, 4].

Data on differentiation in age at death or permanent ventilation, compared to a historical cohort [37], should be interpreted cautiously because of this relatively small open-label design, and we were not able to compare baseline characteristics because of insufficient information [3]. Possibly there was a later age at onset of symptoms and of diagnosis as well as more patients receiving nutritional support in the historical cohort [3, 37]. In both cohorts, the SMA standard of care guidelines published in 2007 were used [42]. The provided standard of care is related to the outcome of SMA patients [43, 44]. Enrollment of patients in the historical cohort was between May 2005 and April 2007 [37].

This review has several limitations. As a loading dose for intrathecal nusinersen was required in the previous studies and because of long half-life time of the drug, one should consider a minimum follow-up length, which was not pre-specified in our search strategy. Though an exact age category was not pre-specified, a younger population was expected because of the natural history of the disease. We did not include trial registries, expert opinions or searched gray literature. The search, data extraction and evaluation of the included trials were only performed by the first author.

Impact of key findings

There is level I evidence for recommendation of intrathecal nusinersen 12 mg or 12 mg EqD in patients with early- and later-onset SMA to obtain improvement in motor function and to develop MM. There is also level I evidence that this treatment prolongs event-free survival and survival in patients with SMA type 1. We suggest that nusinersen should be administered in patients with early- and later-onset SMA as early as diagnosis is sure. This emphasizes the importance for early diagnosis. As cost price is high, in Belgium 88,298 euros per dose of 12 mg, in the USA $125,000 [45], this challenges health institutions and insurance companies. Currently, there is insufficient evidence of efficacy in SMA types 3 and 4, or start of treatment in adults. The clinical spectrum of patients with SMA is also broader than that of the included patients in the studies. Therefore, there is need for studies with broader inclusion criteria to cover the more heterogeneous population, also including more different SMA types and age categories, including adults. The financial burden should be further clarified. Because of the importance of early treatment, awareness of SMA is needed at birth.

Conclusions

Treatment with intrathecal nusinersen in patients with early- and later-onset SMA results in significant and clinically meaningful improvement in motor function (I, high in SMA type 1, moderate in later-onset SMA)—but does not restore age-appropriate function—with better improvement if started earlier in disease course and results in prolonged event-free survival and survival in patients with SMA type 1 (I, moderate). Intrathecal nusinersen has an acceptable safety and tolerability profile. Further trials regarding long-term effects and safety aspects as well as trials including broader SMA and age categories are required and ongoing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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