Evolution of Pompe Disease Therapy

Pompe disease, also known as glycogen storage disease type II, is caused by the lack or deficiency of a single enzyme, lysosomal acid alpha-glucosidase, leading to severe cardiac and skeletal muscle myopathy due to progressive accumulation of glycogen. The discovery that acid alpha-glucosidase resides in the lysosome gave rise to the concept of lysosomal storage diseases, and Pompe disease became the first among many monogenic diseases caused by loss of lysosomal enzyme activities.

1. Next-Generation ERT

Notably, the less than optimal intrinsic quality of alglucosidase alfa was understood years ago, as indicated by the efforts in the early 2000s to enhance the delivery of the therapeutic enzyme to the affected muscle by carbohydrate remodeling of the original enzyme to increase the amount of M6P [1]. This early work and an extended follow-up study [2] led to the development of a modified glycoengineered enzyme with a synthetic oligosaccharide harboring mannose 6-phosphate (M6P) residues. This new recombinant human GAA, called neo-GAA, with much improved affinity for the CI-MPR and uptake by muscle cells, showed more efficient glycogen clearance in immunotolerized KO mice compared to the unmodified enzyme, particularly in younger mice. Muscle glycogen reduction was also achieved in older symptomatic KO mice, but the improvement in motor function was only marginal [2].

Neo-GAA (Avalglucosidase alfa; Sanofi Genzyme, Cambridge, MA, USA), a second-generation glycoengineered recombinant GAA with increased bis-M6P levels, was first evaluated for safety and tolerability in a now completed clinical trial (NCT01898364). The results of this Phase 1/2 open-labeled, ascending-dose (5, 10, and 20 mg/kg biweekly over the course of 24 weeks) study in previously ERT-treated (switch group) and -untreated (naïve group) LOPD patients was recently published [3]. Neo-GAA was overall well-tolerated and safe; only two of the 24 enrolled patients discontinued because of the drug-related serious adverse events. Based on the glycogen levels in baseline quadriceps biopsies (~6% of tissue area), patients from both groups were considered to be mildly affected. Although the assessment of efficacy was not a part of the protocol, exploratory efficacy parameters showed a slight improvement in pulmonary function in ERT-naïve and no decline in ERT-switch patients. A Phase 3 study to compare the safety and efficacy of neo-GAA and alglucosidase alfa in previously untreated LOPD was initiated in 2016 and is ongoing (COMET; NCT02782741). In the randomized, double-blind portion of the study, patients received either neo-GAA or alglucosidase alfa (standard of care) for 49 weeks; thereafter, all patients participated in ongoing open-label treatment with neo-GAA. In addition, the company's clinical development program includes several other exploratory efficacy studies with neo-GAA in LOPD and IOPD patients.

Another new investigational drug, AT-GAA (Amicus Therapeutics, Cranbury, NJ, USA) is the combination of a novel non-modified rhGAA bearing high bis-M6P (Amicus proprietary cell line) with a pharmacological chaperone (AT2221; N-butyldeoxynojirimycin; NB-DNJ, miglustat) for stabilizing the enzyme in the circulation (reviewed in [4]). Both preclinical and clinical studies in Pompe disease patients demonstrated that small molecules chaperones increased the stability and bioavailability of the therapeutic enzyme [5][6][7][8].

In a large preclinical study in KO mice, AT-GAA was shown to significantly outperform alglucosidase alfa in all measured outcomes: GAA uptake and activity, muscle strength, reduction in lysosomal size and glycogen levels, and mitigation of autophagic defect [9]. Furthermore, long-term treatment of KO with AT-GAA completely reversed muscle lysosomal glycogen accumulation, eliminated autophagic buildup in >80% of muscle fibers, and to a large degree restored AMPK/mTORC1 signaling, muscle proteostasis, and metabolic abnormalities [10]. This outcome is in striking contrast with the limited effect of a long-term treatment of KO mice with alglucosidase alfa at a similar dose of 20 mg/kg [11].

AT-GAA was evaluated in Phase 1/2 clinical trial in ERT-switch and naïve non-ambulatory LOPD patients; the drug was well-tolerated with a low number of infusion-associated reactions and showed promising results, as evidenced by improvement in muscle function, increase in upper-body muscle strength, and patient-reported outcomes (reviewed in [4]). Two Phase 3 studies, one comparing AT-GAA with alglucosidase alfa/placebo (PROPEL Study; NCT03729362; active, not recruiting), and the second one (ZIP Study: NCT03911505; recruiting) evaluating the pharmacokinetics, safety, efficacy, and pharmacodynamic of AT-GAA in LOPD patients were initiated in 2018 and 2019 respectively.

