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Current Treatment Approaches for Spinal Muscular Atrophy (SMA) – A Review

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ABSTRACT

SMA is an autosomal recessive neuromuscular disease characterized by progressive degeneration and loss of α-motor neurons in the spinal cord, leading to progressive muscle atrophy. The spectrum of the disease is broad, modified primarily by the number of copies of the SMN2 gene. SMA is caused by a survival motor neuron (SMN) protein deficiency. Before the introduction of disease-modifying therapies such as splicing modification and gene therapy, SMA was the second most common fatal disease after cystic fibrosis and the most common genetic cause of infant mortality. Recent advances in molecular biology provide increasing opportunities to interfere with earlier stages of the process, ultimately leading to SMN protein synthesis. Currently, the only approved disease-modifying therapies are onasemnogene abeparvovec, risdiplam, and nusinersen. A common feature of all three therapies is that intervention in the early presymptomatic period is fundamental to treatment response and can result in normal or near-normal motor development. The key milestones to this treatment have been understanding the genetic causes, regulation of SMN gene splicing, and the variability of disease phenotype and genotype. This review aims to present the aspects of spinal muscular atrophy and discuss the most advanced therapies currently approved for its treatment.

Keywords: spinal muscular atrophy (SMA), treatment, disease-modifying, gene therapy

1. INTRODUCTION

Spinal muscular atrophy (SMA) is a genetic disease caused by a mutation of the SMN1 gene and, consequently, a deficiency of the survival of motor neuron (SMN) protein, essential for regulating gene expression in motor neurons. This deficiency leads to degeneration of the anterior horn cells of the spinal cord and progressive muscle atrophy. Over 95% of mutations in the SMN1 gene are biallelic deletions of exon 7 (Nishio et al., 2023).

The spectrum of the disease is broad, ranging from severe, prenatally presented forms to mild adult-onset forms. In patients with presymptomatic disease, the primary determinant for predicting clinical disease burden and age at onset is the SMN2 gene copy number (Day et al., 2022). The classification of SMA into five types is defined according to the age at symptom onset and motor developmental milestones (Ponomarev et al., 2023). SMA type 0 with one copy of the SMN2 gene is the most severe phenotype. Clinical symptoms arise in utero. Reduced intrauterine movements may be evident prenatally. At birth, affected infants typically have joint contractures, respiratory distress requiring mechanical ventilation, and generalized hypotonia. Without disease-modifying therapy, death occurred within weeks of birth (Wirth et al., 2020).

SMA type 1 presents progressive hypotonia, weakening of the intercostal muscles, malformation of the chest wall, cardiac dysfunction, and dysphagia. Most patients have one to two copies of SMN2. Symptoms develop before 6 months of age. In the absence of immediate treatment, respiratory failure is the leading cause of death (Audic & Barnerias, 2020). SMA type 2 commonly manifests between 6 and 18 months of age. Patients usually achieve the ability to sit but are unable to walk independently. The progression of this type of SMA is variable. A reduction in life expectancy is observed, but many patients, despite progressive disability, survive into adulthood, even without treatment (Ramsey et al., 2017).

SMA type 3, with symptoms onset after 18 months of age, has a slower course and less severe symptoms. Patients have 3 or 4 copies of the SMN2 gene. Patients achieve the ability to move independently, but with time, due to increasing hypotension, they require support. The involvement of the respiratory muscles is rare (Glascock et al., 2018). SMA type 4, with symptoms typically appearing in the third or fourth decade of life. Manifestations are associated with mild weakness of the lower limb muscles and progress very slowly. The survival rate is similar to that observed in healthy individuals (Keinath et al., 2021).

New therapeutic options for SMA that aim to increase the functional level of SMN protein are based on two independent strategies. The first is the exogenous SMN1 gene introduced by a recombinant viral vector encoding the full-length transcript. The second is the enhancement of alternative mRNA splicing, increasing the inclusion of exon 7 in the mature transcript (Ogbonmide et al., 2023).

