The Impact of Nusinersen and Risdiplam on Motor Function for Spinal Muscular Atrophy Type 2 and 3: A Meta-Analysis

Bo Chen[1], Yuanlin Gong[2] and Tengteng Zhou[1]

[1]*Zhihui Medicine and Technology College, Dazhou Vocational and Technical College, Dazhou, China*
[2]*Academic Affairs office, Dazhou Vocational and Technical College, Dazhou, China*

ABSTRACT

Spinal muscular atrophy (SMA) is a prevalent paediatric neuromuscular disorder characterised by muscle weakness and atrophy resulting from degeneration of spinal cord anterior horn α motor neurons. Gene therapy formulations exhibit varying benefits and limitations, driving the need for patient-friendly treatment options tailored to specific populations. The objective of this meta-analysis was to assess the effectiveness of gene therapy for motor function in children with SMA. The analysis encompassed a total of 719 participants from six randomised controlled trials (RCTs) conducted between 2017 and 2023. Among the studies, one demonstrated a significant and large standardised effect size (Cohen's *d*) favouring nusinersen in terms of Hammersmith Functional Motor Scale – Expanded (HFMSE) (d = 0.97) and revised upper limb module (RULM) (d = 0.96). Additionally, another study showed a moderate standardised effect size (Cohen's d) in favour of nusinersen concerning Hammersmith Infant Neurological Examination-Section 2 (HINE-2) (d = 0.48). However, it is important to note that further research with a longer duration of observation is required to strengthen the evidence.

Key Words: *Spinal muscular atrophy, Nusinersen, Risdiplam, Motor function, Cohen's d.*

How to cite this article: Chen B, Gong Y, Zhou T. The Impact of Nusinersen and Risdiplam on Motor Function for Spinal Muscular Atrophy Type 2 and 3: A Meta-Analysis. *J Coll Physicians Surg Pak* 2024; **34(08)**:948-955.

INTRODUCTION

Spinal muscular atrophy (SMA) is an inherited neuromuscular disease caused by a mutation in the *survival motor neuron gene 1 (SMN1)* in, which leads to a functional defect in the survival motor neuron (SMN) protein. It is characterised by muscular weakness and atrophy due to degeneration and loss of α motor neurons in the anterior horn of the spinal cord.[1] SMA is a significant genetic factor associated with infant mortality, with an estimated prevalence ranging from 8.5 to 10.3 cases per 100,000 live births in the absence of intervention.[2] Recently, disease-modifying treatments have been reported effective for improving symptoms and increasing survival rates of up to 70%.[3]

With advancements in molecular medicine, various therapeutic interventions have been explored to ameliorate the impact of SMA, including the use of nusinersen, risdiplam, AAV9 vector and Onasemnogene Abeparvovec.[4]

Correspondence to: Dr. Yuanlin Gong, Academic Affairs Office, Dazhou Vocational and Technical College, Dazhou, China
E-mail: 93334581@qq.com

Received: May 28, 2023; Revised: December 26, 2023; Accepted: February 20, 2024
DOI: https://doi.org/10.29271/jcpsp.2024.08.948

Nusinersen and risdiplam were approved for use in China in 2022. Nusinersen, an antisense oligonucleotide drug, functions by modifying pre-mRNA splicing to enhance the production of SMN protein, ultimately contributing to increased SMN protein production which leads to an elevation in the levels of functional, full-length SMN proteins.[5] Risdiplam, an *SMN2* gene splicing modifier, effectively increases SMN protein levels. This orally-administered drug is recommended to be taken daily after meals at a consistent time. Immediate consumption of the medication upon drawing it into the oral syringe is advised.[6]

Clinical trials have demonstrated the effectiveness and safety of these therapeutic interventions for SMA patients, and they have also exhibited distinct advantages. Motor outcomes demonstrated a significant improvement in the early nusinersen group (93%), whereas the later treatment group showed motor improvement in only 13 out of 29 patients.[7] On the other hand, the administration of risdiplam has been associated with the occurrence of adverse events, particularly in the respiratory domain. The most commonly reported serious adverse events predominantly encompassed respiratory complications, with pneumonia accounting for 32% of the cases, followed by bronchiolitis (5%), respiratory failure (5%), and hypotonia (5%). Patients with hepatic impairment are advised to avoid the use of risdiplam.[8]

Nusinersen, administered through intrathecal injection,[9] applied for presymptomatic, infantile-onset, later-onset SMA,[10-12] populations include ambulant and non-ambulant patients in SMA

Type 1-4. Risdiplam, offered orally to patients older than 2 months,[13] aims to mitigate administration challenges but may encounter issues related to patient adherence to a consistent oral regimen. Both treatments require prolonged and frequent administration, imposing a considerable burden on patients and caregivers. Additionally, the high cost of these therapies raises concerns about their accessibility, particularly in the regions with limited healthcare resources. Furthermore, adverse effects associated with nusinersen and risdiplam necessitate continuous monitoring and management, emphasising the importance of a comprehensive understanding of their safety profiles. Long-term data on the sustained efficacy and safety of these medicines are still evolving, and ongoing research is crucial to uncover their impact over extended periods.

