Progress and Challenges in Clinical AAV Gene Therapy for Neurological and Neuromuscular Disorders

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Abstract

The field of gene therapy is growing at a rapid pace. The discovery and modification of adeno-associated viruses (AAV) as gene therapy vectors has allowed for the development of novel treatments for neurological and neuromuscular disorders. AAV based gene therapy techniques can be utilized to add, replace, or modify genes and their expression in patients, thus providing a potential beneficial therapeutic effect. In many cases, gene therapy has the promising power to change the natural course of debilitating and fatal diseases and give patients a new outcome on life. This mini review will give a brief overview of the AAV gene therapy field, highlighting FDA approved gene therapies and selected current in-clinic AAV-mediated therapeutics for neurological and neuromuscular diseases for which interim data are available. These therapies and the ongoing clinical trials are currently laying the groundwork for future gene therapy strategies and clinical trial design. Ultimately, they will inform the field on promises and limitations that still need to be overcome.

Keywords: Gene Therapy; AAV; Neuromuscular Disorders

Abbreviations: AAV- Adeno-associated virus; RAAV- Recombinant adeno-associated virus; ITRs- Inverted terminal repeats. FDA-Food and Drug Administration; CNS-Central nervous system; IV- Intravenous; NCL-Neuronal ceroid lipofuscinosis; CSF- Cerebrospinal fluid; IT- Intrathecal; PD- Parkinson’s Disease; ALS- Amyotrophic Lateral Sclerosis; DMD- Duchenne Muscular Dystrophy

Introduction

Adeno-associated viruses (AAV) are small, replication-defective, nonenveloped viruses from the family Parvoviridae. First discovered in the mid-1960s, AAV was thought to be a contaminant in adenovirus cultures [1,2]. Over the next 15-20 years, studies to understand basic AAV biology began, characterizing AAV elements such as genome composition and configuration [1,2]. AAV contains a linear single-stranded DNA genome containing approximately 4.7 kilobases [2,3]. As AAV is non-integrating and has a low immunogenic profile, it has become an attractive candidate for viral mediated gene therapies following the unfortunate death of Jesse Gelsinger in 1999. Jesse’s death was caused by immune complications triggered by an adeno viral based gene therapy. Despite the hesitation and fear that resulted from this event, the advent of recombinant AAV (rAAV), showing a lower immunogenic profile compared to adenoviruses, was able to propel the field forward. The first rAAV clinical trial was initiated in 1995 as a treatment for cystic fibrosis [4]. In the early 2000s, new AAV subtypes (serotypes) with the capability to infect various tissues and cell types were discovered in primates, leading to an expansion of the AAV in vivo gene delivery toolbox [2]. The intent of this mini review is to give a brief overview of current Food and Drug Administration (FDA) approved AAV gene therapies as well as to highlight additional AAV vectors currently in clinical trials for neurological and neuromuscular disorders. Due to large number of clinical trials, the mini review will only focus on...
selected programs for which interim data has been made public, as well as on showcasing different gene therapy methods including not only classic gene replacement strategies but also gene expression (mRNA) modulation [5,6]. Moreover, we will shortly discuss the limitations and current hurdles of AAV based therapeutics.

**FDA approved AAV Gene Therapies**

**RPE65 mutation-associated retinal dystrophy:** Fifty-two years after the initial discovery of AAV, the FDA approved the first gene replacement strategy for treatment of a monogenic disorder [7,8]. Voretigene neparvovec-rxzl, or Luxturna, was approved in December 2017 to treat patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy [9]. RPE65 is essential for regeneration of the visual pigment necessary for photoreceptor mediated vision [10]. Without regeneration, the unconverted pigment builds up within the retinal pigment epithelium, blocks the visual cycle, and leads to visual impairment especially in low-light conditions [10]. Luxturna prevents and partially reverses vision loss by restoring expressing of the RPE65 gene delivered to the retinal pigment epithelium via subretinal injection of AAV2 [8,10]. 55% of patients treated in the initial clinical trial were able to navigate an obstacle course at 2 light levels darker compared to testing prior to treatment [8]. The approval of Luxturna demonstrated safety, utility, and effectiveness of AAV mediated gene replacement strategies. However, the site of administration served as an advantage in this case since the eye is an immune-privileged site [11]. For gene therapies targeted to organs outside the eye, the innate immune response can become a greater obstacle.

