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REVIEW OF THERAPEUTICS

Efficacy of risdiplam in spinal muscular atrophy: A systematic review and meta-analysis

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Abstract

This systematic review and meta-analysis aimed to assess the efficacy and safety of risdiplam on motor and respiratory function in spinal muscular atrophy (SMA). We systematically searched Medline, Scopus, Web of Science, and the Cochrane Library from inception to March 2023. We included pre-post studies that determined the effect of risdiplam on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), the 32-item Motor Function Measure (MFM32), the Revised Upper Limb Module (RULM), the Hammersmith Functional Motor Scale – Expanded (HFMSE), respiratory function, and the proportion of risdiplam-related adverse events in a population with SMA (phenotypes 1 and 2/3). Meta-analyses were also performed where possible. Eleven studies were included. After 12 months of treatment, 57% of participants with SMA1 achieved a CHOP-INTEND score ≥ 40 points, and more than half were able to feed orally and had head control. In SMA2/3, MFM32, RULM, and HFMSE increased by 2.09 (1.17, 3.01), 1.73 (1.25, 2.20), and 1.00 (0.40, 1.59) points, respectively. Efficacy on respiratory function in SMA2/3 was inconsistent. Finally, 16% of participants experienced adverse events, but serious adverse events could not be quantified due to a lack of cases. The limited available evidence suggests that risdiplam is an effective and safe drug for the treatment of SMA. In addition, long-term clinical benefit may be partly determined by the stage of disease at which treatment is initiated.

KEYWORDS
meta-analysis, motor neuron disease, neuromuscular diseases, spinal muscular atrophy, systematic review

1 | INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive genetic disease, with an estimated incidence of one per 6000–10,000 live births, and is usually caused by homozygous mutations in the survival motor neuron 1 (*SMN1*) gene, which encodes the SMN protein.[1–3] SMN is essential for the homeostasis and survival of motor neurons, and its absence ultimately leads to their death. Symptoms

of SMA include proximal weakness, muscle hypotonia, bulbar and intercostal muscle involvement, and scoliosis. As the disease progresses, complications such as respiratory failure threaten the patient's life.[4,5] A second reserve gene, the *SMN2* gene, can express up to 10% of the required SMN per copy.

There are various phenotypes of SMA, which are largely correlated by the copies of the *SMN2* gene. SMA type 1 [SMA1, MIM: 253300] has an age of onset of 0–6 months and presents with weakness, hypotonia, areflexia, and respiratory failure. Patients with SMA1 usually have one or two copies of the *SMN2* gene. SMA type 2 [SMA2, MIM: 253550] presents with proximal weakness, hypotonia, hyporeflexia, and scoliosis, and they can sit up without support. Patients with SMA2 usually have three copies of the *SMN2* gene. Finally, SMA type 3 [SMA3, MIM: 253400] also presents with weakness and other typical signs of SMA, although they may be able to walk at some point. Patients with SMA3 usually have three or four copies of the *SMN2* gene.[1,6–8] However, there are other modifiers that explain the wide phenotypic variability, such as a base substitution in exon 7 (c.859G>C) of the *SMN2* gene, which increases its inclusion, and plastin 3 expression.[8]

Classically, the management of SMA has been palliative, treating complications as they developed.[9] However in the last decade, important therapeutic advances have been developed that have dramatically changed the course of the disease. Nusinersen is an intrathecally administered antisense oligonucleotide that binds to intron 7 of *SMN2* mRNA, increasing SMN expression.[10,11] Almost simultaneously, intravenous onasemnogene abeparvovec was developed, which uses an adeno-associated virus9 to introduce the *SMN* gene into motor neurons.[12–14] Finally, risdiplam, a small molecule with high oral bioavailability, has been developed that binds to the 5′ splice site of intron 7 and the exonic splicing enhancer 2 of exon 7 in the *SMN2* pre-mRNA, allowing the inclusion of exon 7 and ultimately the full-size SMN expression. Thus, in animal models and in preclinical studies, both risdiplam and its predecessor, RG7800, increased SMN expression and, in the case of animal models, improved the phenotype. However, development of the RG7800 was discontinued due to safety concerns.[15–18]

A systematic review assessed the effect of these therapies in SMA. However, no trials met the inclusion criteria for risdiplam because of its recent development.[19] Therefore, this systematic review and meta-analysis aimed to estimate the efficacy of risdiplam on motor and respiratory function and the rate of treatment-related adverse events in participants with SMA.

