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# History review of spinal muscular atrophy

## Rys historyczny rdzeniowego zaniku mięśni

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Abstract

Spinal muscular atrophy is a neuromuscular disorder caused by the degeneration of alpha motoneurons in the spinal cord. This autosomal recessively inherited disease manifests with progressive muscular atrophy and weakness. First attempts to diagnose this condition date back to the late 19th century. At that time, many researchers tried to understand the aetiology of these unusual symptoms and to describe for the first time a previously unknown disease entity. Werdnig, Hoffman, Thomson and Beevor have shown the specific clinical picture of spinal muscular atrophy by noticing its hereditary nature. Further observations allowed to create a classification system for different types of spinal muscular atrophy and to conduct genetic research to identify the underlying molecular mechanisms. In the late 1990s, Gillian's team discovered *SMN* gene location. This provided an opportunity to initiate clinical trials into targeted treatment. Many strategies have been used, such as increasing SMN protein levels, modifying invalid splicing or modifying calcium release with troponin regulatory complex. These studies helped develop therapies, such as nusinersen, onasemnogene abeparvovec or risdiplam, which were subsequently approved by the Food and Drug Administration. This review shows a historical timeline of spinal muscular atrophy, highlighting the important milestones in its discovery.

**Keywords:** spinal muscular atrophy, historical review, neuromuscular disease, childhood

Streszczenie

Rdzeniowy zanik mięśni to zaburzenie nerwowo-mięśniowe spowodowane degeneracją motoneuronów alfa – komórek rogów przednich rdzenia kręgowego. Choroba dziedziczona jest w sposób autosomalnie recesywny i objawia się postępującym osłabieniem i zanikiem mięśni. Początki prób diagnozy rdzeniowego zaniku mięśni sięgają końca XIX wieku. Wielu badaczy próbowało wówczas zrozumieć przyczynę tych nietypowych objawów i po raz pierwszy opisać nieznaną wcześniej jednostkę chorobową. Artykuły Werdniga, Hoffmana, Thomsona i Beevora ukazały specyficzny obraz tej choroby, zwracając uwagę na jej dziedziczny charakter. Dalsze obserwacje umożliwiły również stworzenie systemu klasyfikacji poszczególnych typów rdzeniowego zaniku mięśni oraz prowadzenie badań genetycznych poszukających jego molekularnego podłoża. Pod koniec lat 90. XX wieku grupa Gillian dokonała odkrycia polegającego na zlokalizowaniu genu *SMN*. Pozwoliło to na prowadzenie badań nad celowanym leczeniem choroby. W tym celu wykorzystywano wiele strategii, takich jak zwiększanie poziomu białka SMN, modyfikacja nieprawidłowego splicingu czy wpływ na uwalnianie wapnia za pomocą kompleksu regulatora troponiny. Dzięki tym badaniom opracowano takie leki, jak nusinersen, onasemnogene abeparvovec czy risdiplam, które następnie zostały zatwierdzone przez Agencję Żywności i Leków. Celem niniejszej pracy jest przegląd piśmiennictwa na temat historii rdzeniowego zaniku mięśni i jego leczenia.

**Słowa kluczowe:** rdzeniowy zanik mięśni, rys historyczny, choroba nerwowo-mięśniowa, dzieciństwo

## INTRODUCTION

Spinal muscular atrophy (SMA) is one of the most common neuromuscular disorders caused by alpha motor neuron degeneration (Darras et al., 2009; Kroczka et al., 2009). The incidence is approximately 1:11,000 live births and the carrier frequency is 1:54 individuals (Finkel et al., 2017; Mendell et al., 2017). This is a progressive autosomal recessive disorder caused by mutation and/or deletion in the survival motor neuron 1 (*SMN1*) gene, which is responsible for insufficient production of SMN protein. The lack of this protein manifests in progressive muscular atrophy and weakness of limbs and trunk, disappearance of tendon reflexes, respiratory disorders and inhibition of motor development (Bertini et al., 2017; Ross and Kwon, 2019). Attempts at diagnosis date back to the 19th century, when Werdnig described the first cases of SMA. In their first published works, Hoffmann, Thomson, Sylvestre and Beevor attempted to understand the causes of this disorder. This posed a challenge for scientists due to the wide spectrum of symptoms and short lifespan of patients. However, advances in the field of medicine contributed to improved diagnostic possibilities in this group of patients (Dubowitz, 2009; Ross and Kwon, 2019).