Despite the promising results from clinical trials, gaps in the existing literature warrant further exploration. Real-world effectiveness studies are limited, and there is a need for more comprehensive evidence beyond the controlled environments of clinical trials. Comparative studies between nusinersen and risdiplam are scarce, hindering a detailed understanding of their relative efficacy and tolerability. Research on the impact of these treatments across diverse patient populations, encompassing different SMA types and genetic profiles, is lacking. The optimal timing for initiating the treatment remains unclear, requiring more focused investigations to determine the most effective intervention window. Moreover, comprehensive studies exploring the health economic implications and quality of life improvements associated with nusinersen and risdiplam are essential for a holistic assessment of their value in managing SMA. Long-term outcomes, encompassing motor function, survival rates, and quality of life, need more extensive investigations to provide a clearer picture of the lasting effects of these treatments on individuals with SMA.

Hence, the aim of this meta-analysis was to evaluate the efficacy of nusinersen and risdiplam in enhancing motor function among children with spinal muscular atrophy Type 2 and 3.

METHODOLOGY

This meta-analysis was registered following the study protocol with INPLASY, named International Platform of Registered Systematic Review and Meta-Analysis Protocols (Number: INPLASY202350072). This has been reported under the guidance of Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[14] Appropriate patients / population, intervention, comparison, and outcomes (PICO) regulations were established in advance[15] as participants (children diagnosed with 5q SMA under 18 years); interventions (disease-modifying treatment); and comparison (physiotherapy, respiratory and nutritional support therapy, conventional therapy, and combination treatment or placebo); and outcomes (valid and reliable outcome measures created for motor function or upper limb function in SMA). Only Phase III randomised controlled trials, published in English were included in the study, provided that they explicitly mentioned appropriate ethics approval. Studies were excluded if they were patients who complicated any other neuromuscular disorders or combined additional neurological conditions (e.g. XL-SMA or SMAX2, SMARD1, congenital myasthenic syndromes, muscular dystrophy, and multi-system disorders). Conference abstracts, *in vitro* and *in vivo* experimental studies, grey literature, and unpublished studies were also excluded. Full articles that were not available were also excluded.

An extensive literature search was carried out on the following eight online bibliographic databases, involving PubMed, Web of Science, IEEE Electronic Library, Scopus, EMBASE, the Cochrane Library, and CINAHL plus databases, till May 2023. The search terms applied were spinal muscular atrophy or SMA, disease-modifying treatment or nusinersen or risdiplam, and motor function, or upper limb function, or lower limb function, or motor milestone, or revised upper limb module (RULM), or motor function measure, or Hammersmith Functional Motor Scale – Expanded, (HFMSE) or Hammersmith Infant Neurological Examination – Section 2 (HINE), or Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, or 6-minute walk test or their related abbreviations.

The full searches for different databases were adapted appropriately such as the application of MeSH terms or free text (e.g. spinal muscular atrophy, motor function, upper limb function, disease-modifying treatment etc.), and their synonyms. Additionally, a hand search of the reference lists in the included study and relevant systematic review were also performed. The authors contacted corresponding authors of relevant publications if the full articles were not available.

To ensure accuracy, duplicates were manually eliminated from the search results. Following this, two authors (BC and TZ) independently assessed the remaining reports for eligibility, adhering to the predefined inclusion / exclusion criteria. The screening process involved firstly evaluating the titles, then abstracts, and lastly full text of the articles. In cases of disagreement, resolutions were reached through discussions involving the corresponding author (YG). The inclusion criteria were established as patients had a confirmed diagnosis of 5q SMA;[16] interventions involved nusinersen and risdiplam;[17] comparators were placebo or other basic treatments; and primary outcomes measured were the upper limb function measured by RULM, motor function measured by HFMSE, motor function measure (MFM), 6-minute walk test, adverse events.[18] Studies were excluded if they were not randomised controlled clinical trials; with other neurodegeneration diseases; not published in English, or were animal studies or studies for which full articles were not available.

The selection of outcome measures for assessing motor function in SMA Type 2 and 3 encompasses a comprehensive set of tools, including the HFMSE, RULM, MFM, and the 6-minute walk test. The HFMSE, a versatile scale assessing overall motor function, provides a holistic evaluation applicable across age groups.[18]

The RULM, designed for upper limb assessment, focuses on fine motor skills crucial for daily activities.[19] The MFM's multidimensional approach covers a spectrum of motor activities, ensuring a nuanced understanding of SMA-related challenges.[20] Additionally, the inclusion of the 6-minute walk test addresses the assessment of ambulatory function, providing valuable insights into the endurance and walking capacity of individuals with SMA. This comprehensive toolkit of outcome measures enhances the sensitivity of the evaluation, allowing the study to discern meaningful changes in motor function resulting from interventions such as nusinersen and risdiplam.