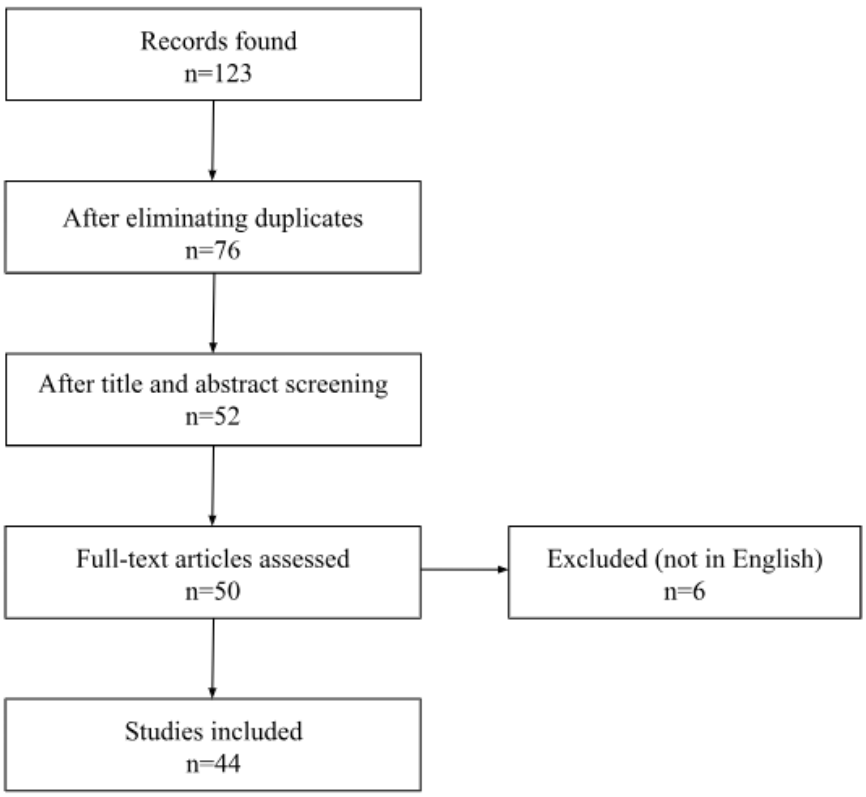

Figure 1 Flowchart

2. MATERIALS AND METHODS

A comprehensive literature review was conducted using digital databases, including PubMed and Google Scholar. This review includes clinical studies, systematic reviews, and meta-analyses focusing on the newest methods of chronic treatment in patients with spinal muscular atrophy, published after 2017. The keywords used in the literature search included: "Spinal Muscular Atrophy (SMA)", "Treatment", "Disease-modifying", and "Gene Therapy". The number of records identified through database searches was 123. After investigating the articles for these criteria, 44 studies that matched the purpose of this review were selected. Articles in languages other than English were excluded from consideration (figure 1).

3. RESULTS AND DISCUSSION

Exogenous SMN1 Gene Therapy

Gene therapy in SMA involves delivering a functional copy of the gene encoding the full length of the human SMN protein to motor neurons. Delivery of the unmutated SMN1 gene to cells is possible using the vector AAV (adeno-associated virus). AAVs are non-pathogenic viruses that can effectively enter central nervous system cells (Issa et al., 2023).

The use of AAV9 containing complementary DNA (cDNA) as a vector delivering the correct nucleotide sequence of the human SMN1 gene allowed the development of a therapeutic drug, onasemnogene abeparvovec, AVXS-101, with the trade name Zolgensma (Mendell et al., 2017). AAV serotype 9 can be administered to patients by intrathecal injection or systemically, as the virus can cross the blood-brain barrier (Qu et al., 2019). Patients harboring antibodies against AAV9 should be excluded from therapy to avoid premature immune system reactions and undesirable side effects (Kang et al., 2023).

Gene therapy with onasemnogene abeparvovec has shown promising results in treating spinal muscular atrophy (SMA), especially in children who started treatment early before the first symptoms of the disease appeared (Schorling et al., 2020). The START study (AVXS-101-CL-101), the first clinical test of this therapy, involved 15 infants with SMA type 1. All children who received a high dose of the drug survived until the end of the observation period. Moreover, their motor function was most significantly improved, as assessed using the specialist CHOP INTEND scale (Mendell et al., 2017).

These findings were supported by the phase III STR1VE-US trial involving 22 infants with SMA type 1. In this study, 91% of participants survived 14 months without requiring permanent ventilation, and 59% achieved independent sitting, with an average age of 9.2 months. The therapy was generally tolerated, and no new safety concerns were identified (Day et al., 2021). One of the most significant findings comes from the SPR1NT study, which evaluated Zolgensma in presymptomatic infants with genetically confirmed SMA. In the group of children with two copies of the SMN2 gene, 100% achieved independent sitting. Among those with three copies of SMN2, 92% managed to walk without assistance (Strauss et al., 2022).