Further development in medical sciences allowed to identify the genetic cause of this disorder, which translated into improved effectiveness of SMA therapy. Initially, research began with the use of substances previously known from other therapies, such as asthma treatment or sickle cell anaemia medications. Then, animal models and gene therapy were gradually introduced (Dubowitz, 2009, 2019; Kolb and Kissel, 2011; Ross and Kwon, 2019).

The aim of this paper is to offer a historical perspective on the origins of SMA diagnosis and treatment.

## HISTORY OF SPINAL MUSCULAR ATROPHY

The origins of SMA go back to the 19th century, when in 1891 Guido Werdnig from the University of Vienna described this disease for the first time. During Werdnig's lecture entitled "On a case of muscular dystrophy with positive spinal cord findings", he told the story of two brothers who at the age of 10 months presented with alarming symptoms (Ross and Kwon, 2019). The infants showed signs of progressive lower limb weakness and muscle tremors (Kolb and Kissel, 2011). Both cases ended with early death. One of the brothers died of pertussis and hydrocephalus, while the other died at the age of six (Dubowitz, 2009). Autopsy of these patients showed bilateral symmetrical loss of anterior horn cells. Similar cases were reported by Thomson. His report, clinically and pathologically, was better illustrated and of better quality (Ross and Kwon, 2019).

The same year, Johann Hoffmann of Heidelberg University described patients with similar symptoms. He was the first one to introduce spinale Muskelatrophie (spinal muscular atrophy) terminology. Like Werdnig, Hoffmann noticed progressive weakness, tremors and early death in this group of patients. Additionally, he emphasised that these children were born to healthy parents whereas their siblings also presented similar symptoms (Ross and Kwon, 2019). In his revolutionary articles from 1893, 1897 and 1900, Hoffmann reviewed two of Werdnig's cases and added seven of his patients from three families (Dubowitz, 2009; Kolb and Kissel, 2011). In his papers, he included histological illustrations of the muscle tissue and central nervous system, as well as demonstrated degeneration of the anterior horn cells in the spinal cord (Dubowitz, 2009). It is worth noting that Werdnig–Hoffmann disease was finally identified as a severe infantile form of SMA, which was later found to be of intermediate severity (Kolb and Kissel, 2011).

In 1893, Thomson and Bruce published another case of SMA. The child presented with intermediate severity of symptoms, although the authors emphasised the progressive nature of scoliosis, for the first time. In their work, they also mentioned typical muscle changes and the loss of anterior horn cells. In 1894, Werdnig wrote another review, but it did not bring any important contribution to medical literature (Dubowitz, 2009). In 1898, Haushalter described a case of a young girl who, from the first month of her life, started to lose strength in limb muscles. After six months, she could barely lift her hands up to her mouth, there was no contraction in the abdominal muscles and the weakness led to total lower limb paralysis and partial upper limb paralysis (Beevor, 1902).

The first severe case of SMA was described in 1899 by Sylvestre (Kolb and Kissel, 2011). During a meeting of the Paediatric Society of Paris, he presented a two-month-old infant case with flaccid paralysis of all four extremities and trunk, excluding the diaphragm, neck and head muscles. The infant also had a deformed thorax and hereditary history, which showed that two sisters, among five siblings, had similar symptoms of paralysis and died at the age of three and five months from pulmonary complications. Neither case was autopsied (Beevor, 1902; Dubowitz, 2009).

In 1901, Bruns described three cases with the same signs and symptoms as those from Werdnig and Hoffmann in every detail. The only exception was that the first child survived to the age of sixteen, while the second and third were twelve and six at the time of writing the paper. In the first and the third case, the disease began when children could already walk, at the age of two (Beevor, 1902).