**Spinal Muscular Atrophy:** The first intravenous (IV) delivered AAV9 gene therapy was approved by the FDA in 2019 for treatment of infants below 2 years of age suffering from Spinal Muscular Atrophy [9]. Loss of the SMN1 gene is detrimental to motor neuron survival and leads to whole body muscle weakness [12]. Death typically occurs by two years of age due to respiratory failure [13]. Onasemnogene abeparvovec-xioi (Zolgensma) is an AAV9 based gene therapy that contains the coding sequence of the SMN protein [14]. Treatment allowed SMA patients to achieve new motor milestones, like sitting without assistance, and successfully prevents early death [15]. The first treated patients are now five years of age [15]. Zolgensma’s market approval was a landmark success for the SMA field and solidified the idea for translation of AAV based gene replacement strategies as an effective option for other neuromuscular disorders. Additional clinical trials are currently testing Onasemnogene abeparvovec-xioi in older patients using intrathecal delivery of the vector into the cerebrospinal fluid (CSF). To date, Voretigene neparvovec-rxzl and Onasemnogene abeparvovec-xioi are the only FDA approved AAV gene therapies on the market, but over 100 clinical trials are currently ongoing using different AAVs and delivery routes for a wide range of diseases.

**Selected ongoing clinical trials for neurological and neuromuscular disorders with published interim data**

**Batten disease:** Batten Disease encompasses a number of neuronal ceroid lipofuscinoses (NCL) disorders which mostly affect children [16]. Mutations in CLN genes generally result in accumulation of lipofuscin granules in neuronal cells and lead to blindness, regression in cognitive and intellectual ability, seizures, loss of motor function, and early death [16]. Nationwide Children’s Hospital (Columbus, OH, USA) developed gene therapy approaches for Batten Disease CLN6 and CLN3 which were later licensed by Amicus Therapeutics. Both Phase I/II gene replacement clinical trials are currently ongoing [17]. For CLN6 Batten Disease, AAV9. CLN6 (AT-GTX-501) is injected directly at a dose of 1.5e13vg/kg into the cerebrospinal fluid (CSF) via lumbar intrathecal delivery [17]. As of November 2020, efficacy data from the 24-month follow-up visit has been reported for eight children [18]. Compared to subjects from the natural history study, who had a mean rate of decline of 2.4 points over 24 months, treated patients had a mean rate of decline of only 0.6 points on the Hamburg motor and language scale [18]. Amicus also reported safety data that showed treatment was well-tolerated [18]. The treatment for CLN3 Batten Disease with AAV9.CLN3 (AT-GTX-502) began in late 2018, but sufficient interim data has yet to be reported [19]. In addition to these therapies, several ongoing or upcoming clinical studies are being dedicated to treatment of CLN2 Batten Disease, including those from Weill Cornell Medical School (AAVrh10.CLN2), Spark Therapeutics (SPK-1001), and REGENXBIO (RGX-181) [20-22].