SMN2 Gene Discovery

The SMN gene in the human genome occurs in at least two copies: SMN1 and SMN2. The SMN2 gene is highly homologous to the SMN1 gene, exhibiting over 99% nucleotide sequence identity. Most SMN2 transcripts are an alternative spliced form lacking exon 7. A cytosine to thymine substitution at position 6 in the coding region disrupts the exonic splicing enhancer (ESE) and generates an exonic silencing sequence (ESS), leading to exon 7 skipping during transcription. These transcripts cannot oligomerize and are rapidly degradable (Angilletta et al., 2023).

A small proportion of transcripts derived from the SMN2 sequence contain exon 7 and are transcribed into the full-length SMN protein, which has the same role as the SMN2 gene product. Differences in SMN2 copy number are associated with disease severity. The complete absence of the SMN protein, in conjunction with the loss of the SMN1 and SMN2 genes, is a fatal defect. More SMN2 copies are usually associated with higher SMN levels and a milder disease course (Rao et al., 2018). The discovery of the SMN2 gene, which can produce small amounts of functional SMN protein through alternative splicing, has enabled the development of molecular therapies to restore SMN expression (Ribero et al., 2023).

Modification of SMN2 Gene Splicing

Another approach in SMA therapy is the modification of SMN2 gene splicing. Antisense oligonucleotides, blocking the intronic splicing silencer ISS-N1 in intron 7 and small molecule modulators, enhancing the binding of the U1 snRNP complex, and promoting the inclusion of exon 7 in SMN2 mRNA (Lejman et al., 2023; Ottesen et al., 2024).

Nusinersen

ASOs (antisense oligonucleotides) are single, short strands of chemically modified nucleic acids complementary to a specific mRNA sequence (Godfrey et al., 2017). Depending on the binding site, ASOs affect transcript inactivation and modulation of pre-mRNA splicing. The use of appropriate oligonucleotides in treating spinal muscular atrophy allows for the inclusion of exon 7 in the SMN2 gene transcript (Tsai et al., 2024). Nusinersen is a therapeutic antisense 2'-methoxyethyl phosphate oligonucleotide directed at binding a specific silencing sequence in the intron of the SMN2 pre-mRNA (Shchaslyvyi et al., 2023). This medication is administered intrathecally in 4 loading doses over 2 months and maintenance doses every 4 months and is approved for all patients regardless of age (Yeo et al., 2020).

Repeated administration by lumbar puncture into the cerebrospinal fluid is related to the size of the antisense oligonucleotide molecules that exhibit limited blood-brain barrier penetration (Finkel et al., 2016).

Nusinersen in Clinical Trials

The open-label NURTURE study included 25 presymptomatic infants with a mutation in the SMN1 gene (two and three copies of the SMN2 gene). Initiation of nusinersen before the onset of clinical symptoms resulted in near-normal motor development. The WHO motor milestone (sitting without support) was achieved by 25 patients (100%), and all children also mastered sucking and swallowing. Among older patients, independent walking was achieved by 77 percent of patients (De Vivo et al., 2019).

Subsequent years of follow-up in NURTURE demonstrate the durability of the benefits with continued improvement associated with nusinersen treatment. After ~5 years, all children had achieved previously unattainable motor milestones, many within the typical developmental time frame, emphasizing the value of early diagnosis and initiation of nusinersen treatment (Crawford et al., 2023).

The ENDEAR study evaluated the safety and clinical efficacy of nusinersen in 121 infants with early-onset SMA. In the final analysis, a statistically more significant proportion of patients in the nusinersen group positively affected event-free survival and overall survival. Additionally, response criteria were observed for motor milestones and an improvement of more than 4 points from baseline on the CHOP INTEND scale. Nusinersen was also found to significantly reduce the likelihood of requiring mechanical ventilator support (Finkel et al., 2017).

The randomized CHERISH study included 126 children with late-onset SMA. In the final analysis, a statistically significant improvement in motor function, as assessed by the Hammersmith functional motor scale expanded (HFMSE), was observed in patients receiving nusinersen compared to patients in the control group (Mercuri et al., 2018).

