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## SMA Therapy in Poland: New Hopes and Challenges

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Abstract: Spinal muscular atrophy (SMA) is a genetically inherited disease whose symptoms appear in children at a fairly early age. The main cause of the disease is a mutation of the SMN1 gene, which causes the lack of production of SMN This results in the disappearance of motoneurons, which consequently leads to the disappearance of the patient's ability to move and his death. An important element of coping with the disease is its early detection in newborn screening, because the earlier we start the drug, the greater the chance that the patient will maintain motor efficiency. The article describes treatment options for children in Poland, i. e. the use of such drugs as Nusinersen, which increases the amount of SMN protein, gene therapy Onasemnogen aeparvovec, which increases the amount of SMN gene, Ridisplam, which increases the amount of SMN protein, and salbutamol, which helps patients to breathe. The article also provides information about new drug therapies for the treatment of SMA and the stage of clinical trials at which they are currently being developed. It is important to look for new solutions in the treatment of SMA.

Objective: To familiarize the readers of the article with the problems of SMA treatment in Poland, as well as to broaden their knowledge of new available drugs for the treatment of this disease.

SMA Therapy in Poland: New Hopes and Challenges

Background

Spinal muscular atrophy is an inherited autosomal recessive disease, characterized by the progressive weakness and atrophy of the muscles. It is one of the most common and at the same time severe genetic disorders. Its estimated incidence in Poland is approximately 1 in 8300 live births [1]. The disease is caused by mutations in the SMN1 (survival of motoneuron 1) gene, which was identified in chromosome 5q13. Homozygous mutations lead to the deficiency of the SMN protein and thus result in the degeneration of the motor neurons in the anterior horns of the spinal cord. SMN protein is also encoded by the SMN2 gene, however its transcripts, due to alternative splicing, predominantly exclude exon7, which results in a shorter, non-functional protein. The produced inconsiderable amount of the full-length SMN is not enough to stop the degeneration of motoneurons and the symptoms from manifesting. However, the number of copies of the SMN2 gene is a significant factor modifying the phenotype of the patient – in general, usually, a higher SMN2 gene copy number correlates with a later onset of the symptoms and a milder average clinical presentation [2][3].

SMA can be divided into 5 subtypes (SMA0-SMA4) based on the time of the first appearance of the symptoms and the acquired milestones. SMA type 0 – prenatal – is very rare (<1%) and life expectancy is around 1 month. The most common types are SMA1 (60%) and SMA2 (30%). The SMA type 1 patients, if not treated, start to present symptoms before they are 6 months old and the children are not able to sit without support. SMA type 2 patients during the first months of their life often show proper child development. Initially, the children have a proper motor trajectory, obtain milestones such as sitting without support, and may learn to stand with support. However, between 6. and 18. month their development is stalled and starts to regress. The child weakens and does not acquire the ability to walk. In the case of SMA type 3, the first symptoms of the disease may start to occur between 18. month and adulthood. Patients obtain the ability to walk, but with time become weaker, cannot walk without support, and may need help with everyday tasks. SMA type 4 is a very rare disease with the onset of symptoms in adulthood. The disease is progressive, just like in the other types, however, SMA4 usually does not lead to the loss of the ability to walk [4].

In Poland, since September of 2022, there have been three available and reimbursed disease-modifying drugs – nusinersen (which had been included in the reimbursement list since 2019), risdiplam and onasemnogen abeparwowek [5]. Two of them - nusinersen and risdiplam – have their mechanism of action based on modifying the splicing of mRNA produced thanks to the SMN2 gene. The modification of splicing of the mRNA results in a higher amount of functional SMN protein. Onasemnogen abeparwowek is nowadays the only registered gene therapy available as a treatment option for patients with SMA. Onasemnogen abeparwowek is administered as a single dose through intravenous infusion. Its mechanism of action is based on the delivery to the organism of the patient a working SMN1 gene, which is carried by a vector AAV9 (composed of adenoassociated virus serotype 9). The working SMN1 gene ensures the production of the functioning full-length SMN protein [6].

The introduction of the three treatments mentioned above options changed the clinical approach to spinal muscular atrophy. SMA used to be considered an incurable disease, with few treatment options, inevitably leading to premature death or severe disability. Now, thanks to the new disease-modifying drugs, patients have a chance to have a higher quality of life. However, the success of the treatment relies heavily on prompt intervention, even before the symptoms start to manifest. Thus, early recognition of the disease plays a pivotal role in making a favorable prognosis for the patient. In connection to the importance of early recognition of the disease, since the 28$^{th}$ of March 2022, newborns in all regions of Poland are undergoing screening for SMA. Up to the 29$^{th}$ of September 2022, over 330 thousand of newborns have been screened for SMA, and 47 of them have been diagnosed with SMA. The introduction of the screening for SMA and reimbursement of the 3 disease-modifying drugs made Poland one of the leaders in the treatment of SMA in Europe [7].