**Duchenne muscular dystrophy (DMD):** DMD is an X-linked recessive disorder characterized by severe muscle weakness and loss of ambulation affecting children around the ages of 8-13 [23]. The disease later progresses to respiratory complications, cardiac abnormalities, and eventual death [23]. The disorder is caused by mutations in the DMD gene, which encodes the dystrophin protein [23]. Without dystrophin, the plasma membrane (sarcolemma) of muscle cells becomes unstable which leads to muscle degeneration and myofiber loss [24]. Unfortunately, the DMD mRNA is too big and therefore cannot be packaged into AAV vectors [25]. However, in 1990, a researchers described a milder form of muscular dystrophy in patients expressing a truncated form of the protein that still had functional properties [25]. As a result, researchers began developing truncated dystrophin proteins, termed micro and mini dystrophin, that could be packaged into AAV and still have therapeutic effects [25]. Three micro-dystrophin constructs are currently being tested in clinical trials: Sarepta Therapeutics (rAAVrh74; SRR-9001), Pfizer (AAV9), and Biosciences (AAV9) [26-28]. All constructs were delivered intravenously and in varying doses ranging from 5e13 vg/kg to 2e14vg/kg [23,29,30]. Overall, the treatments were well tolerated with the exception of the Biosciences trial, which was...
Parkinson's Disease (PD) is an adult-onset neurodegenerative disease with motor and cognitive impairment resulting from the loss of striatal dopaminergic neurons in the substantia nigra of the brain. In PD, motor impairment manifests as bradykinesia, tremor, and rigidity. Non-motor impairments include cognitive, mood, and behavioral dysfunction, sleep disturbances, pain, and autonomic disturbances [45]. The most effective pharmacological treatment for PD is levodopa, a dopamine precursor amino acid, but as the disease progresses, the benefits of levodopa treatment decline due to the loss of Aromatic L-Amino Acid Decarboxylase (AADC), an enzyme that converts levodopa to dopamine [46]. Neurocrine Biosciences, in collaboration with University of California San Francisco, Feinstein Institute for Medical Research, Oregon Health and Science University, and Voyager Therapeutics, recently completed a clinical trial safety study of AADC gene therapy as a treatment for PD [47]. In this study, fifteen patients received bilateral putamen injections of AAV2 containing AADC cDNA (VV-AADC01) at the dose of 7.5e11 vg/kg (n=5), 1.5e12 vg/kg (n=5), or 4.7e12 vg/kg (n=5) [47]. Results from this study show a dose dependent putaminal coverage of VV-AADC01 expression and dose dependent increases in AADC activity, as well as a reduction of ant parkinsonism medications at 6 months [46]. The Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) was used to evaluate changes in motor and non-motor complications and showed clinically meaningful dose-dependent improvements at 12 months and increased Quality of Life measurements even with

**Limbgirdle muscular dystrophy (LGMD):** Limbgirdle Muscular Dystrophies (LGMD) are a distinct class of muscular dystrophies with 34 identified variants, each showing significant phenotypic heterogeneity [41]. LGMD Type 2E (LGMD2E) is a childhood to adolescent onset LGMD characterized by progressive weakness in the pelvic-girdle and shoulder-girdle muscles, typically resulting from mutations in the beta-sarcoglycan gene (SGCB) [42]. Sarepta Therapeutics has an ongoing AAV-mediated gene replacement clinical trial for the treatment of patients with LGMD2E [43]. In this trial, cohort 1 patients, 4-15 years of age with a confirmed beta-sarcoglycan gene mutation in both alleles, received a single IV injection of AAVrh74 containing human SGCB cDNA under the control of the muscle specific MHCK7 promoter (AAVrh74/MHCK7.SGCB) at the dose of 5e13 vg/kg [43,44]. Muscle biopsies taken 3 months post-treatment from 3 patients show an average of 51% SGCB positive muscle fibers, a 90% reduction in CK levels, and restoration of the sarcoglycan complex to the membrane [25,44]. At the 90-day patient follow-up, 2 patients had elevated liver enzymes as a side effect of the AAV treatment, which resolved with supplemental steroid treatment [44]. Cohort 2 patient dosing will be based on results from cohort 1 patients and may be escalated [43].