Risdiplam

Risdiplam is the only orally administered medication approved for treating patients with spinal muscular atrophy (SMA) types 1, 2, or 3 aged two months and older (Kakazu et al., 2021). It binds to two sites in the SMN2 pre-mRNA: the 5 'splicing site (5' ss) of intron 7 and the exon splicing enhancer 2 (ESE2) in exon 7. By modifying the splicing of the SMN2 gene, risdiplam promotes exon 7 to be incorporated into SMN2 mRNA transcripts, leading to increased levels of SMN protein (Sturm et al., 2018; Messina & Sframeli, 2020). This medication enhances the SMN2 mRNA ratio in a dose-dependent manner (Yeo & Darras, 2020).

Therapeutic Efficacy of Risdiplam

Risdiplam demonstrates high therapeutic efficacy in patients with various forms of spinal muscular atrophy (SMA), both in infants and in older children. Infants with type 1 SMA exhibited the highest increase in SMN protein levels (Baranello et al., 2021).

In the second part of the FIREFISH study, covering infants with SMA type 1, after 24 months of treatment, 83% of children did not require continuous respiratory support, and 44% of patients demonstrated the ability to sit independently for at least 5 seconds - which does not occur in the natural course of the disease (Masson et al., 2022). Additionally, the SUNFISH study, aimed at patients aged 2 to 25 years with type 2 or non-ambulatory type 3 SMA, showed significant improvement in motor functions measured by the MFM32 scale and favorable medication tolerability (Mercuri et al., 2022).

Comparison of SMA Treatment Strategies

Comparative analyses suggest that gene therapy (onasemnogene abeparvovec) may be superior to nusinersen and risdiplam regarding overall survival, improved motor function, and independence from permanent ventilator support in symptomatic infants with SMA type 1 (Dabbous et al., 2019).

The meta-analysis included 3418 patients with spinal muscular atrophy (SMA) types 1 and 2. Participants receiving gene therapy showed the highest survival rate (95%), clearly outperforming risdiplam (86%) and nusinersen (60%). Additionally, onasemnogene abeparvovec and risdiplam achieved comparable results in improving motor function, as assessed by the CHOP INTEND scale, with 92% and 90% of patients, respectively, showing an improvement of at least 4 points. Nusinersen showed a lower percentage of improvement at 74% (Chongmelaxme et al., 2024).

Due to the potential to completely stop the development of SMA symptoms in the preclinical phase, gene therapy is often considered the most effective, provided it is administered very early. However, this therapy was initially indicated for patients below 2 years of age because the efficacy and safety in older patients have not been sufficiently studied (Sawada et al., 2023). In turn, nusinersen demonstrates long-term efficacy in various types of SMA, including in adolescents and young adults. Implementing this treatment method is particularly valuable in patients with types 2 and 3 SMA, where gene therapy is not approved (Hagenacker et al., 2024). The disadvantage is the need for repeated, invasive cerebrospinal fluid administration. Intrathecal administration allows for direct delivery of the drug to the central nervous system; however, this involves repeated lumbar punctures, which may be a limitation, especially in patients with spinal deformities and after orthopedic surgeries (Qiao et al., 2023).

Risdiplam is a valuable therapeutic alternative for patients who are not eligible for intrathecal nusinersen or gene therapy due to age, clinical condition, or contraindications. As an oral drug, risdiplam is distributed to the central nervous system and peripheral tissues, which may be particularly important in the context of extraneuronal manifestations of SMA (Ribero et al., 2022). This medication was well tolerated in the JEWELFISH study, which included patients previously treated with other SMA therapies. It caused a significant increase in SMN protein levels in a dose-dependent manner, even in patients with advanced disease (Chiriboga et al., 2023).

4. CONCLUSIONS

In recent years, the treatment of spinal muscular atrophy (SMA) has undergone a revolution with the introduction of three modern, registered therapies: nusinersen, risdiplam, and gene therapy. Each of these methods significantly changes the natural course of the disease, but they differ in their mechanism of action, method of administration, target population, and range of efficacy. Risdiplam offers the convenience and possibility of home administration; nusinersen has a stable action profile and can be used long-term, while gene therapy provides a potentially groundbreaking, one-time solution, albeit limited to a selected group of patients. The selection of appropriate SMA therapy should account for many factors, including age, disease type, neurological status, number of SMN2 gene copies, patient preferences, and treatment availability.