The following year, Beevor presented another comprehensive publication. He described two cases (a boy and a girl) with similar symptoms, bringing attention to the progressive paralysis of all muscles of the lower extremities and the trunk with the exclusion of the diaphragm. Patients also had a bell-shaped chest with atrophy of the intercostal muscles. Both cases were delivered by the same obstetrician – James Collier. The first case was a boy whose symptoms began at the age of five weeks. There were no additional cases or symptoms in the rest of the family except for eight siblings. The oldest sister was completely paralysed at the end of her



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first month. She was hospitalised when four months old and died after two weeks. Another sister was able to move all of her limbs at birth, but she developed symptoms at the age of six months and gradually got weaker and died at the age of eight months. There was also an affected brother among the siblings, who developed properly after birth, but developed progressive paralysis starting in the left upper extremity at the age of six weeks. The other siblings were healthy. The mother reported not feeling any child movement in her obstetric history. William (the boy's name) appeared to be developing properly and be well-nourished, but there was complete paralysis of intercostal muscles with exception of the diaphragm, with flaccid and immobilised extremities. Additionally, clinical examination showed a lack of reflexes and sensory disturbances. The child died of cyanosis, which developed at the age of eight weeks. The autopsy revealed anterior horn cellular degeneration of the spinal cord (Beevor, 1902).

In another case, a six-week-old girl presented with similar symptoms to William's. Her birth was heavily complicated with brachial plexus injury and cervical haematomyelia. What is more, despite the injury, she was able to move this extremity, while the other ones showed signs of paralysis. Family history was unremarkable. Four of the siblings were healthy. Her diaphragm was moving freely, but there was no intercostal muscle movement. She died at the age of 15 weeks due to bronchitis and cyanosis complications (Beevor, 1902). Beevor conducted an interesting comparative study based on these two cases, verifying similarities between traumatic, perinatal haematomyelia and anterior horn cell atrophy (Dubowitz, 2009). In his article, he drew attention to multiple similarities, previously described by Werdnig and Hoffmann; however, the children presented by him showed alarming symptoms earlier and the rate of progression was faster (William's case showed specific symptoms in the prenatal period) (Beevor, 1902).

The first clinical picture of the severe form of SMA was illustrated in his personal copy of paediatric textbook by Jonathan Hutchinson published in 1910 (Dubowitz, 2019). It presented a child with a bell-shaped chest (indicating retraction and wasting of intercostal muscles), prominent abdomen and upper extremity position in internal rotation and flexion. Another work on SMA was a monography by Sven Brandt from 1950, created for his doctoral dissertation thesis. As a part of his PhD work, he described 112 cases from 89 Danish families, with 97 being under one year and presenting with the most severe form of SMA (Dubowitz, 2009).

At the end of the fifth decade of the 20$^{th}$ century, Wohlfart, Fez and Eliasson presented a milder form of SMA in their work. In a publication from 1956, they described cases of patients with ability to stand and walk, whose lifespan was comparable to that of the general population (Kolb and Kissel, 2011). This was also described in more detail by Kugelberg and Welander (Ross and Kwon, 2019). In all of these cases attention was brought to finding the cause, i.e. loss of the anterior horn cells, and to the symmetrical characteristics of proximal weakening of the extremities affecting axial, intercostal and eyeball muscles (Kolb and Kissel, 2011).

In the last sixty years, many cases of SMA were described. Nonetheless, it was only in 1961 that an attempt to classify SMA was made. Byers and Banker divided SMA patients into three categories: the first group consisted of cases with symptom onset in the prenatal period or during the first two months of their life, characterised by weakness and early death. The second group showed symptoms between the second and twelfth month of their life with more localised weakness and a longer lifespan. The third group included patients who developed symptoms after one year of life (Ross and Kwon, 2019).

In 1964, Dubowitz described thirteen patients with the intermediate SMA. The symptoms occurred between 4 and 24 months of age and each patient was noted to survive at least six years. The author concluded that the patients described and those with Werdnig–Hoffmann or Kugelberg–Welander forms do not represent separate diseases, but different variations of the same physiological process with a wide range of symptoms (Dubowitz, 2009). In 1967, the first-ever classification of SMA was improved with more in-depth descriptions of the three forms. During another half-century, there was a controversy if the types of SMA concern the same or perhaps some other diseases (Kolb and Kissel, 2011).