SCREENING

Screening of newborns is one of the most important preventive measures enabling early detection of congenital diseases. Screening is designed to detect the disease at the stage when a patient doesn’t have clinical symptoms

yet. Detecting a congenital defect at such an early stage reduces patient mortality and the risk of severe disease. Early implementation of specialized treatment reduces the likelihood of irreversible complications, both physical and intellectual; associated with disease progression. The long-term effects of screening newborns are also a reduction in the costs of treatment and care for children burdened with congenital defects [8]. Screening is free of charge and is performed on all newborns usually at least 24 hours after birth. The tests consist of taking capillary blond from the heel, then the blond is applied to the appropriate tissue paper and sent to the laboratory. Parents receive information about positive screening results after 1-2 weeks [9]. According to the government program for screening newborns in Poland for 2019-2026, tests are carried out for 30 congenital diseases, such as congenital hypothyroidism (CHT), phenylketonuria (PKU), cystic fibrosis (CF), congenital adrenal hyperplasia (CAH), metabolic defects and spinal muscular atrophy (SMA). Thanks to the screening of newborns in Poland, every year about 450 children with congenital defects are diagnosed [8]. Moreover, during the hospital stay, newborns have more examination: screening of heating, examination for heart defects (pulse oximetric test), and examination for hip dysplasia.

## SMA TREATMENT IN POLAND

Spinal muscular atrophy was once considered as an incurable disease, and therapy was limited to symptomatic treatment. However, medications are now available that effectively halt the progression of the disease and even offer hope for a cure [10]. Being a monogenetic neuromuscular disease, the resulting phenotypic spectrum is complex, and SMA is generally viewed as a systemic disease. Consequently, the care of patients with SMA requires multidisciplinary management of problems [11].

In Poland, we can divide the treatment of SMA into three components. Among them, we distinguish pharmacological treatment, symptomatic treatment and conservative treatment. Symptomatic treatment aims to reduce the discomfort associated with the development of the disease. Depending on the severity of the disease, complications can include: generalized muscle weakness, respiratory failure, inability to swallow, muscle contractures, scoliosis, and incidence of infectious diseases. The patient is therefore treated with rehabilitation, orthoses, mechanical respiratory support, gastrostomy, surgical correction of scoliosis, and others. Proper rehabilitation increases muscle flexibility and improves muscle function, and can reduce contractures and scoliosis and the pain they cause. During a respiratory infection, it is often necessary to support the cough reflex with a coflator. Loss of muscle function makes it necessary for patients to use various types of equipment to move around, and to hold their heads. Preventive treatment is aimed at preventing complications associated with SMA. Intensive rehabilitation is used, non-invasive breathing support is introduced as a preventive measure, some patients are given a special diet, corsets are used to delay the onset of spinal curvature and immunizations are administered. [12]

A breakthrough in the treatment of SMA came with the introduction of the first drug: nusinersen- Spinraza [13]. It is the world's first drug for the causal treatment of the disease. It has been used in the European Union since 2017 [12], now fully reimbursed in Poland [13]. Nusinersen is an antisense oligonucleotide that specifically binds to a repressor in exon 7 of SMN2 to enhance exon 7 inclusion and increase the production of functional SMN protein. Nusinersen is the first new oligonucleotide-based drug to target the central nervous system for the treatment of SMA [14]. With increased amounts of this protein, degeneration of motoneurons stops and the disease stops progressing. If the disease is not fully advanced and the muscles have not yet atrophied, together with proper physiotherapy and multispecialty medical care, this drug can bring significant improvement to the patient. The effects last as long as the drug is taken. Following treatment, the gene undergoes partial repair and begins to encode a larger (by about 40%) amount of SMN protein. This is usually sufficient to stop further degeneration of motoneurons [12]. Based on studies, improvements in motor function have been noted, including improved milestones of motor development in all types of SMA, including SMA type 3[16]. The best motor response was observed with early initiation of treatment. Significantly, the pre-symptomatic treatment prevented the onset of disease symptoms [15]. Nusinersen therapy is a permanent therapy, to be taken indefinitely. All patients regardless of age and weight take the same dose of the drug. Due to its size, the nusinersen molecule does not cross the so-called blood-brain barrier, which separates the central nervous system

from the bloodstream. To reach the motoneurons, nusinersen is administered directly into the cerebrospinal fluid in a procedure known as lumbar puncture [12, 16].

The second medication used for treatment in Poland is Zolgensma. It is a medication developed for the treatment of spinal muscular atrophy and available on the market since 2019, and in the European Union since May 2020. The causative action is to raise the level of SMN protein in motoneurons, the deficiency of which underlies spinal muscular atrophy [12]. Onasemnogen abeparwowek (formerly AVXS-101, Zolgensma) is a gene therapy based on a viral vector related to adenovirus serotype 9, abbreviated as AAV9 designed to deliver a functional copy of the SMN1 gene to motor neurons via a single intravenous infusion [12,17]. Once the drug is administered to a patient, the viruses "infect" the body's cells, and the DNA sequence makes its way into the cell nucleus, where it begins making the missing SMN protein [12]. Zolgensma is approved in the European Union for the treatment of patients with spinal muscular atrophy who either have clinical signs of the first form of SMA or have no more than three copies of the SMN2 gene regardless of the form of SMA [18]. A major advantage of the Zolgensma drug is its rapid onset of action. The drug significantly raises SMN protein levels within hours of administration - so much so that the level of the protein is comparable to that of a healthy person. This makes the drug exceptionally useful for treating infants and young children whose SMA symptoms have not yet appeared or have appeared very recently. Another advantage of this drug is that it is used once, unlike other medications that must be taken continuously. This is because permanent immunity is produced in the body of a person who has taken the drug based on the AAV class of virus. The Zolgensma drug is administered in a hospital setting as an intravenous infusion, lasting about an hour. In Poland, the drug has been reimbursed by the National Health Fund since September 1, 2022, for the treatment of children with SMA up to 6 months of age who have been included in Poland's newborn screening program and who have not started treatment with another SMA drug.