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Author's Contributions

Patrycja Pysz- Conceptualization, review and editing, investigation, methodology
Kinga Świtała- Methodology, investigation, visualization, supervision
Karolina Jałocha- Conceptualization, visualization, resources
Marek Borecki- Review, data curation, investigation
Dominik Tomczak- Resources, writing- rough preparation, data curation
Maria Mroczka- Visualization, data curation, investigation
Agnieszka Czernecka- Review, visualization, formal analis
Justyna Kuciel- Supervision, writing- rough preparation, data curation
Kinga Erazmus- Review and editing, formal analis, supervision
Roksana Hrapkowicz- Resources, writing- rough preparation, formal analis
Project administration- Patrycja Pysz

Informed consent

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Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data associated with this study are present in the paper.

REFERENCES

1. Angilletta I, Ferrante R, Giansante R, Lombardi L, Babore A, Dell'Elice A, Alessandrelli E, Notarangelo S, Ranaudo M, Palmarini C, De Laurenzi V, Stuppia L, Rossi C. Spinal Muscular Atrophy: An Evolving Scenario through New Perspectives in Diagnosis and Advances in Therapies. Int J Mol Sci. 2023;24(19):14873. doi: 10.3390/ijms241914873.
2. Audic F, Barnerias C. Spinal muscular atrophy (SMA) type I (Werdnig-Hoffmann disease). Arch Pediatr. 2020;27(7S):7S15-7S17. doi: 10.1016/S0929-693X(20)30271-2.
3. Baranello G, Darras BT, Day JW, Deconinck N, Klein A, Masson R, Mercuri E, Rose K, El-Khairi M, Gerber M, Gorni K, Khwaja O, Kletzl H, Scalco RS, Seabrook T, Fontoura P, Servais L; FIREFISH Working Group. Risdiplam in Type 1 Spinal Muscular Atrophy. N Engl J Med. 2021;384(10):915-923. doi: 10.1056/NEJMoa2009965.
4. Chiriboga CA, Bruno C, Duong T, Fischer D, Mercuri E, Kirschner J, Kostera-Pruszczyk A, Jaber B, Gorni K, Kletzl H, Carruthers I, Martin C, Warren F, Scalco RS, Wagner KR, Muntoni F; JEWELFISH Study Group. Risdiplam in Patients Previously Treated with Other Therapies for Spinal Muscular Atrophy: An Interim Analysis from the JEWELFISH Study. Neurol Ther. 2023;12(2):543-557. doi: 10.1007/s40120-023-00444-1. Epub 2023 Feb 13. Erratum in: Neurol Ther. 2023;12(5):1799-1801. doi: 10.1007/s40120-023-00503-7.
5. Chongmelaxme B, Yodsurang V, Vichayachaipat P, Srimatimanon T, Sanmaneechai O. Gene-based therapy for the treatment of spinal muscular atrophy types 1 and 2 : a systematic review and meta-analysis. Gene Ther. 2024. doi: 10.1038/s41434-024-00503-8.
6. Crawford TO, Swoboda KJ, De Vivo DC, Bertini E, Hwu WL, Finkel RS, Kirschner J, Kuntz NL, Nazario AN, Parsons JA, Pechmann A, Ryan MM, Butterfield RJ, Topaloglu H, Ben-Omran T, Sansone VA, Jong YJ, Shu F, Zhu C, Raynaud S, Lago TR, Paradis AD, Foster R, Chin R, Berger Z; NURTURE Study Group. 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):157-170. doi: 10.1002/mus.27853.
7. Dabbous O, Maru B, Jansen JP, Lorenzi M, Cloutier M, Guérin A, Pivneva I, Wu EQ, Arjunji R, Feltner D, Sproule DM. Survival, Motor Function, and Motor Milestones: Comparison of AVXS-101 Relative to Nusinersen for the Treatment of Infants with Spinal Muscular Atrophy Type 1. Adv Ther. 2019;36(5):1164-1176. doi: 10.1007/s12325-019-00923-8.
8. Day JW, Finkel RS, Chiriboga CA, Connolly AM, Crawford TO, Darras BT, Iannaccone ST, Kuntz NL, Peña LDM, Shieh PB, Smith EC, Kwon JM, Zaidman CM, Schultz M, Feltner DE, Tauscher-Wisniewski S, Ouyang H, Chand DH, Sproule DM, Macek TA, Mendell JR. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021;20(4):284-293. doi: 10.1016/S1474-4422(21)00001-6.
9. Day JW, Howell K, Place A, Long K, Rossello J, Kertesz N, Nomikos G. Advances and limitations for the treatment of spinal muscular atrophy. BMC Pediatr. 2022;22(1):632. doi: 10.1186/s12887-022-03671-x.
10. De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, Kirschner J, Kuntz NL, Parsons JA, Ryan MM, Butterfield RJ, Topaloglu H, Ben-Omran T, Sansone VA, Jong YJ, Shu F, Staropoli JF, Kerr D, Sandrock AW, Stebbins C, Petrillo M, Braley G, Johnson K, Foster R, Gheuens S, Bhan I, Reyna SP, Fradette S, Farwell W; NURTURE Study Group. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord. 2019;29(11):842-856. doi: 10.1016/j.nmd.2019.09.007.
11. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, Yamashita M, Rigo F, Hung G, Schneider E, Norris DA,