2 | METHODS

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Collaboration Handbook.[20,21] We have previously registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42023405058).

2.1 | Search strategy

A systematic search of the databases Medline (via PubMed), Scopus, Web of Science, and the Cochrane Library was conducted from inception to March 2023. We also searched gray literature and clinical trial registries including OpenGrey, Google Scholar, ClinicalTrials.gov, and EudraCT. The following search terms were included: risdiplam, Evrysdi, RG7916, RO7034067, spinal muscular atrophy, SMA, spinal muscular atrophy type 1, spinal muscular atrophy type 2, spinal muscular atrophy type 3, type 1 spinal muscular atrophy, type 2 spinal muscular atrophy, and type 3 spinal muscular atrophy. Where necessary, we tried to contact the authors of the studies. We also reviewed the references of the included studies. The full search is detailed in Appendix S1.

The search was carried out independently by two authors (CP-M and IC-R).

2.2 | Inclusion/exclusion criteria

Inclusion criteria were as follows: (1) participants: participants with SMA; for the statistical analysis of efficacy, the SMA 1 and SMA2-3 groups were considered, whereas for the safety profile they were analyzed together; (2) design: pre-post studies; (3) intervention: risdiplam, alone or in combination with nusinersen or onasemnogene abeparvovec; (4) outcomes: (i) in SMA1, motor function was assessed by the proportion of participants achieving a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score ≥ 40, the proportion of participants with an increase in CHOP-INTEND ≥4 points, and the proportion of motor milestones achieved (i.e., responders on the Hammersmith Infant Neurological Exam [HINE-2] scale, crawls, feed orally, head control, sitting >5 s, sitting >30 s, standing unaided, walking unaided, and no requirement of continuous ventilatory support); (ii) in SMA2/3, motor function was assessed by change in the 32-item Motor Function Measure (MFM32), Revised Upper Limb Module (RULM), and Hammersmith Functional Motor Scale – Expanded (HFMSE) scales, and respiratory function by the change in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), peak cough flow (PCF), and sniff nasal inspiratory pressure (SNIP), determined as %predicted where applicable; (iii) the safety profile was assessed by the proportion of participants with risdiplam-related total and serious adverse events. Table S1 provides a brief description of the scales mentioned (objective and range of scores).

Exclusion criteria were as follows: (1) participants: cohorts of participants with SMA and other neuromuscular diseases, where it was not possible to separate participants with SMA; (2) design: (i) case report studies; (ii) communications/abstracts of clinical trials whose manuscripts have been published in peer-reviewed journals; (3) Outcomes: trials that describe an improvement in any of the outcomes listed above, but do not specify that other participants did not achieve.

Study selection was carried out independently by two reviewers (CP-M and IC-R), and disagreements were resolved by consensus or by a third reviewer (VM-V).

2.3 | Data extraction

An ad hoc table was performed with the following data extracted from the included studies: (1) reference (author and year of publication); (2) country/ies; (3) trial (Clinicaltrials.gov registration number, if applicable); (4) participants (type of SMA, sample size, and age at infusion); (5) previous gene therapy interventions; (6) intervention (dose, length); (7) outcomes: motor function, respiratory function, safety profile.

Data extraction was carried out independently by two reviewers (CP-M and IC-R), and disagreements were resolved by consensus or by a third reviewer (VM-V).

2.4 | Risk of bias assessment

Risk of bias was assessed using the Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group from the United States National Institutes of Health National Heart, Lung, and Blood Institute.[22] This tool includes 12 items that assess the study design, statistical analysis, and development of the intervention. If there were less than two items at risk of bias, the overall bias was good; if there were two items at risk of bias, the overall bias was fair; and if there were more than two items at risk of bias, the overall bias was poor.