An attempt was made to target both lysosomal and extra-lysosomal glycogen accumulation in the affected muscle. VAL-1221 (Valerion Therapeutics, Concord, MA, USA) is a CHO-produced fusion protein containing the 110 kDa human GAA precursor and the Fab fragment of a murine lupus anti-DNA antibody, 3E10. This monoclonal anti-DNA antibody were shown to penetrate living cells and move to the nucleus through the equilibrative nucleoside transporter 2 (ENT2) [12][13][14]. Experiments in cultured L6 myoblasts and fibroblasts derived from Pompe disease patients as well as in vivo studies in KO mice suggested a potential benefit of this fusion protein [15]. However, VAL-1221 in KO mice did not show any improvement in muscle glycogen content (unpublished data). A Phase 1/2 dose-escalation clinical trial (NCT02898753) of VAL-1221 in previously treated LOPD patients was initiated in 2017 [16], but the results of this study were not validated by peer review. As of June 2020, the company terminated this trial in the US and UK.

Finally, a combination of alglucosidase alfa with β2 agonists, clenbuterol, or albuterol, was shown to enhance the efficacy of the therapeutic enzyme owing to the increased expression of CI-MPR in skeletal muscle [17][18]. A pilot study of albuterol plus ERT in LOPD patients who were not improving further following more than two years on ERT alone showed the benefit of this approach [19]. A phase 1/2 double-blind, randomized, placebo-controlled 52-week study (NCT01942590) of clenbuterol in LOPD patients treated with ERT provided evidence for safety and showed a modest improvement in motor function [20]. This study (initiated in 2013) is now completed. **Table 1** summarizes the above-mentioned clinical trials.

Table 1. Next generation therapies for Pompe disease.

Intervention/Treatment	Characteristics/Delivery Method	Company/Institution	Clinical Trial Phase/Identifier	References
ERT				
neo-GAA	**Glycoengineered recombinant GAA with increased bis-M6P levels (avalglucosidase alfa)**	**Genzyme, a Sanofi Company**	**Completed/NCT01898364 Phase 3/NCT02782741**	**Zhu et al. [2] Pena et al. [3]**
AT-GAA (ATB200/AT2221)	**rhGAA bearing high bis-M6P with a pharmacological chaperone (miglustat)**	**Amicus Therapeutics**	**Phase 3/NCT03729362 Phase 3/NCT03911505**	**Khanna et al. [7] Xu et al. [9] Meena et al. [10]**
VAL-1221	**Fusion protein containing antibody 3E10 and rhGAA**	**Valerion Therapeutics**	**Terminated/NCT02898753**	**Weisbart et al. [13][14] Yi et al. [15] Kishnani et al. [16]**
ERT + Clenbuterol	**Alglucosidase alfa with β2-adrenergic agonist clenbuterol**	**Duke University**	**Completed/NCT01942590**	**Koeberl et al. [17][18][19] [20]**
Gene Therapy				
rAAV2/1-CMV-hGAA	**Intramuscular injection into the diaphragm**	**University of Florida**	**Completed/NCT00976352**	**Smith et al. [21] Byrne et al. [22] Corti et al. [23]**
rAAV9-DES-hGAA	**Intramuscular re-administration**	**Lacerta Therapeutics/University of Florida**	**Phase 1/2/NCT02240407**	**Salabarria et al. [24]**
AAV2/8-LSPhGAA	**Screening for eligibility Ascending dose intravenous administration**	**Duke University Asklepios Biopharmaceutical/Duke University**	**Completed/NCT03285126 Phase 1/2/ NCT03533673**	**Kishnani et al. [25] Han et al. [26]**

Intervention/Treatment	Characteristics/Delivery Method	Company/Institution	Clinical Trial Phase/Identifier	References
SPK-3006 (AAV liver directed secretable GAA)	Intravenous administration	Spark Therapeutics	Phase 1/2/ NCT04093349	Puzzo et al. [27] Cagin et al. [28]

ERT: enzyme replacement therapy; M6P: mannose-6-phosphate; clinical trials listed in this table are registered as of August 2020.

❙ 2. Gene Therapy

There is a dramatic surge in the number of drug candidates for gene therapy to combat human diseases, and Pompe disease is no exception. The limitations of the currently available ERT, along with the requirement for frequent life-long i.v. infusions, and the inability of the therapeutic enzyme to cross BBB, make the development of gene therapy for Pompe disease an attractive option. Over the past years, the field has witnessed the explosion of gene therapy studies testing different types of vectors, various promoters, numerous elements of the transgene expression cassette, and routes of delivery in preclinical setting. These studies are discussed in several recent reviews [24][29][30][31][32].

Based on the results of the early preclinical studies evaluating the effect of systemic or intramuscular administration of AAV vectors in KO mice [33][34][35], the first-in-human trial of gene therapy for Pompe disease began in 2006, thus marking a milestone in the field. This was an open label, Phase 1/2 trial (NCT00976352) using direct injection of rAAV2/1-CMV-hGAA into the diaphragm of a small group of children who required assisted ventilation despite ERT. The study confirmed safety and showed a tendency to improve respiratory function in some patients [21][22][23].