Data extraction in the included studies were independently carried out by two authors. The predetermined extraction form encompassed research source; population characteristics, including sample size, age, gender, and SMA subtype; details of treatment, including type, duration, dose, and frequency; study outcomes and duration of follow-up; and information on adverse events, specifying type and frequency. In case of any missing data, the correspondence email as a mean of communication with original authors, was executed. In case of discrepancies, discussions or consultations with the corresponding author (YG) were employed to achieve resolution.

For the sake of a widespread assessment of the eligible studies, two authors (BC and YG) separately judged the methodological quality of included articles through the Cochrane Collaboration's risk of bias tool 2 (ROB 2).[21] The tool used in this study facilitated the evaluation of five distinct domains for assessing bias as randomisation process bias, blinding process, improper handling of missing data, outcomes assessment, and as a result of selective reported results. Additionally, the tool provided a thorough measurement of the risk of bias. In instances where data were found to be missing, the authors of the included studies were contacted to provide supplementary sources. The data obtained from ROB2 assessment were inputted into RevMan Web (available from: http://revman.cochrane.org/#/myReviews), which facilitated the generation of visual representations depicting the results.

Meta-analyses were carried out *via* Review Manager Version 5.1, the Cochrane Collaboration Software, following the synthesis of all the available data. Weighted mean differences were applied for continuous outcomes, while odds ratios were employed for dichotomous outcomes. A random-effects model was applied if a significant statistical heterogeneity was noted ($I^2 \geq 50\%$, $p < 0.10$). Conversely, a fixed-effect model was used if no heterogeneity was recognised ($I^2 < 50\%$, $p > 0.10$). For two-group studies, Cohen's *d* was used to express standardised effect sizes, representing the difference in pooled standard deviation units. The formula is:

$$d = \frac{\bar{X}_1 - \bar{X}_2}{s}$$

Where x_1 and x_2 are the means of the two groups being compared, *s* is the pooled standard deviation. Specific thresholds were employed to categorise effect sizes as small (0.2), medium (0.5), and large (0.8).

RESULTS

The initial search yielded 1,988 search hits from seven online databases and other sources, resulting in 1,647 remaining records after removing duplicates. Subsequently, 1,382 papers were excluded during the screening process based on an assessment of titles and abstracts, as they were deemed irrelevant to the research objectives. After a thorough examination of the full-text articles in accordance with the selection criteria, five eligible studies[11,13,22-24] were identified and included for the quality assessment and subsequent data synthesis. The PRISMA flow diagram (Figure 1) provides a comprehensive summary of the screening process.

The systematic review encompassed a total of six studies, involving a combined participant count of 719 individuals. The sample sizes in the studies varied, ranging from 21 to 240 participants. In the control groups, a total of 273 participants were randomised, and results from 267 participants were analysed. In the intervention groups, 434 participants were randomised, and results from 429 participants were analysed. Comprehensive information regarding participant characteristics, includ-ing age, gender, SMA type, and group allocation, can be found in Table I.

The application of the ROB 2 tool revealed the presence of bias in all the included studies, as illustrated in Figure 2 (A and B). Regarding the assessment of selection bias, a majority of the studies (five out of six) were deemed to have an unclear risk due to the absence of reported allocation concealment procedures. Most studies were judged as a low-risk performance and detection bias. Overall, The Cochrane ROB 2 tool revealed that 50% of the included studies exhibited a high risk of bias, while the remaining studies were found to have varying degrees of concerns in terms of bias.

Across the studies, a variety of MFM were employed for different SMA subtypes. The treatment effect between groups, expressed as the mean change from baseline, along with the corresponding standardised effect sizes, are presented in Table II.

Two types of gene therapy were administrated across the six studies, with three of the studies (268 participants) involving nusinersen intrathecal injection and three risdiplam (451 participants) *via* oral. Four of these studies performed an outcome measure for upper limb function, including SMA Type 2 and 3. Two of these studies conducted an outcome measure for motor milestone, including SMA Type 1 and 2. All the studies included different outcome measures for motor function according to the motor ability of the participants. The standardised effect sizes (*d*) for these studies ranged from 0.03 related to MFM to 0.97 related to HFMSE.

All the studies presented the mean change from baseline of outcome measures instead of mean (SD). The meta-analysis showed that motor function in the control group decreased significantly, while increased in the treatment group (Figure 3). Outcomes in control group degraded in terms of MFM (Figure 3A), HFMSE (Figure 3B), HINE-2 (Figure 3C), and RULM (Figure 3D).