The year 1990 was a breakthrough, when Gilliam's team in New York conducted research in a group of extended Amish families with a mild variation of SMA, which allowed to determine the location of the *SMN* gene. Shortly after that, Melki's group in Paris confirmed this discovery. The gene locus was then verified by both groups. With the findings of this gene, geneticists were able to confirm SMA in cases with an atypical presentation of the disease (Dubowitz, 2009). In 1991, a meeting of clinicians and geneticists was held in New York to promote research on the identification of the gene. They divided infants into numerical types taking into account the highest level of mobility i.e. type three presented with standing and walking, type two with achieving unsupported sitting. The inability to sit unsupported was the most severe form. This group was subdivided into two types IA and IB, depending on the onset of the symptoms or breathing disorder (Dubowitz, 2019). In 1992, another meeting of this committee was held to discuss the value of standardising the clinical database for SMA patients based on the first clinical trials (Munsat and Davies, 1992).

It was discovered that 95% of SMA cases, regardless of the type, were caused by homozygous deletion in the *SMN1* gene on chromosome 5q13.3 (Kolb and Kissel, 2011). Melki's team isolated and characterised *SMN*, later named the survival motor neuron gene. They concluded that it was a complex gene, as this part of chromosome five is duplicated and healthy individuals have two copies of this gene – active *SMN1* and inactive *SMN2*. Severe cases have exon 7



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deletion in the active gene with no changes in *SMN2*. Milder types also show a deletion in *SMN1*, but have increased copies of *SMN2*, which gives them some compensation for the *SMN1* deficit. This research provided essential database to conduct further clinical trials and created an opportunity to launch further research on causal treatment (Lefebvre et al., 1995).

In 2005, The International Standard of Care Committee for Spinal Muscular Atrophy was created. Its goal was to determine guidelines for the clinical procedures in this group of patients. The Committee consisted of 12 main members cooperating with more than 60 SMA experts. Together they reached a consensus on five care areas: diagnostic/new interventions, pulmonary, gastrointestinal/nutrition, orthopaedics/rehabilitation and palliative care (Wang et al., 2007). Ching H. Wang, in cooperation with a panel of experts, published a consensus statement which standardised care for SMA patients, depending on SMA types. This document provides guidelines for diagnosis, assessment and monitoring of this group of patients and is regularly updated (Mercuri et al., 2012).

In order to better illustrate the above information, a flow chart showing the timeline of events is presented (Fig. 1).

## SPINAL MUSCULAR ATROPHY – TREATMENT

The identification of the SMN gene in 1995, the development of animal models and a targeted approach to the topic of increased SMN protein levels accelerated the research on the development of SMA treatment (Bharucha-Goebel and Kaufmann, 2017). In the experiments conducted on mice, increased SMN expression was discovered through small molecule and nonsense oligonucleotide therapies. The correlation between the number of *SMN2* copies and phenotype disease intensity was also confirmed. Furthermore, animal models helped identify a therapeutic window, outside of which induction of the gene expression is less effective (Bharucha-Goebel and Kaufmann, 2017; Kolb and Kissel, 2011).

Both gene and nonsense oligonucleotide-based therapies showed the greatest effects when administered in the first few days after birth in mice. It was found that in the case of swine models, the moment of symptom appearance still showed improvement in proximal weakness and in electrophysiological tests, which suggests that the therapeutic window may be a little wider with humans (Bharucha-Goebel and Kaufmann, 2017; Farrar et al., 2013).

There have been many attempts to treat SMA. Calder and co-authors conducted studies on histone deacetylase (HDAC) inhibitors and related mechanisms. In their publication in 2003, they showed that valproic acid, HDAC inhibitor, causes 2–4 times more increase in SMN protein levels with fibroblasts cultured from SMA patients. This was then proven by increased median lifespan in mice models (Bharucha-Goebel and Kaufmann 2017; Brichta et al., 2003; Calder et al., 2016). Following the positive results in animal models, clinical trials were launched. The CARNI-VAL I study conducted in 2005–2007 included 61 sedentary patients at the age of 2 to 8 years. SMA patients received valproic acid or placebo for six months. Nonetheless, there was no noticeable functional improvement and 80% of patients experienced side effects in the form of increased body weight, as presented in a 2010 publication (Swoboda et al., 2010). Other CARNI-VAL II study assessed 33 SMA 3 patients with walking ability between the ages of 3 and 17 years. They received valproic acid and placebo for 12 months. 17% of patients showed 20% increase in body weight. Both CARNI-VAL I and II studies showed that valproic acid is not effective in improving strength or motor function in SMA patients (Kissel et al., 2011).