Phase 1/2 clinical trial evaluating the feasibility of two successive intramuscular (into tibialis anterior muscle) administration of an AAV9 vector expressing GAA is ongoing and is recruiting patients with LOPD (NCT02240407). The recombinant AAV carries the codon-optimized acid alpha-glucosidase under the control of human desmin enhancer/promoter (rAAV9-DES-hGAA). The immune modulation strategy using Rituximab and Sirolimus prior and after the first administration of the vector is designed to prevent the immune response against the AAV capsid and the transgene, thus allowing for the second vector administration. The same group of researchers from University of Florida are planning to initiate a new Phase 1/2 clinical trial of systemic injection of rAAV9-DES-GAA in 3–5-year-old IOPD patients.

Another approach-hepatic gene transfer-relies on a remarkable ability of hepatocytes to produce and secrete the expressed protein into the bloodstream, thus providing a steady supply of the therapeutic enzyme for the uptake by other tissues. Early studies on KO mice demonstrated that a single i.v. administration of a modified adenovirus (AV) vector encoding human GAA resulted in efficient liver transduction, secretion of the GAA precursor, and clearance of lysosomal glycogen accumulation in skeletal and cardiac muscles [36]. These results along with the follow-up studies [37][38] provided a solid foundation for using what is now called "liver depot gene therapy" in Pompe disease. However, the use of AAV vectors is now highly preferred for achieving a long-term persistent therapeutic gene transfer.

The unique immunologic properties of the liver allow for the induction of immune tolerance to foreign antigens through a regulatory T-cell mediated mechanism (reviewed in [39]). Indeed, AAV-mediated liver-specific expression of human GAA in KO mice was shown to prevent the formation of anti-GAA antibody when the vector was administered prior to the start of ERT, thus improving ERT efficacy [40][41][42]. The concept of induction of tolerance to the therapeutic enzyme delivered during ERT by low-dose AAV vector administration is termed "immunomodulatory gene therapy" [43]. Multiple preclinical studies have explored the impact of different AAV serotypes and promoters, vector dosages, and modifications of the GAA sequence, such as the signal peptide and codon optimization, to enhance GAA secretion into the bloodstream and to better control humoral immune responses (reviewed in [25][31][32]). These studies have culminated in the first liver gene therapy clinical trials for Pompe disease.

A Phase 1 clinical trial (NCT03533673) of liver depot gene therapy in adult patients is designed to evaluate an rAAV serotype 8 vector carrying the human GAA under the control of liver-specific promoter (AAV2/8-LSPhGAA). This is an ongoing open label, randomized study (currently recruiting). A careful consideration of the vector dosage for this trial was based on the preclinical data showing effective biochemical correction of skeletal muscle at a dose of 2×10^{12} vg/kg, and induction of immune tolerance to the ERT delivered rhGAA (with only partial correction of the muscle defect) at a minimum effective dose of 2×10^{11} vg/kg [26]. These data justified a starting dose of 1.6×10^{12} vg/kg for Phase 1 clinical trial [25].

This clinical trial was preceded by a Pompe gene therapy trial (NCT03285126; completed), designed to determine eligibility for the forthcoming trial in adults with LOPD.

Another Phase 1/2 liver transfer gene therapy clinical trial (NCT04093349; RESOLUTE), initiated by Spark Therapeutics is recruiting patients with LOPD receiving ERT. The study is designed to evaluate the safety, tolerability, and efficacy of investigational liver-directed AAV gene therapy of the secretable GAA (SPK-3006) in adults, treated in sequential dose-level cohorts. Preclinical studies using this AAV8-mediated liver gene transfer of an engineered secretable GAA (secGAA) resulted in high and stable levels of GAA in the circulation and rescued muscle and CNS pathology in adult and severely affected older KO mice without development of humoral immune responses to the enzyme [27][28].

An inherent limitation of hepatic gene transfer is that AAV episomal vectors will be diluted over time in the developing and growing liver, eventually leading to the loss of vector genomes and transgene expression. This creates a major problem for treatment of pediatric patients with the disease, who are likely to require a second round of vector administration and immunosuppression to prevent the formation of neutralizing antibodies. In general, the success of liver-directed gene therapy for Pompe disease relies on both secretion of large amount of precursor GAA and its efficient CI-MPR-mediated uptake and lysosomal trafficking in distant organs. As with traditional ERT, the same requirement for high M6P content and affinity for the CI-MPR applies to the liver-produced secreted GAA to achieve efficient targeting and correction of muscle defect. This raises a possibility of generating an "ideal" transgene expression cassette to allow for the maximally reduced dose of vector. Although challenging, the era of gene therapy for Pompe disease has arrived, and the therapy has the potential to one day become a lifelong cure.

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