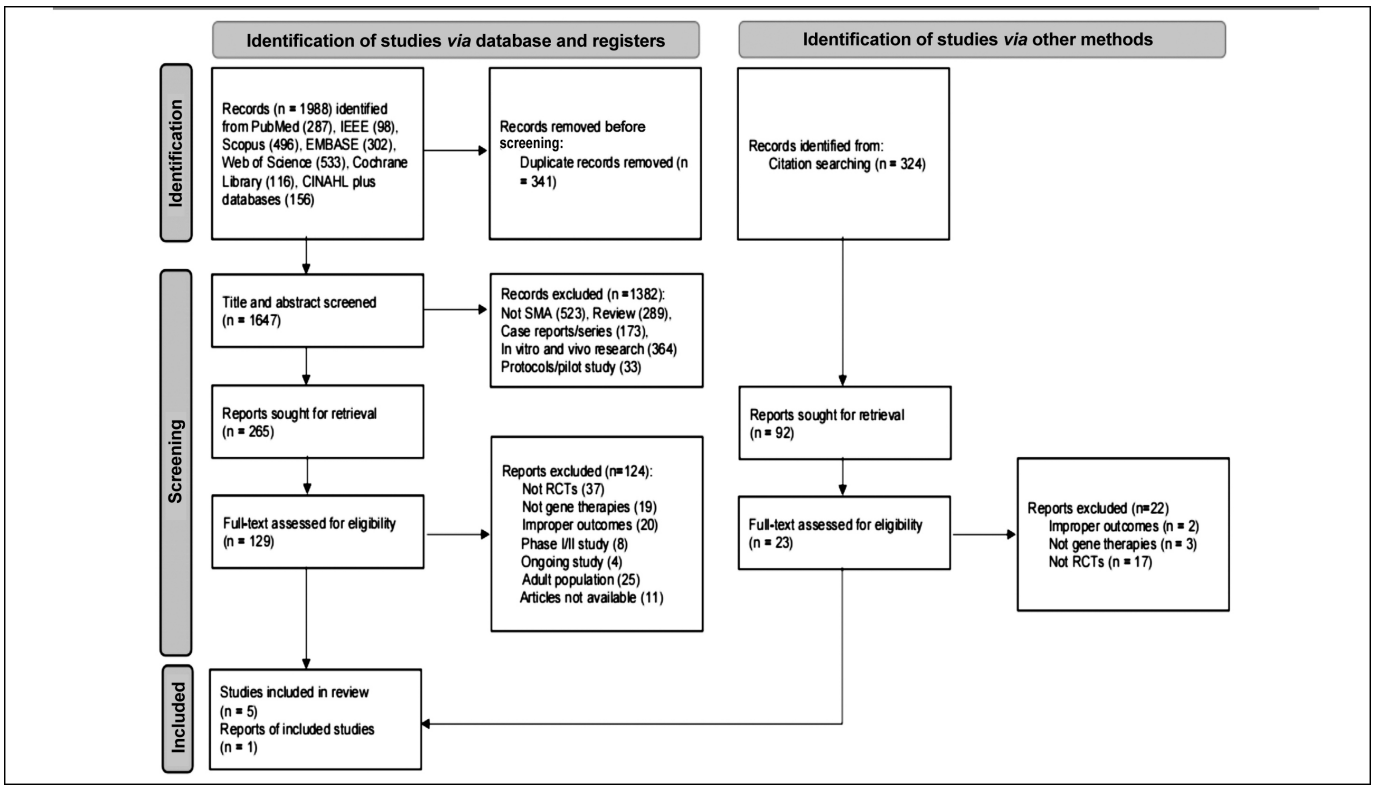

Figure 1: Flow diagram of screening and identifying process of studies.