Further trials were undertaken with trichostatin A, which is the strongest HDAC inhibitor (Bharucha-Goebel and Kaufmann, 2017). Research in mice showed increased body weight and stability of motor functions, which was confirmed in 2008 publications, but further treatment was abandoned due to excessive toxicity in chronic treatment of SMA patients (Calder et al., 2016; Narver et al., 2008).

Subsequently, smaller trials were conducted on albuterol, which is an antagonist of beta-adrenergic receptor used mostly in asthma treatment. A pilot trial published in 2002 showed a statistically significant increase in muscle function, but due to the lack of placebo-controlled group, no wide range of albuterol use for SMA treatment was proven (Kinali et al., 2002). Another tested medicine for SMA was hydroxyurea, previously used in the treatment of solid tumours or anaemia drepanocytica. Despite high hopes, the treatment carried out in 2007 failed to show any benefits in 28 patients (Bharucha-Goebel and Kaufmann, 2017; Calder et al., 2016; Chen et al., 2010). Other studies have also attempted to change the intended usage with some additional treatments. These included creatinine, riluzole, ceftriaxone and aclarubicin (Bharucha-Goebel and Kaufmann, 2017).

Olesoxine has shown survival of motoneurons in stress conditions in premedical trials. A total of 160 patients with SMA II or III aged 3 to 25 years were included in clinical trials conducted between 2010 and 2011. Olesoxine was shown to appear safe and well tolerated, but the primary endpoint has not been achieved. Despite that, the secondary endpoints indicated that the medicine could maintain motor functions in SMA for the duration of 24 months (Bertini et al., 2017; Bharucha-Goebel and Kaufmann, 2017).

The Astellas team in cooperation with the Cytokinetics have developed CK-107/CK-2127107, which is a rapid activator of skeletal muscles, designed to slow down the release of calcium with troponin regulator complex. The therapy is intended to increase contractility of skeletal muscles and time to improve capacity at the same time. A research conducted in 2018 found that compared to previous tirasemtiv therapy, the drug demonstrates better tolerability and less potential for drug-drug interactions (Andrews et al., 2018). After positive safety results in the first phase of clinical trials

