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Short Communication

# Antisense Oligonucleotides Therapy: An Appropriate Approach for Spinal Muscular Atrophy Genetic Management

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## DESCRIPTION

In the area of genetic disorders few conditions are as devastating as Spinal Muscular Atrophy (SMA). SMA is a group of inherited neuromuscular disorders characterized by the loss of motor neurons and progressive muscle wasting leading to severe disability and often early death [1]. Historically treatments for SMA were limited offering mainly supportive care to manage symptoms and slow progression. However the emergence of Antisense Oligonucleotide (ASO) therapies has bought in a new era of hope and targeted treatment for this challenging disease.

SMA is caused by mutations in the Survival Motor Neuron 1 *SMN (F)* gene which encodes the protein critical for motor neuron function [2]. In individuals affected by SMA there is a deficiency or absence of functional SMN protein due to mutations that disrupt normal gene function. The severity of SMA varies depending on the number of copies of a related gene *SMN2* which produces a small amount of functional SMN protein [3].

### The role of ASOs in SMA treatment

Antisense Oligonucleotides (ASOs) represent a innovative approach to treating SMA by targeting the splicing of the *SMN2* gene [4]. *SMN2* normally produces a truncated and unstable form of the SMN protein due to alternative splicing events. ASOs are synthetic short DNA or RNA molecules designed to bind complementary RNA sequences, thereby modulating gene expression or splicing patterns. In SMA ASOs are used to promote the inclusion of exon 7 in *SMN2* messenger RiboNuclic Acid (mRNA) resulting in the production of more functional SMN protein.

**Mechanism of action of ASOs:** ASOs designed for SMA typically target specific regions of the *SMN2* pre-mRNA where splicing occurs [5]. By binding to these regions ASOs can alter the splicing process leading to increased inclusion of exon 7 in mature mRNA transcripts. This modification enables the production of more full-length SMN protein which is critical for maintaining motor neuron health and function [6].

**Development of ASO therapies for SMA:** The development of ASO therapies for SMA has been a collaborative effort involving researchers, clinicians, pharmaceutical companies and patient advocacy groups. The drive from laboratory study to clinical application has been marked by significant milestones including preclinical studies in animal models of SMA and multiple phases of clinical trials to evaluate safety and efficacy in human patients.

### Preclinical studies

Early preclinical studies laid the foundation for ASO therapy in SMA. These studies involved testing different ASO designs and delivery methods in animal models of SMA to assess their ability to increase SMN protein levels, improve motor function and prolong survival. The results in the animal studies provided the rationale for advancing ASO therapies into clinical trials.

### Clinical trials

Clinical trials are essential for evaluating the safety, tolerability and efficacy of ASO therapies in human patients with SMA. These trials are conducted in multiple phases each designed to address specific experimental questions and regulatory requirements.

**Phase 1 trials**: Focus on evaluating the safety and pharmacokinetics of ASO therapy in a small number of healthy volunteers or patients with SMA. These trials provide initial data on dosage, administration route and potential side effects.

**Phase 2 trials**: Expand to include a larger group of patients with SMA to further assess safety and begin to evaluate efficacy endpoints such as improvements in motor function or respiratory function. These trials help refine dosing strategies and identify potential biomarkers of treatment response.

**Phase 3 trials**: Involve a larger and more diverse population of patients with SMA to confirm efficacy and further evaluate long-term safety. These pivotal trials are important for obtaining regulatory approval and bringing ASO therapies to market.

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## Approved ASO therapies for SMA

The success of ASO therapies in clinical trials has led to the approval of several ASO-based treatments for SMA by regulatory agencies around the world. These therapies have transformed the treatment perspective for SMA offering new hope and improved outcomes for patients and their families.

**Nusinersen (spinraza)**: Developed by Biogen nusinersen was the first ASO therapy approved for the treatment of SMA. It targets the *SMN2* gene to increase the production of functional SMN protein and has been shown to improve motor function and survival in patients with SMA [7].

**Risdiplam (evrysdi)**: Developed by Roche/Genentech risdiplam is an oral ASO therapy that enhances *SMN2* gene splicing to increase SMN protein levels. Approved for use in infants, children and adults with SMA risdiplam offers a convenient treatment option with demonstrated efficacy and safety [8-10].

## Challenges and future directions

While ASO therapies represent a significant advancement in the treatment of SMA challenges remain that warrant continued studies and innovation.

**Accessibility and affordability**: ASO therapies are complex biologic drugs that require specialized manufacturing processes and can be costly. Ensuring broad access to these therapies globally remains a challenge particularly in low-resource settings.

**Long-term safety and efficacy**: Long-term data on the safety and efficacy of ASO therapies in SMA are still evolving. Continued monitoring and study are needed to understand the durability of treatment effects and potential late-emerging adverse events.

# CONCLUSION

Atrophy by targeting the underlying genetic cause of the disease and increasing production of functional Survival Motor Neuron (SMN) protein. Exploring combination therapies such as ASO therapy with other treatment modalities (e.g., gene editing, neuroprotective agents) may offer synergistic benefits and further enhance outcomes for patients with SMA.

From preclinical studies to clinical trials and regulatory approval ASO therapies have demonstrated remarkable efficacy in improving motor function and quality of life for patients with SMA. As studies continues and new innovations emerge, ASO therapies hold potential not only for SMA but also for other genetic disorders prepare for personalized and targeted treatments in the field of Genetic Antisense Iligonucleotide (ASO) therapies have revolutionized the treatment of spinal muscular medicine.

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