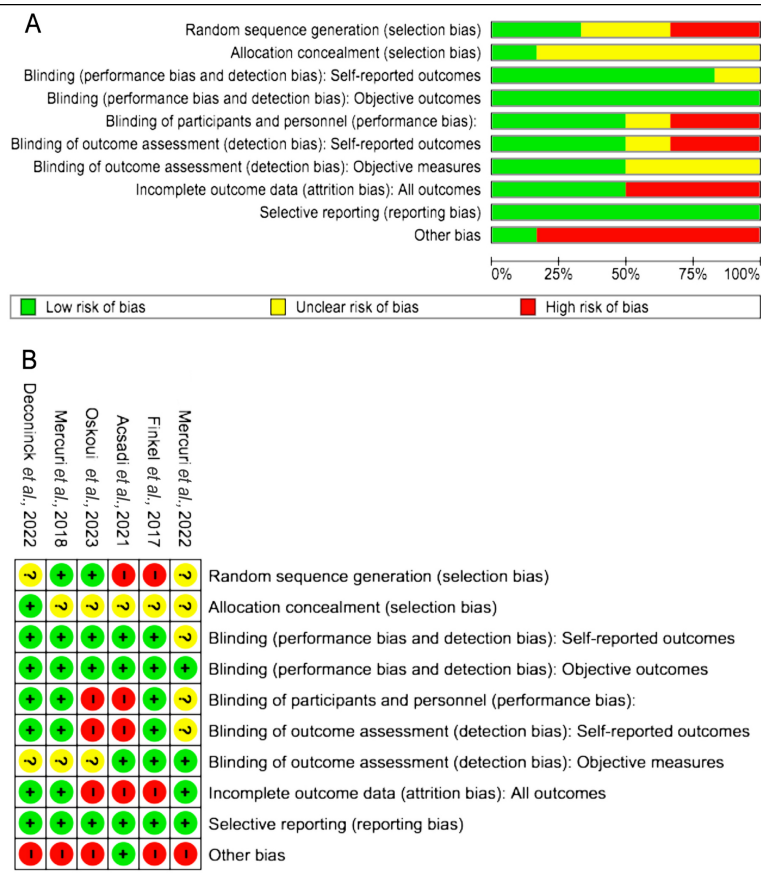

Figure 2: Risk of bias assessment for the involved studies. (A) Risk of bias graph: The percentages indicating determined on individual risk of bias item across the eligible studies. (B) Risk of bias summary: Determined on individual risk of bias item for each article. +, low-risk of bias; -, high-risk of bias; ?, unclear risk of bias.[24]

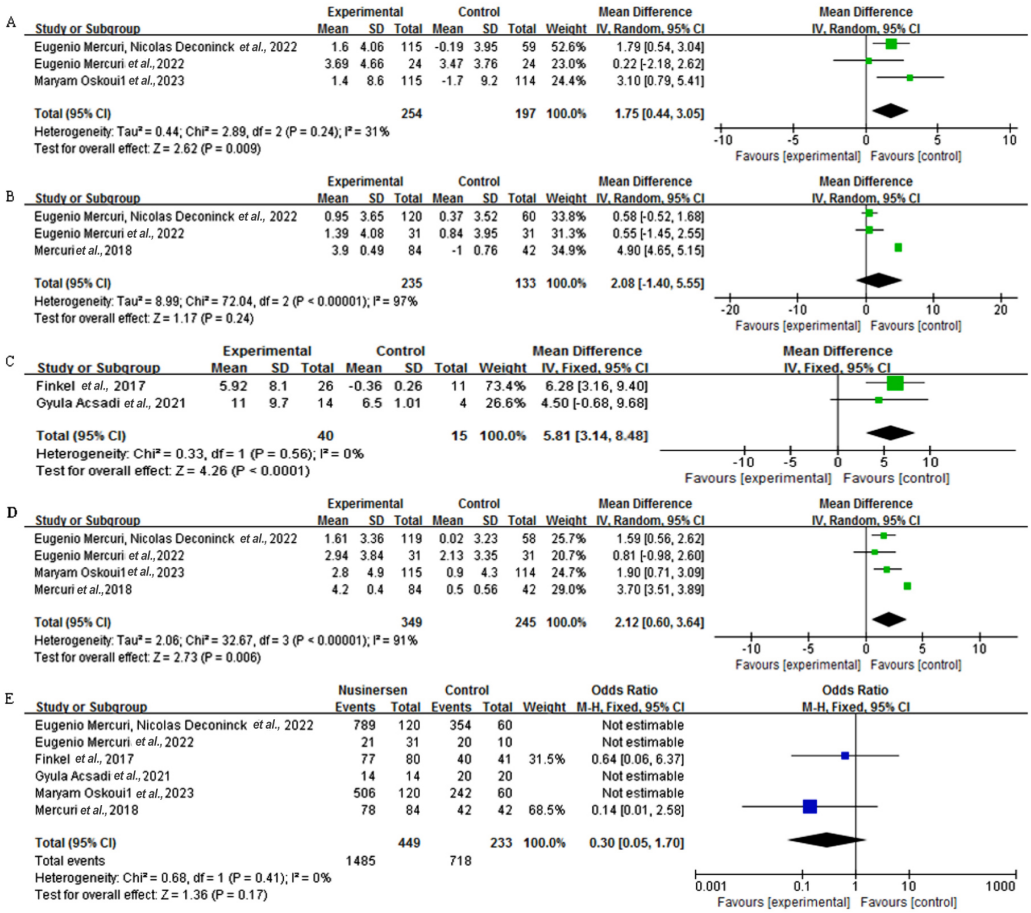

Figure 3: Efficacy and adverse events of nusinersen and risdiplam. (A) MFM, Motor function measure; (B) HFMSE, Hammersmith functional motor scale-expanded; (C) HINE-2, Hammersmith infant neurological examination-2; (D) Revised upper limb module; (E) Adverse events.