Risk of bias was assessed independently by two reviewers (CP-M and IC-R), and disagreements were resolved by consensus or by a third reviewer (VM-V).

2.5 | Data synthesis

An ad hoc table of data from each study and a narrative synthesis of the data were performed. Continuous outcomes were expressed as pre-post mean difference and 95% confidence interval (95% CI), while continuous variables were expressed as proportions of participants achieving the outcome and 95% CI.

Random effects meta-analyses were performed[23] when two or more studies reported the effect of risdiplam on the same outcome in the same type of population (i.e., SMA1 and SMA2/3) over a similar time period (e.g., 12 months). The I^2 statistic was used to assess heterogeneity, which was classified as not important if less than 30%, moderate if 30%–50%, substantial if 50%–75%, and considerable if greater than 75%, and was considered statistically significant if $p < 0.05$.[21,24] Due to study limitations, publication bias was not assessed nor were subgroup studies, meta-regressions, or sensitivity analyses performed.

Statistical analyses were conducted with Stata v15 (StataCorp). For dichotomous outcomes, the statistical package metaprop was used.

2.6 | Modifications to the registered protocol CRD42023405058

The registered protocol included SMN blood levels as an outcome and the pre-post difference in CHOP-INTEND as a quantitative outcome, but this was not possible due to the limited number of trials and the estimation of these data as medians and absolute ranges (minimum–maximum). It was also not possible to estimate efficacy in SMA2 and SMA3 separately.

3 | RESULTS

Of the 582 records identified, 11 studies were included in the systematic review (Table 1, Figure 1),[25–36] and seven were included in the meta-analyses, while 10 studies were excluded with justified reasons (Table S2).

The studies were conducted in the Americas, Asia, and Europe (Table S3). A total of 641 participants were included and, in general, the studies investigated SMA1 or SMA2/3. The mean (or median) age ranged from 26.5 days to 34.5 years of age. Eight studies included cohorts with no prior gene therapy treatment, while three studies included participants treated with nusinersen, onasemnogene abeparvovec, or RG7800. Doses were generally 0.20 mg/kg/day for children under 2 years, 0.25 mg/kg/day for children over 2 years and under 20 kg, and 5 mg/day for children over 20 kg, while efficacy assessment was generally assessed at 12 and 24 months. Finally, eight studies assessed motor function, five studies assessed respiratory function, and six studies assessed treatment-related adverse events.

3.1 | Systematic review

Tables S4–S7 summarize the results obtained in the different studies.

In SMA1 or probable SMA1 (i.e., two copies of SMN2), CHOP-INTEND ≥40 points was achieved in more than half of the participants at 12 months, and in 100% of the presymptomatic participants. At 24 months, 76% of participants achieved CHOP-INTEND ≥40 points. In addition, 85% were able to feed orally, 71% had head control, 44% were able to sit for >30 s, and 90% did not require permanent ventilatory support at 24 months. One participant who started treatment at the pre-symptomatic stage was also able to walk at 12 months.

In SMA2/3, the MFM32 improved 1.7–2.66 points after 12 months of treatment, with stabilization at 24 months. Furthermore, the RULM improved from 1.72 to 1.90 points at 12 months, with a trend toward improvement at 24 months of treatment. The HFMSE also showed a trend toward improvement at 24 months compared with 12 months in one of the studies. Regarding respiratory function, FVC and FEV1 tended to decrease at 12 and 24 months, while PCF remained stable and SNIP tended to improve. There was no difference in motor and respiratory function between participants treated with risdiplam alone or in combination with other therapies.

Finally, risdiplam-related adverse events were 13%–19% and 17%–24% at 12 and 24 months of treatment, while risdiplam-related serious adverse events were anecdotal. The most common risdiplam-related adverse events, serious or not, were gastrointestinal disorders (i.e., diarrhea and constipation), some skin disorders

TABLE 1 Baseline characteristics of the participants in the included studies.