**Parkinson’s disease (PD):** Parkinson’s Disease (PD) is an adult-onset neurodegenerative disease with motor and cognitive impairment resulting from the loss of striatal dopaminergic neurons in the substantia nigra of the brain. In PD, motor impairment manifests as bradykinesia, tremor, and rigidity. Non-motor impairments include cognitive, mood, and behavioral dysfunction, sleep disturbances, pain, and autonomic disturbances [45]. The most effective pharmacological treatment for PD is levodopa, a dopamine precursor amino acid, but as the disease progresses, the benefits of levodopa treatment decline due to the loss of Aromatic L-Amino Acid Decarboxylase (AADC), an enzyme that converts levodopa to dopamine [46]. Neurocrine Biosciences, in collaboration with University of California San Francisco, Feinstein Institute for Medical Research, Oregon Health and Science University, and Voyager Therapeutics, recently completed a clinical trial safety study of AADC gene therapy as a treatment for PD [47]. In this study, fifteen patients received bilateral putamen injections of AAV2 containing AADC cDNA (VV-AADC01) at the dose of 7.5e11 vg/kg (n=5), 1.5e12 vg/kg (n=5), or 4.7e12 vg/kg (n=5) [47]. Results from this study show a dose dependent putaminal coverage of VV-AADC01 expression and dose dependent increases in AADC activity, as well as a reduction of ant parkinsonism medications at 6 months [46]. The Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) was used to evaluate changes in motor and non-motor complications and showed clinically meaningful dose-dependent improvements at 12 months and increased Quality of Life measurements even with
ALS is an adult-onset neurodegenerative disease characterized by progressive loss of motor neurons in the brain and spinal cord. As there is currently no cure, the disease is always fatal with patients succumbing to death within 2-5 years of symptom onset. In July 2020, The New England Journal of Medicine published results from a compassionate-use patient study for the treatment of familial ALS. The study was conducted at University of Massachusetts and Massachusetts General Hospital and included treatment of two patients with SOD1-mediated ALS [49]. The gene therapy construct contains a microRNA sequence that reduces expression of the superoxide dismutase 1 (SOD1) protein. Mutated forms of this protein cause approximately 2% of all ALS cases. Two patients were intrathecally injected with AAVrh10-miR-SOD1 at the dose of 4.2e14 vector genomes [49]. Patient 1 experienced an adverse inflammatory response to the viral vector causing severe pain which decreased over time but was not resolved [49]. Patient 1 had transient improvements in the strength of his right leg after treatment, but no change in vital capacity, and succumbed to the disease 15.6 months post treatment [49]. The gene therapy treatment led to a 90% reduction of SOD1 protein in the post-mortem lumbosacral spinal cord of Patient 1 but there was no change in SOD1 levels in the cerebrospinal fluid with treatment [49]. Western Immunoblot analysis of SOD1 protein in the spinal cord showed no differences in the cervical spinal cord, though there was a reduction in SOD1 enzyme activity [49]. For Patient 2, a more rigorous immunosuppressive regimen was used to reduce chances of a strong inflammatory response and the patient did not have increased hepatic aminotransferase levels or sensory dysfunction following treatment [49]. As patient 2 has a milder form of the disease and a slower disease progression, additional data on the disease course is expected to be collected over time.

**Conclusion**

The field of AAV mediated gene therapy has grown exponentially over the last decade, with a massive increase in publications, preclinical studies, and ongoing or completed clinical trials [2]. Though many results so far are exciting, these clinical studies also underline challenges the field is still attempting to overcome. In all the aforementioned trials, pre-existing immunity, measured in form of antibodies, were designated as exclusion criteria. This is a significant barrier to treatment for patients in need, and much of the field is dedicated to finding strategies that can temporarily evade or dampen the immune response of patients that have been naturally exposed to AAV viruses [9,50]. These strategies, such as the use of immunomodulatory enzymes, plasmapheresis, or modified AAV capsids, may also be useful in the event patients need a second administration of vector to maintain expression of the transgene in cell types that continue to divide and therefore might lose the AAV construct over time [9]. For the treatment of neurological and neuromuscular diseases, choosing an appropriate route of administration is vital to the success of a therapy. Local routes of delivery, such as direct brain injections, allow for sufficient local targeting but increase the risk of injury at the site of injection [51]. Several of the described studies are currently utilizing IV delivery of AAV constructs capable of targeting muscles but also brain and spinal cord. The caveat of IV delivery is that high doses are required for sufficient transduction of target cell types, especially in the central nervous system (CNS). As a result, several studies have reported serious adverse events related to liver toxicity, an organ that is highly targeted with IV delivery [39,52,53]. Alternatively, CSF delivery via intrathecal (IT) route offers several advantages over IV delivery for neurological disorders because it allows for sufficient transduction of neuronal cell types with a lower required dose, thereby limiting immunogenic response and liver targeting [54]. The CSF delivery route could potentially lead to toxicity in other organs, as a recent study performed in non-human primates suggests this route may induce dorsal root ganglion (DRG) pathology [55]. To date, DRG pathology or clinical signs thereof have not been reported in patients dosed intrathecally in the ongoing Batten disease trials or the clinical trials currently conducted with Zolgensma for older patients (NCT03381729). Another consideration is when to dose patients for maximal therapeutic effect. In general, it seems the highest benefit is achieved in patients that are dosed early in disease progression with as few symptoms as possible, as symptom reversion seems to be more challenging. The currently ongoing clinical trials and newly initiated studies will be highly informative and will help advance the exciting field of AAV gene therapy further.

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**Conflict of Interest**

KM and NW Royalties from intellectual property licensed by Amicus Therapeutics and Audentes Therapeutics.

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