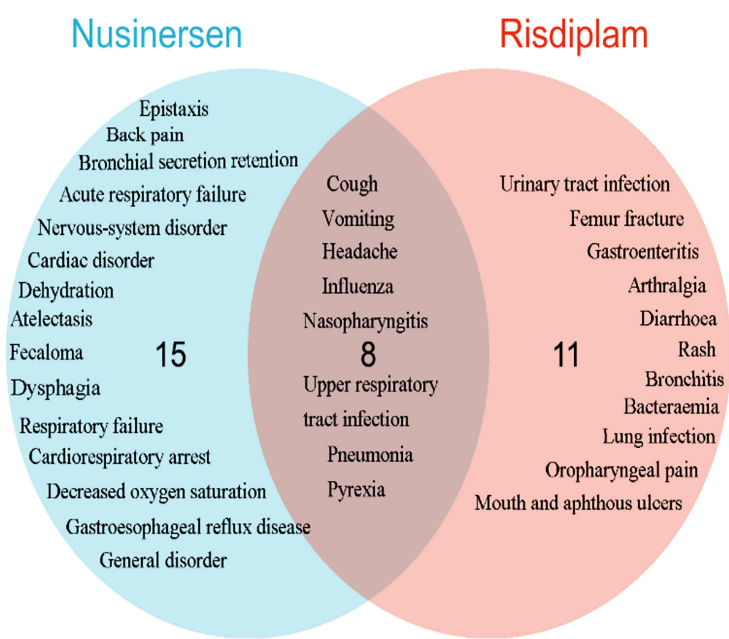

Figure 4: Summary of adverse events.

Table I: Characteristics of the included studies.

Included studies	Sample sizes	No. of participants Gender M / F	Age mean / median		SMA type	Intervention	Duration of treatment (months)	Outcomes
		Treatment	Control	Treatment	Control			
Mercuri *et al*., 2018	126	84 38/46	42 21/21	4 years	3 years	2	Nusinersen	9	HFMSE WHO RULM
Finkel *et al*., 2017	121	80 37/43	40 16/24	5 months	6 months	2	Nusinersen	9	CHOP INTEND
Acsadi *et al*., 2021	21	14 9/5	7 2/5	16 months	18 months	2	Nusinersen	24	HINE-2
Mercuri *et al*., 2022	31	21	10	5 years		2, 3	Risdiplam	24	MFM RULM HFMSE
Deconinck *et al*., 2022	180	120 59/61	60 30/30	9 years	9 years	3	Risdiplam	24	MFM RULM HFMSE
Oskoui *et al*., 2023	240	115 55/60	114 52/62	10 years	8 years	2, 3	Risdiplam	24	MFM RULM HFMSE

Table II: Estimates of treatment effect and standardised effect sizes.

Study	Group (n)	Outcome measure	Mean change from baseline; mean (SD)	Standardised effect size
Mercuri *et al*., 2018	1. Experimental- nusinersen (84) 2. Control-sham procedure (42)	HFMSE	3.9 (0.49) -1 (0.76)	*d* = 0.97
		RULM	4.2 (0.4) 0.5 (0.56)	*d* = 0.96
Finkel *et al*., 2017	1. Experimental- nusinersen (26) 2. Control-sham procedure (11)	HINE-2	5.92 (8.1) -0.36 (0.26)	*d* = 0.48
Mercuri *et al*., 2022	1. Experimental- risdiplam 24m 2. Control-risdiplam 12m	MFM	3.69 (4.66) 3.47 (3.76)	*d* = 0.03
		RULM	2.94 (3.84) 2.13 (3.35)	*d* = 0.11
		HFMSE	1.39 (4.08) 0.84 (3.95)	*d* = 0.06
Acsadi *et al*., 2021	1. Experimental- nusinersen (14) 2. Control-sham procedure (4)	HINE-2	11 (9.7) 6.5 (1.01)	*d* = 0.31
Mercuri *et al*., 2022	1. Experimental- risdiplam (115) 2. Control-placebo (59)	MFM	1.36 (4.06) -0.19 (3.95)	*d* = 0.19
	1. Experimental- risdiplam (119) 2. Control-placebo (58)	RULM	1.61 (3.36) 0.02 (3.23)	*d* = 0.23
	1. Experimental- risdiplam (120) 2. Control-placebo (60)	HFMSE	0.95 (3.65) 0.37 (3.52)	*d* = 0.08
Oskoui *et al*., 2023	1. Experimental- risdiplam (115) 2. Control-placebo (114)	MFM	1.4 (8.6) -1.7 (9.2)	*d* = 0.17
		RULM	2.8 (4.9) 0.9 (4.3)	*d* = 0.21

d = Cohen's d standardised effect size, SD = Standard deviation, m = Month, HFMSE = Hammersmith functional motor scale–expanded, RULM = Revised upper limb module, MFM = Motor function measure, HINE-2 = Hammersmith Infant Neurological Examination Section-2.