			Participants				Intervention		Included outcomes		
Reference	Region	Trial	Type SMA	Sample	Age at infusion[a]	Pre-intervention	Dose	Length	MF	RF	SF
Baranello et al. (2021)[25]	America Europe	NCT02913482 (FIREFISH 1)	SMA1	21	6.7 m (3.3–6.9)	Native	0.08 mg/kg 0.20 mg/kg	12 months	✓	–	–
Chiriboga et al. (2023)[26]	America Europe	NCT03032172 (JEWELFISH)	SMA 1, 2, and 3	174	14.0 y (1–60)	Oxesoxime: 71 RO6885247: 13 Nusinersen: 76 Onasemnogene abeparvovec: 14	0.20 mg/kg (<2 years) 0.25 mg/kg (>2 years and <20 kg) 5 mg (>20 kg)	12 months	–	–	✓
Darras et al. (2021)[27]	America Asia Europe	NCT02913482 (FIREFISH 2)	SMA1	41	5.3 m (2.2–6.9)	Native	0.20 mg/kg	12 months	✓	✓	–
Finkel et al. (2022)[28,29]	NS	NCT03779334 (RAINBOWFISH)	Presym. SMA[b]	7	26.5 d	Native	NS	12 months	✓	–	–
Kwon et al. (2022)[30]	America	Trial	SMA1 and 2	155	13.0 ± 10.0 y	Native: 26 Nusinersen: 101 Onasemnogene abeparvovec: 9 Both: 11 Unknown: 8	0.20 mg/kg (<2 years) 0.25 mg/kg (>2 years and <20 kg) 5 mg (>20 kg)	4.8 months	–	–	✓
Masson et al. (2022)[31]	America Asia Europe	NCT02913482 (FIREFISH 2)	SMA1	41	5.3 m (4.2–6.8)	Native	0.20–0.25 mg/kg	24 months	✓	–	✓
McCluskey et al. (2023)[32]	Europe	Trial	SMA2	6	34.5 ± 7.2 y	Native	NS	9 months	✓	✓	–
Mercuri et al. (2022)[33]	Europe	NCT02908685 (SUNFISH 1)	SMA2 and 3	51	7.0 y (2.0–24.0)	Native	0.25 mg/kg (2–11 y) 5 mg (12–25 y)	24 months	✓	✓	✓
Mercuri et al. (2022)[34]	America Asia Europe	NCT02908685 (SUNFISH 2)	SMA2 and 3	180	10.0 y (2.0–25.0)	Native	0.25 mg/kg (<20 kg) 5 mg (>20 kg)	12 months	✓	✓	✓
Ñungo Garzón et al. (2023)[35]	Europe	NCT04256265	SMA2	6	33.0 ± 12.2 y	Native: 4 Nusinersen: 2	0.25 mg/kg (<20 kg) 5 mg (>20 kg)	12 months	✓	✓	–
Oskoui et al. (2023)[36]	America Asia Europe	NCT02908685 (SUNFISH 2)	SMA 2 and 3	180	10.0 y (2.0–25.0)	Native	0.25 mg/kg (<20 kg) 5 mg (>20 kg)	24 months	✓	✓	✓

Abbreviations: MF, motor function; NS, not specified; RF, respiratory function; SF, safety profile; SMA, spinal muscular atrophy.

[a]Age at infusion described as years (y), months (m) or days (d).

[b]Presymptomatic participants. Four participants with two copies of the *SMN2* gene (probable SMA1) and three participants with more than two copies of the *SMN2* gene (probable SMA2 or 3) were included.