Xia S, Bennett CF, Bishop KM. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet. 2016;388(10063):3017-3026. doi: 10.1016/S0140-6736(16)31408-8.

12. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, Chiriboga CA, Saito K, Servais L, Tizzano E, Topaloglu H, Tulinius M, Montes J, Glanzman AM, Bishop K, Zhong ZJ, Gheuens S, Bennett CF, Schneider E, Farwell W, De Vivo DC; ENDEAR Study Group. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017;377(18):1723-1732. doi: 10.1056/NEJMoa1702752.
13. Glascock J, Sampson J, Haidet-Phillips A, Connolly A, Darras B, Day J, Finkel R, Howell RR, Klinger K, Kuntz N, Prior T, Shieh PB, Crawford TO, Kerr D, Jarecki J. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. J Neuromuscul Dis. 2018;5(2):145-158. doi: 10.3233/JND-180304.
14. Godfrey C, Desviat LR, Smedsrød B, Piétri-Rouxel F, Denti MA, Disterer P, Lorain S, Nogales-Gadea G, Sardone V, Anwar R, El Andaloussi S, Lehto T, Khoo B, Brolin C, van Roon-Mom WM, Goyenvalle A, Aartsma-Rus A, Arechavala-Gomeza V. Delivery is key: lessons learnt from developing splice-switching antisense therapies. EMBO Mol Med. 2017;9(5):545-557. doi: 10.15252/emmm.201607199.
15. Hagenacker T, Maggi L, Coratti G, Youn B, Raynaud S, Paradis AD, Mercuri E. Effectiveness of Nusinersen in Adolescents and Adults with Spinal Muscular Atrophy: Systematic Review and Meta-analysis. Neurol Ther. 2024;13(5):1483-1504. doi: 10.1007/s40120-024-00653-2.
16. Issa SS, Shaimardanova AA, Solovyeva VV, Rizvanov AA. Various AAV Serotypes and Their Applications in Gene Therapy: An Overview. Cells. 2023;12(5):785. doi: 10.3390/cells12050785.
17. Kakazu J, Walker NL, Babin KC, Trettin KA, Lee C, Sutker PB, Kaye AM, Kaye AD. Risdiplam for the Use of Spinal Muscular Atrophy. Orthop Rev (Pavia). 2021;13(2):25579. doi: 10.52965/001c.25579.
18. Kang L, Jin S, Wang J, Lv Z, Xin C, Tan C, Zhao M, Wang L, Liu J. AAV vectors applied to the treatment of CNS disorders: Clinical status and challenges. J Control Release. 2023;355:458-473. doi: 10.1016/j.jconrel.2023.01.067.
19. Keinath MC, Prior DE, Prior TW. Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. Appl Clin Genet. 2021;14:11-25. doi: 10.2147/TACG.S239603.
20. Lejman J, Panuciak K, Nowicka E, Mastalerczyk A, Wojciechowska K, Lejman M. Gene Therapy in ALS and SMA: Advances, Challenges and Perspectives. Int J Mol Sci. 2023;24(2):1130. doi: 10.3390/ijms24021130.