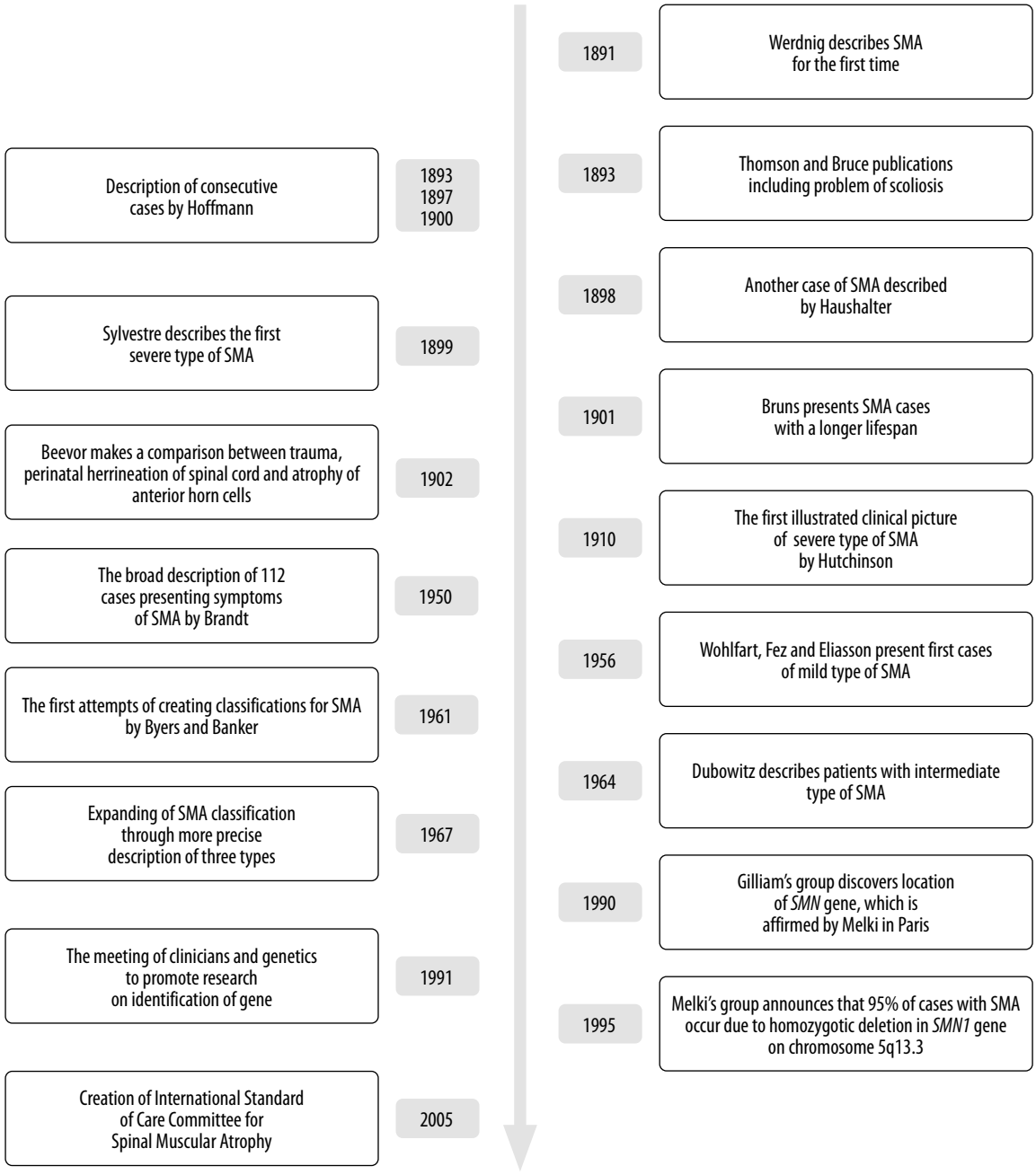


*Fig. 1. Timeline of spinal muscular atrophy*

the drug has been started in phase two of double-blind placebo-controlled trial to verify the impact of this medicine on skeletal muscle activity in patients with SMA 2, 3 and 4 (Bharucha-Goebel and Kaufmann, 2017).

PTC Therapeutics in cooperation with Roche conducted research to investigate the RG7800 compound in the form of an oral bioavailable medicine. The phase I study with single, increasing dosage proved that this compound is safe and well tolerated in healthy individuals. Recruitment for randomised, placebo-controlled phase IIb/IIa clinical trials in adults and children with SMA was initiated in 2015. The research was suspended due to the results of the long-term clinical trials, which showed an unexpected eye condition (Bharucha-Goebel and Kaufmann, 2017; Scoto et al., 2017). In January 2016, Roche group initiated research in healthy adults with alternative but similar compound RG7916 – later called risdiplam.

Risdiplam (Evrysdi) is an orally administrated drug developed by Roche, PTC Therapeutics and SMA Foundation. The treatment consists of *SMN2* directed splicing modifier, which increases the level of full-length and functional SMN protein. The company has launched two phase I/II



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studies in order to evaluate safety, tolerance and pharmacokinetics in infants. Both trials in SMA type 1 (FIREFISH) and in types 2 and 3 (SUNFISH) demonstrated significant improvement of motor function and SMN protein level. In August 2020, the drug received the first approval in the USA for the treatment of patients over 2 months old (Dhillon, 2020; Scoto et al., 2017).