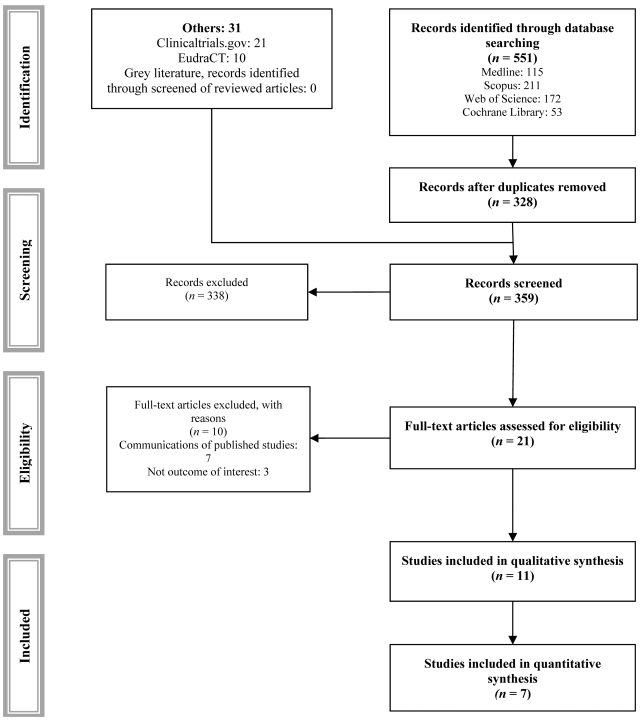

FIGURE 1 PRISMA flowchart of study selection.

(i.e., skin photosensitivity, rash, and skin discoloration), deep vein thrombosis, or elevation of transaminases.

3.2 | Risk of bias assessment

According to the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group from the United States National Institutes of Health National Heart, Lung, and Blood Institute, 1 of 11 was rated as fair and the rest as good. There were three studies with some concerns about sample size, while overall there was no blinding of participants. The risk of bias assessment is detailed in Table S8.

3.3 | Meta-analysis

In SMA1, the proportion of participants who achieved a CHOP-INTEND ≥40 points at 12 months was 0.57 (0.44, 0.70), and the proportions who were able to feed orally, had head control, and sat for more than 5 s were 0.85 (0.76, 0.94), 0.53 (0.41, 0.66), and 0.32 (0.20, 0.44), respectively. Other outcomes could not be meta-analyzed because the ratio was 0 or 1 in one of the studies (Figure 2).

On motor function in SMA2/3, risdiplam had an effect of 2.09 (1.17, 3.01) and 2.13 (1.24, 3.02) points in the MFM32 and 1.73 (1.25, 2.20) and 2.67 (2.05, 3.28) points in the RULM after 12 and 24 months of treatment, respectively. For the HFMSE, a statistically significant effect of 1.00 (0.40, 1.59) points was observed only at 12 months. Furthermore, in respiratory function, FVC tended to decrease with −2.34% (−7.93, 3.24) and −5.18% (−10.47, 0.11) at 12 and 24 months of treatment, while FEV1 decreased by −4.88% (−8.87, −0.89) at 24 months. Conversely, PCF remained stable and SNIP improved by 4.41% (1.63, 7.19) (Figure 3).

Finally, the proportion of participants with risdiplam-related adverse events was 0.16 (0.12, 0.21) and 0.19 (0.13, 0.24) at 12 and 24 months, while the proportion of participants with risdiplam-related serious adverse events could not be estimated due to a lack of cases (Figure 4).

Overall, heterogeneity was neither important nor statistically significant, except for the HFMSE at 24 months ($I^2 = 74.4\%$, $p = 0.048$) and FVC at 12 months ($I^2 = 89.4\%$, $p = 0.002$).

4 | DISCUSSION

4.1 | Main findings

This systematic review provides an assessment of the efficacy and safety profile of risdiplam in SMA. Our results showed an improvement in motor function in all three SMA phenotypes, with 57% of participants with SMA1 achieving a CHOP-INTEND ≥40 points and more than half of participants feeding orally and controlling their head after 12 months of treatment, something rarely seen in historical cohorts. In SMA1, there was also evidence that the effect may be greater in pre-symptomatic participants. In addition, in SMA2/3, an improvement of approximately two points on the MFM32 and RULM and one point on the HFMSE was observed. Finally, although 15%–20% of participants experienced drug-related adverse events, these were rarely considered serious.