The third registered medication in Poland is Risdiplam. It is a drug developed for the causal treatment of SMA. It is on the market as a syrup that is taken orally once a day [12]. Risdiplam is an orally administered small molecule that modifies RNA splicing of the SMN2 pre-messenger and increases functional SMN protein levels [19]. Risdiplam is a drug that targets SMN2 to improve the production of viable SMN protein and is the first oral drug approved for the treatment of SMA. In the FIREFISH and SUNFISH clinical trials, risdiplam improved motor function in patients of all ages, with improvements sustained after 24 months of treatment. Risdiplam was generally well tolerated in these trials, with a favorable benefit-to-risk ratio. As an orally administered drug, risdiplam provides a convenient and useful treatment option across a wide range of patient ages and SMA subtypes [20]. Based on ongoing studies, risdiplam has received approval for use in SMA patients older than 2 months of age who have SMA types 1, 2 or 3, or who are pre-symptomatic and have no more than four copies of the SMN2 gene. As of September 1, 2022, risdiplam is reimbursed in Poland for the treatment of patients who have contraindications to nusinersen [12].

In addition to the basic drugs, salbutamol is also used. Based on clinical trials, long-term oral administration of salbutamol was found to benefit respiratory function in children with SMA and seemed to increase inspiratory muscle strength in a small cohort of SMA II patients [21].

New SMA Drug Therapies

One of the challenges in the treatment of SMA is to find drugs that temporarily stop the progression of the disease or cause it to be completely cured. Currently, there are about 17 substances in the studies that are supposed to affect the course of SMA [22]. One of the main areas of research is to find substances that: replace a copy of the modified SMN1 gene, activate rapid skeletal troponin, and are antibodies to promiostatin. Unfortunately, the drug registration process is lengthy.

The following substances are currently in Phase 3 clinical trials:

- Apitegromab (SRK-015) is a human monoclonal antibody against promiostatin that is being manufactured. Myostatin is an enzyme that inhibits muscle development. The action of the drug is thus

to improve motor neuron functions and increase muscle mass of the body [23]. The clinical trial is called SAPPHIRE, and the results of the trial are expected in December 2024, the drug is being tested in children aged 2 to 21 years with SMA type 2 and 3 to confirm the supportive effect of apitegromab for Risdiplam or Nusinersen therapy [24]. In Phase 2 clinical trials, TOPAZ was shown to increase motor function by approximately 4 points on the Hammersmith Motor Performance Scale for SMA [25].

- Onasemnogene abeparvovec-xioi, is a drug already registered in children for the treatment of SMA type 1, which has contributed significantly to improving their quality of life. Currently, large clinical trials are underway to confirm its effectiveness in different target groups. The target group of one clinical trial in children aged 2 years to 18 years with type 2 SMA, the STEER clinical trial is scheduled to end in September 2024 and another study in children aged 12 months and older up to 21. 5 kg SMART [26,27].

Other promising drugs in clinical trials include:

- Reldesemtiv activator of rapid skeletal troponin, which sensitizes muscle sarcomeres to calcium, leading to an increased response to neuromuscular impulse and thus an increase in muscle contraction [28]. Phase 2 studies showed that the drug increased exercise tolerance in subjects. They included 70 people with SMA types 2, 3, and 4 over 12 years of age [29].
- RO7204239 in combination with Ridisplam in symptomatic children with SMA type 2 aged 2 to 10 years MANATEE [30].

It usually takes about 10-15 years from the invention of a medicinal substance to its introduction into circulation. That is why it is important that so many pharmaceutical companies invest money in drug trials because it increases the likelihood that a substance will pass preclinical and clinical trials. [31]

Conclusions

Spinal muscle atrophy for many years has been considered an incurable disease, with no effective treatment options. Nowadays, thanks to the intensive research focused on the new drugs in SMA, the therapeutic landscape has changed. Patients have a chance at living longer life in relatively good health. Screening newborns for the disease made it possible to start the treatment as soon as possible – even before the onset of the first symptoms, which made the therapy more effective. However, it is important to note, that because the new therapeutic options have become available to patients only recently, it is impossible to foresee all potential side effects, which may manifest many years after the administration of a drug. More research is needed to ensure that the treatment of SMA is as effective and safe as possible

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