Nusinersen (Spinraza) is an antisense oligonucleotide developed by Ionis and Biogen. The drug is administered directly to the central nervous system using intrathecal injection, and it binds to SMN-2 pre-RNA and corrects splicing (Bharucha-Goebel and Kaufmann, 2017). Phase 2 trial enrolled 20 participants between 2013 and 2014 and showed acceptable safety and tolerability in clinical trial (Finkel et al., 2016). Then, the group conducted clinical trials in 122 patients with SMA type I, diagnosed before the age of 7 months from August 2014 till November 2016 (Finkel et al., 2017). Motor endpoints in the exams included e.g. head control, sitting, kicking in supine position, rolling, crawling, standing and walking. Its efficacy was confirmed in double blind trials. This was followed by a temporary analysis of 82 patients, which showed motor improvement in 40% of patients receiving active treatment in comparison to patients from the sham group (Bertini et al., 2017; Scoto et al., 2017). The clinical trials were expanded to the different types of SMA between 2014 and 2017 (Mercuri et al., 2018). On 23$^{th}$ December 2016, Food and Drug Administration approved the use of nusinersen – the first drug to cure patients by increasing SMN protein levels (Ross and Kwon, 2019; Scoto et al., 2017).

Onasemnogene abeparvovec (Zolgensma) is the first gene therapy approved in May 2019 for SMA 1 patients aged up to 2 years. The drug has been developed by AveXis (Novartis company) and is an adeno-associated virus 9 (AAV9) designed to distribute complementary DNA to target motor neurons. The treatment is administrated in one-time intravenous infection for over 60 min. Clinical trials were initiated in May 2014. A total of 15 SMA 1 patients with 2 copies of *SMN2* participated in open-label phase I study. The results showed a significant improvement in motor function and survival. The preliminary data from an ongoing open-label phase 3 trial also confirmed these promising results (Chen et al., 2010; Hoy, 2019).

Currently, the ongoing research and first clinical trials of gene therapy have shown promising results with SMA treatment. Branaplam (LMI070) clinical trials were launched in July 2019, with preliminary results indicating improved motor functions after 86 days of treatment. Another drug, R07204239 and celecoxib also showed promising data for SMA patients (Chong et al., 2021). Coordination of clinical research is possible due to organisations such as TREAT-NMD (Translational Research in Europe–Assessment and Treatment of Neuromuscular Diseases) or SMA Foundation. Their goals is to accelerate and coordinate research to introduce effective treatment and improve the standards of care.

## CONCLUSIONS

The beginnings of SMA go back to 1891, when Werdnig and then Hoffmann first described cases of patients with SMA. Gradually, other publications started to appear presenting infants with progressive weakness of extremities and premature death. Different types of SMA have been distinguished over time. Cases of children dying in a few weeks after birth or patients who despite showing initially normal development and achieving functions such as walking became weaker over time. The research development allowed understanding of the pathophysiological background of the disease and made it possible to create a qualification system supported by a genetic basis (Dubowitz, 2009; Kolb and Kissel, 2011; Ross and Kwon, 2019).

Following the discovery of the *SMN* gene at the end of the 20$^{th}$ century, first clinical trials of targeted treatment were made. Better results were obtained in medical treatment by using animal models, nonsense oligonucleotide therapies or eventually gene therapy. The positive results of the research allowed for approving intrathecal injection of nusinersen for widespread usage in 2016. Since 1$^{st}$ January 2019, nusinersen has been completely reimbursed in Poland. Individual cases supported by external funding have the possibility of genetic treatment. Unfortunately, this therapy is very expensive and only a few can benefit from it (Bharucha-Goebel and Kaufmann, 2017; Darras et al., 2009; Finkel et al., 2017).

Research on improving the gene therapy for SMA patients is in progress (Meyer et al., 2015). Gradually, other medications are approved for public use like risdiplam, whose administration is less invasive than intrathecal injection of nusinersen. There is also growing discussion around implementing SMA screening in newborns (Bharucha-Goebel and Kaufmann, 2017; Darras et al., 2009; Ratni et al., 2018). In Poland, the Ministry of Health started to implement the screening in April 2021. By November 2022, all newborns will be screened for SMA.

### Conflict of interest

*The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.*

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