4.2 | Interpretation

After 12 months of treatment, 57% of participants with SMA1 achieved CHOP-INTEND ≥40 points, while more than half were able to maintain head control and feed orally and a third were able to sit unaided for more than 5 s. Most interestingly, the improvement was maintained for at least 24 months of treatment. This improvement represents a dramatic change from historical cohorts where these motor milestones and motor function are rarely achieved.[37,38] Although tempting, these results cannot be compared with other gene therapies, such as onasemnogene abeparvovec.[39] This comparison is complicated by the necessarily limited sample size of some of the onasemnogene abeparvovec trials and the fact that participants were in different cohorts without randomization to one treatment or the other, which may lead to differences in baseline motor function, for example. However, as with onasemnogene abeparvovec, the preliminary results from NCT03779334 suggest that the greatest clinical benefit is achieved when risdiplam is administrated to pre-symptomatic participants.[28,29] Although the sample size was very small, it is significant that all participants were able to sit unaided for more than 5 s and one participant was able to walk.

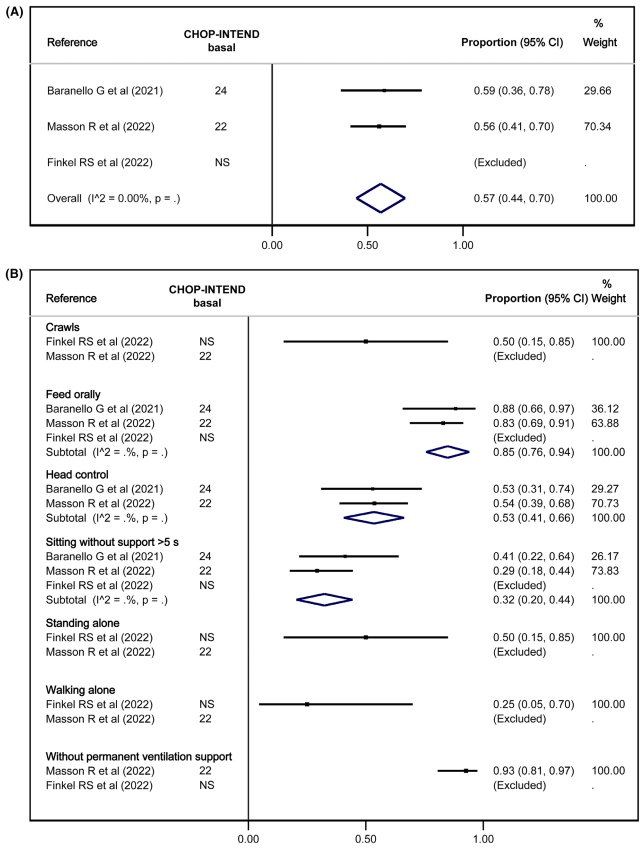

FIGURE 2 Meta-analyses of the proportion of participants achieving a CHOP-INTEND score ≥ 40 points (A) and the proportion of participants achieving the proposed motor milestones (B) on SMA1. CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA1, spinal muscular atrophy phenotype 1.

In SMA2/3, risdiplam improved MFM32, RULM, and HFMSE after 12 months of treatment. In addition, RULM continued to improve for at least 24 months. In addition, although not included in the review, the three presymptomatic participants with more than two copies of *SMN2* were able to walk independently at 15 months of age. However, at later ages, the effect of risdiplam on motor function did not depend on age at start of treatment, but was more evident in respiratory function where it had a greater effect in older participants. However, this should be considered with caution because the trials in older participants had SMA2 and 3, whereas the trials in younger participants had SMA2. These data contrast with those observed in historical cohorts, which show a clear decline. In untreated patients, the RULM decreased by −0.79 points and the MFM32 by −2.08 points over 24 months, while the HFMSE decreased by −0.54 points over 12 months.[40–42] These improvements are consistent with the results shown by nusinersen in adults.[43] Although inconsistencies in the HFMSE were observed in the 24-month meta-analysis, this was due to the random effects model of the meta-analysis (i.e., one study showed no change while the other showed a trend toward an increase, thus increasing the confidence interval). This improvement and subsequent stabilization is directly related to increased SMN expression, which doubles its expression as suggested by the