Both the treatments were presented for SMA safety, no significant differences in the adverse events between nusinersen and risdiplam were observed (WMD = 0.3, 95% CI = 0.05 to 1.7, p >0.05, Figure 3E). Adverse events of nusinersen and risdiplam and their common symptoms are presented in Figure 4.

DISCUSSION

This current systematic review and meta-analysis integrated the latest five years of RCTs to provide evidence for the efficacy and safety of nusinersen and risdiplam for motor function in children with SMA Type 2 and 3. The results showed that nusinersen and risdiplam were effective for the improvement of motor function in SMA such as standing and walking. Nusinersen has been particularly observed in improving upper limb function in the affected individuals. The observed improvements may have broader implications for functional independence. Enhanced upper limb function, as assessed by the RULM, is particularly crucial for tasks involving fine motor skills, such as self-care activities and manipulation of objects. Population's disease duration in the studies ranges from 13 weeks to 40 months. Long duration of disease leads to degenerative joint structure and muscle function, which may lead to less treatment effects. The incidence of adverse events after nusinersen and risdiplam was low, mild, self-limiting, and comparable to that of conventional treatments or placebo.

The observed improvements in motor function, as evidenced by changes in outcome measures, such as the HFMSE, RULM, and MFM, hold significant clinical implications for the quality of life and functional independence of children with spinal muscular atrophy. The enhancements in motor function suggest a potential positive impact on the overall quality of

life for these children. Improved motor abilities can contribute to increased autonomy in daily activities, fostering a sense of accomplishment and reducing dependence on caregivers. This, in turn, may lead to improved psycho-social well-being as children experience greater engagement in social interactions and recreational activities.

These findings can guide clinicians and policymakers in several ways. Firstly, they underscore the importance of considering a multi-dimensional approach to spinal muscular atrophy treatment, addressing not only motor function but also factors such as quality of life and functional independence. Clinicians may find value in tailoring interventions to individual needs, incorporating a combination of therapies that target various aspects of motor function. It offers policymakers evidence to inform decisions related to treatment access and healthcare planning.

Despite the promising results, the quality of the included RCTs was moderate, with a low risk of bias, particularly for blinding and patients' self-reporting outcomes. Limitations includes the short-term follow-up stages, which may limit the ability to capture long-term effects, particularly for interventions with prolonged treatment regimens. Variations in therapies and patient populations introduce heterogeneity that might impact the generalisability of the results. Furthermore, the study acknowledges a moderate quality of the included randomised controlled trials, particularly concerning the risk of bias. A more in-depth exploration of the specific biases identified and their potential impact on the findings is warranted. Therefore, further well-designed RCTs with a long-term follow-up period are required to support the efficacy and safety and to establish the optimal doses and treatment regimens of nusinersen and risdiplam in spinal muscular atrophy. Future studies should focus on new phenotype and continuous improvement may emerge with long-term intervention. Based on this study's findings, the authors recommend the inclusion of physiotherapy in the management of spinal muscular atrophy to prevent joint contracture following disease onset.