21. Masson R, Mazurkiewicz-Bełdzińska M, Rose K, Servais L, Xiong H, Zanoteli E, Baranello G, Bruno C, Day JW, Deconinck N, Klein A, Mercuri E, Vlodavets D, Wang Y, Dodman A, El-Khairi M, Gorni K, Jaber B, Kletzl H, Gaki E, Fontoura P, Darras BT; FIREFISH Study Group. Safety and efficacy of risdiplam in patients with type 1 spinal muscular atrophy (FIREFISH part 2): secondary analyses from an open-label trial. Lancet Neurol. 2022;21(12):1110-1119. doi: 10.1016/S1474-4422(22)00339-8.
22. Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, Lowes L, Alfano L, Berry K, Church K, Kissel JT, Nagendran S, L'Italien J, Sproule DM, Wells C, Cardenas JA, Heitzer MD, Kaspar A, Corcoran S, Braun L, Likhite S, Miranda C, Meyer K, Foust KD, Burghes AHM, Kaspar BK. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. N Engl J Med. 2017;377(18):1713-1722. doi: 10.1056/NEJMoa1706198.
23. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, Iannaccone ST, Kirschner J, Kuntz NL, Saito K, Shieh PB, Tulinius M, Mazzone ES, Montes J, Bishop KM, Yang Q, Foster R, Gheuens S, Bennett CF, Farwell W, Schneider E, De Vivo DC, Finkel RS; CHERISH Study Group. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med. 2018;378(7):625-635. doi: 10.1056/NEJMoa1710504.
24. Mercuri E, Deconinck N, Mazzone ES, Nascimento A, Oskoui M, Saito K, Vuillerot C, Baranello G, Boespflug-Tanguy O, Goemans N, Kirschner J, Kostera-Pruszczyk A, Servais L, Gerber M, Gorni K, Khwaja O, Kletzl H, Scalco RS, Staunton H, Yeung WY, Martin C, Fontoura P, Day JW; SUNFISH Study Group. 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. Erratum in: Lancet Neurol. 2022;21(2):e2. doi: 10.1016/S1474-4422(22)00006-0. Erratum in: Lancet Neurol. 2022;21(3):e3. doi: 10.1016/S1474-4422(22)00038-2.
25. Messina S, Sframeli M. New Treatments in Spinal Muscular Atrophy: Positive Results and New Challenges. J Clin Med. 2020;9(7):2222. doi: 10.3390/jcm9072222.
26. Nishio H, Niba ETE, Saito T, Okamoto K, Takeshima Y, Awano H. Spinal Muscular Atrophy: The Past, Present, and Future of Diagnosis and Treatment. Int J Mol Sci. 2023;24(15):11939. doi: 10.3390/ijms241511939.
27. Ogbonmide T, Rathore R, Rangrej SB, Hutchinson S, Lewis M, Ojilere S, Carvalho V, Kelly I. Gene Therapy for Spinal Muscular Atrophy (SMA): A Review of Current Challenges