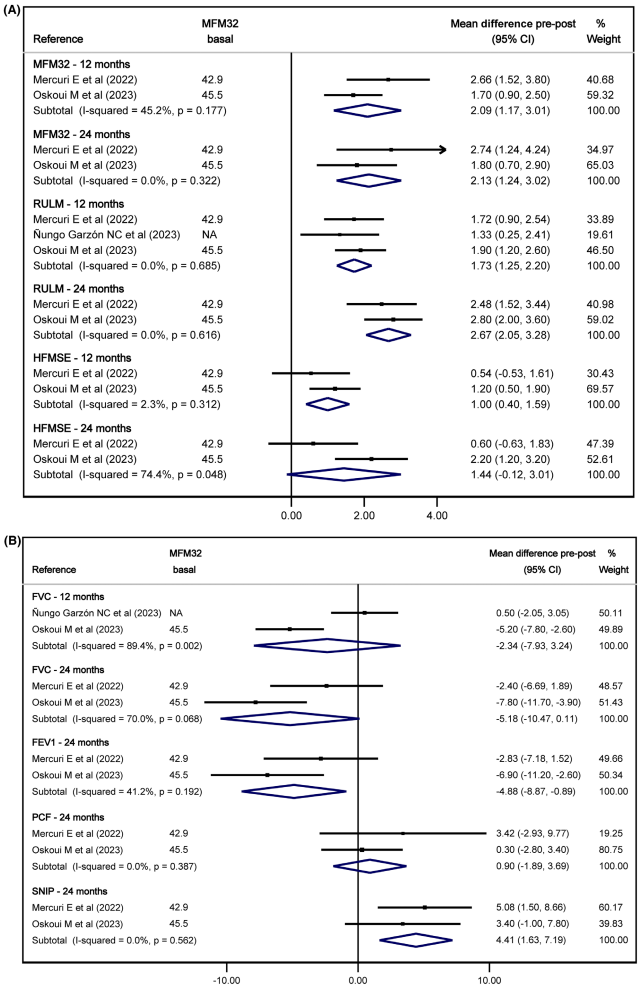

FIGURE 3 Meta-analyses of the effect of risdiplam on MFM32, RULM, and HFSME (A) and on FVC, FEV1, PCF, and SNIP (B) on SMA2/3. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HFSME, Hammersmith Functional Motor Scale – Expanded; MFM32, 32-item Motor Function Measure; PCF, peak cough flow; RULM, revised upper limb module; SMA2/3, spinal muscular atrophy phenotypes 2/3; SNIP, sniff nasal inspiratory pressure.

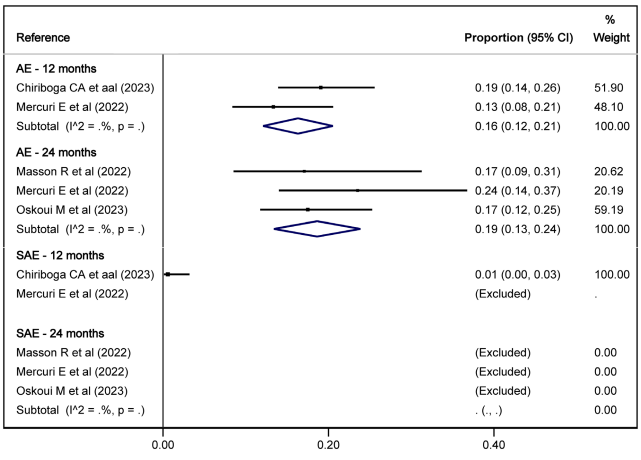

FIGURE 4 Meta-analysis of the proportion of participants with treatment-related adverse events. AE, adverse event; SAE, serious adverse event.

authors.[33] This expression leads to the survival and better function of the remaining motor neurons,[44] but the benefit would be limited precisely by this number of motor neurons.[36]