CONCLUSION

This study provides evidence for the efficacy and safety of nusinersen and risdiplam for motor function in children with SMA Type 2 and 3. These findings suggest that nusinersen could be an optimal treatment in the improvement of upper limb function. The results of this study provide a valuable resource for clinicians, researchers, and policymakers to inform the development of evidence-based guidelines for the use of nusinersen and risdiplam for motor function in SMA.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
BC: Study planning, research process, and manuscript writing.
TZ: Literature search, data extraction, and quality assessment.
YG: Resolving discrepancies and offering valuable critique and feedback on the manuscript.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Grunseich C, Fischbeck KH. Spinal and bulbar muscular atrophy. *Neurol Clin* 2015; **33(4)**:847-54. doi: 10.1016/j.ncl.2015.07.002.
2. Lally C, Jones C, Farwell W, Reyna SP, Cook SF, Flanders WD. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. *Orphanet J Rare Dis* 2017; **12(1)**:175. doi: 10.1186/s13023-017-0724-z.
3. Ogbonmide T, Rathore R, Rangrej SB, Hutchinson S, Lewis M, Ojilere S, *et al*. Gene therapy for spinal muscular atrophy (SMA): A review of current challenges and safety considerations for onasemnogene abeparvovec (zolgen-sma). *Cureus* 2023; **15(3)**:e36197. doi: 10.7759/cureus.36197.
4. Pattali R, Mou Y, Li XJ. AAV9 vector: A novel modality in gene therapy for spinal muscular atrophy. *Gene Ther* 2019; **26(7-8)**:287-95. doi: 10.1038/s41434-019-0085-4.
5. Belancic A, Strbad T, Kucan Stiglic M, Vitezic D. Effectiveness of nusinersen in type 1, 2 and 3 spinal muscular atrophy: Croatian real-world data. *J Clin Med* 2023; **12(8)**:2839. doi: 10.3390/jcm12082839.
6. Kakazu J, Walker NL, Babin KC, Trettin KA, Lee C, Sutker PB, *et al*. Risdiplam for the use of spinal muscular atrophy. *Orthop Rev (Pavia)* 2021; **13(2)**:25579. doi: 10.52965/001c.25579.
7. Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: Current perspectives. *Ther Clin Risk Manag* 2019; **15**:1153-61. doi: 10.2147/TCRM.S172291.
8. Paik J. Risdiplam: A review in spinal muscular atrophy. *CNS Drugs* 2022; **36(4)**:401-10. doi: 10.1007/s40263-022-00910-8.
9. Snoj Z, Salapura V. Ultrasound-guided transforaminal approach for nusinersen delivery in adult spinal muscle atrophy patients with challenging access. *Muscle Nerve* 2022; **65(5)**:585-9. doi: 10.1002/mus.27518.
10. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, *et al*. Nusinersen *versus* sham control in infantile-onset spinal muscular atrophy. *N Engl J Med* 2017; **377(18)**:1723-32. doi: 10.1056/NEJMoa1702752.
11. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, *et al*. Nusinersen *versus* sham control in later-onset spinal muscular atrophy. *N Engl J Med* 2018; **378(7)**:625-35. doi: 10.1056/NEJMoa1710504.
12. Crawford TO, Swoboda KJ, De Vivo DC, Bertini E, Hwu WL, Finkel RS, *et al*. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. *Muscle Nerve* 2023; **68(2)**:157-70. doi: 10.1002/mus.27853.
13. Mercuri E, Deconinck N, Mazzone ES, Nascimento A, Oskoui M, Saito K, *et al*. Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy

(SUNFISH part 2): A phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Neurol* 2022; **21(1)**:42-52. doi: 10.1016/S1474-4422(21)00367-7.

14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Rev Esp Cardiol (Engl Ed)* 2021; **74(9)**:790-9. doi: 10.1016/j.rec.2021.07.010.
15. Akobeng AK. Principles of evidence based medicine. *Arch Dis Child* 2005; **90(8)**:837-40. doi: 10.1136/adc.2005.071761.
16. Born AP, Werlauff U. [Early diagnosis of spinal muscular atrophy]. *Ugeskr Laeger* 2021; **183(51)**:V05210462. Available from: http://europepmc.org/abstract/med/ 34981731.
17. Rao VK, Kapp D, Schroth M. Gene therapy for spinal muscular atrophy: An emerging treatment option for a devastating disease. *J Manag Care Spec Pharm* 2018; **24 (12-a Suppl)**:S3-16. doi: 10.18553/jmcp.2018.24.12-a.s3.
18. Pera MC, Coratti G, Forcina N, Mazzone ES, Scoto M, Montes J, *et al*. Content validity and clinical meaningfulness of the HFMSE in spinal muscular atrophy. *BMC Neurol* 2017; **17(1)**:39. doi: 10.1186/s12883-017- 0790-9.
19. Mazzone ES, Mayhew A, Montes J, Ramsey D, Fanelli L, Young SD, *et al*. Revised upper limb module for spinal muscular atrophy: Development of a new module. *Muscle Nerve* 2017; **55(6)**:869-74. doi: 10.1002/mus.25430.
20. Trundell D, Le Scouiller S, Le Goff L, Gorni K, Vuillerot C. Assessment of the validity and reliability of the 32-item motor function measure in individuals with Type 2 or non-ambulant Type 3 spinal muscular atrophy. *PLoS One* 2020; **15(9)**:e0238786. doi: 10.1371/journal.pone.0238786.
21. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al*. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**:d5928. doi: 10.1136/bmj.d5928.
22. Mercuri E, Baranello G, Boespflug-Tanguy O, De Waele L, Goemans N, Kirschner J, *et al*. Risdiplam in types 2 and 3 spinal muscular atrophy: A randomised, placebo-controlled, dose-finding trial followed by 24 months of treatment. *Eur J Neurol* 2023; **30(7)**:1945-56. doi: 10.1111/ene.15499.
23. Oskoui M, Day JW, Deconinck N, Mazzone ES, Nascimento A, Saito K, *et al*. Two-year efficacy and safety of risdiplam in patients with type 2 or non-ambulant type 3 spinal muscular atrophy (SMA). *J Neurol* 2023; **270(5)**:2531-46. doi: 10.1007/s00415-023-11560-1.
24. Acsadi G, Crawford TO, Muller-Felber W, Shieh PB, Richardson R, Natarajan N, *et al*. Safety and efficacy of nusinersen in spinal muscular atrophy: The EMBRACE study. *Muscle Nerve* 2021; **63(5)**:668-77. doi: 10.1002/mus.27187.