and Safety Considerations for Onasemnogene Abeparvovec (Zolgensma). Cureus. 2023;15(3):e36197. doi: 10.7759/cureus.36197.

28. Ottesen EW, Singh NN, Seo J, Singh RN. U1 snRNA interactions with deep intronic sequences regulate splicing of multiple exons of spinal muscular atrophy genes. Front Neurosci. 2024;18:1412893. doi: 10.3389/fnins.2024.1412893.
29. Ponomarev AS, Chulpanova DS, Yanygina LM, Solovyeva VV, Rizvanov AA. Emerging Gene Therapy Approaches in the Management of Spinal Muscular Atrophy (SMA): An Overview of Clinical Trials and Patent Landscape. Int J Mol Sci. 2023;24(18):13743. doi: 10.3390/ijms241813743.
30. Qiao Y, Chi Y, Gu J, Ma Y. Safety and Efficacy of Nusinersen and Risdiplam for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Brain Sci. 2023;13(10):1419. doi: 10.3390/brainsci13101419.
31. Qu Y, Liu Y, Noor AF, Tran J, Li R. Characteristics and advantages of adeno-associated virus vector-mediated gene therapy for neurodegenerative diseases. Neural Regen Res. 2019;14(6):931-938. doi: 10.4103/1673-5374.250570.
32. Ramsey D, Scoto M, Mayhew A, Main M, Mazzone ES, Montes J, de Sanctis R, Dunaway Young S, Salazar R, Glanzman AM, Pasternak A, Quigley J, Mirek E, Duong T, Gee R, Civitello M, Tennekoon G, Pane M, Pera MC, Bushby K, Day J, Darras BT, De Vivo D, Finkel R, Mercuri E, Muntoni F. Revised Hammersmith Scale for spinal muscular atrophy: A SMA specific clinical outcome assessment tool. PLoS One. 2017;12(2):e0172346. doi: 10.1371/journal.pone.0172346.
33. 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-S16. doi: 10.18553/jmcp.2018.24.12-a.s3.
34. Ribero AV, Martí Y, Batson S, Mitchell S, Gorni K, Gusset N, Oskoui M, Servais L, Sutherland CS. Systematic Literature Review of the Natural History of Spinal Muscular Atrophy: Motor Function, Scoliosis, and Contractures. Neurology. 2023;101(21):e2103-e2113. doi: 10.1212/WNL.0000000000207878.
35. Ribero VA, Daigl M, Martí Y, Gorni K, Evans R, Scott DA, Mahajan A, Abrams KR, Hawkins N. How does risdiplam compare with other treatments for Types 1-3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison. J Comp Eff Res. 2022;11(5):347-370. doi: 10.2217/cer-2021-0216.
36. Sawada T, Kido J, Yae Y, Yuge K, Nomura K, Okada K, Fujiyama N, Ozasa S, Nakamura K. Gene therapy for spinal muscular atrophy is considerably effective when administered as early as possible after birth. Mol Genet Metab Rep. 2023;35:100973. doi: 10.1016/j.ymgmr.2023.100973.
37. Schorling DC, Pechmann A, Kirschner J. Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care. J Neuromuscul Dis. 2020;7(1):1-13. doi: 10.3233/JND-190424.
38. Shchaslyvyi AY, Antonenko SV, Tesliuk MG, Telegeev GD. Current State of Human Gene Therapy: Approved Products and Vectors. Pharmaceuticals (Basel). 2023;16(10):1416. doi: 10.3390/ph16101416.
39. Strauss KA, Farrar MA, Muntoni F, Saito K, Mendell JR, Servais L, McMillan HJ, Finkel RS, Swoboda KJ, Kwon JM, Zaidman CM, Chiriboga CA, Iannaccone ST, Krueger JM, Parsons JA, Shieh PB, Kavanagh S, Wigderson M, Tauscher-Wisniewski S, McGill BE, Macek TA. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. Nat Med. 2022;28(7):1390-1397. doi: 10.1038/s41591-022-01867-3.
40. Sturm S, Günther A, Jaber B, Jordan P, Al Kotbi N, Parkar N, Cleary Y, Frances N, Bergauer T, Heinig K, Kletzl H, Marquet A, Ratni H, Poirier A, Müller L, Czech C, Khwaja O. A phase 1 healthy male volunteer single escalating dose study of the pharmacokinetics and pharmacodynamics of risdiplam (RG7916, RO7034067), a SMN2 splicing modifier. Br J Clin Pharmacol. 2019;85(1):181-193. doi: 10.1111/bcp.13786.
41. Tsai LK, Ting CH, Liu YT, Hsiao CT, Weng WC; Society for Neurological Rare Disorders-Taiwan. Recent Advance in Disease Modifying Therapies for Spinal Muscular Atrophy. Acta Neurol Taiwan. 2024;33(3):81-88.
42. Wirth B, Karakaya M, Kye MJ, Mendoza-Ferreira N. Twenty-Five Years of Spinal Muscular Atrophy Research: From Phenotype to Genotype to Therapy, and What Comes Next. Annu Rev Genomics Hum Genet. 2020;21:231-261. doi: 10.1146/annurev-genom-102319-103602.
43. Yeo CJJ, Darras BT. Overturning the Paradigm of Spinal Muscular Atrophy as Just a Motor Neuron Disease. Pediatr Neurol. 2020;109:12-19. doi: 10.1016/j.pediatrneurol.2020.01.003.
44. Yeo CJJ, Simeone SD, Townsend EL, Zhang RZ, Swoboda KJ. Prospective Cohort Study of Nusinersen Treatment in Adults with Spinal Muscular Atrophy. J Neuromuscul Dis. 2020;7(3):257-268. doi: 10.3233/JND-190453.