Although our main objective was not to investigate the safety profile and adverse events related to risdiplam, and the number of trials did not allow for a comprehensive analysis in this regard, some data from our review and the included trials are worth mentioning. Thus, 15%–20% of participants experienced a risdiplam-related adverse event related, but dose changes were rarely required and serious adverse events were anecdotal. In addition, and as described by the authors of the included trials,[25,27,31] some adverse events such as skin disorders and retinal toxicity, which were potentially serious in animal models if treatment was not discontinued, did not occur in the study population.[44]

Another aspect to highlight was the improvement in patient-reported outcome measures in SMA which include physical function, mental health and cognition, fatigue, communication and speech, pain, and systemic issues.[45] Although not included as an outcome in our review due to the large number of variables, the observations of some of the included studies should be highlighted.[32,35] These studies in adults showed improvements in some participants' fatigue, cognition, overall strength, manual dexterity and strength, speech, well-being, and quality of life. This shows an improvement in the lives of these people beyond the improvement in clinical parameters.

Our study has some clinical and research implications. First, regardless of whether nusinersen or onasemnogene abeparvovec is more or less effective than risdiplam (which is difficult to study and perhaps impractical for the clinic), it is likely that the use of risdiplam from an early age may optimize its benefit. In addition, the use of risdiplam as adjuvant or maintenance therapy in patients treated with nusinersen or onasemnogene abeparvovec is something that should be explored in more detail, as is the possibility of using risdiplam in patients with an incomplete response to nusinersen or onasemnogene abeparvovec. Second, the ease of administration compared with nusinersen, which can be complex in patients with scoliosis or other spinal disorders, may make risdiplam the therapy of choice in these individuals. Third, although respiratory function parameters decreased or tended to decrease, it is precisely the spine and the thoracic cage disorders, muscle contractures, etc., that cause part of this decrease, and this must be considered. Studying the effect of risdiplam and gene therapies administered from the early stages of the disease on respiratory outcomes could shed light on this issue, as they should theoretically improve respiratory function.

4.3 | Limitations

Our review had several limitations that need to be considered. First, few studies were included due to the recent development of risdiplam. Furthermore, some studies had insufficient sample sizes to provide robust results. Second, sensitivity analyses, meta-regressions according to baseline motor function, and assessment of publication bias were not performed because of the above. Third, due to the severity of the disease, there was no external control group, which was compared, in some studies, with historical cohorts. This may limit the interpretability of drug efficacy. Fourth, the copy number of *SMN2* in SMA1 and the specific phenotype of SMA1 were not considered. In addition, when SMA type was not reported by the authors, *SMN2* copy number was considered as a proxy for SMA type (e.g., trials in presymptomatic individuals), although their association is not perfect. On the other hand, efficacy may be slightly different for SMA2 and SMA3. Fifth, some adverse events may have been unrelated to risdiplam or vice versa. Sixth, a subgroup analysis based on the use of risdiplam alone or in combination with other therapies could not be done due to a lack of trials. In addition, differences in the baseline characteristics of the participants make it difficult to interpret the few trials that included people who received risdiplam in combination with other therapies.

5 | CONCLUSIONS

Risdiplam is an effective and safe treatment for all three types of SMA. It stabilizes or improves motor function in SMA1 as assessed by CHOP-INTEND and in SMA2/3 as assessed by MFM32, HFMSE, and RULM. The effect is likely to be greater in pre-symptomatic or early stage patients, although this is a hypothesis that needs to be confirmed in future studies. Conversely, risdiplam did not appear to have a significant effect on respiratory function, perhaps because of the thoracic cage alterations and scoliosis associated with SMA, which could hypothetically be prevented by early administration. Finally, although adverse events were common, they were rarely serious and/or required dose modification or discontinuation of the drug.

AUTHOR CONTRIBUTIONS

Conceptualization: CP-M; methodology: CP-M and IC-R; data curation and investigation: CP-M and IC-R; formal analysis: CP-M, IM-G, NM-H, CA-B and AS-L; validation and visualization: IM-G, NM-H, CA-B and AS-L; writing—original draft preparation: CP-M, IC-R and VM-V; writing—review and editing: all authors; supervision: IC-R and VM-V; funding acquisition: VM-V; project administration: VM-V. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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