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WORLD Symposium 2018, San Diego

Visit Report, Allan Muir, 15 December 2018

WORLD*Symposium*™ is an annual research conference dedicated to lysosomal diseases.
W.O.R.L.D. is an acronym standing for ***We're Organizing Research on Lysosomal Diseases***.

Overview

The WORD Symposium is held every year in either San Diego, California or Orlando Florida. It attracts all those with an interest in Lysosomal Storage Disease research, including medical professionals, pharmaceutical and biotechnology companies and patient groups. Many global organisations use the occasion to coordinate their own meetings and so it is an excellent event for networking with the international LSD community. Registrations were reported to have risen to over 1700 delegates this year.

The conference programme started on the Monday with the Council of Patient Advocates, a meeting where patient groups discuss LSD research with the aim of involving patients in the application of research grants, particularly from the National Institutes of Health (NIH).

The following three days provided research presentations including natural history studies, novel therapies, new-born screening and sponsored satellite symposia. Several hundred posters were also displayed including one that I was a co-author, showcasing the work of the UK LSD Collaborative (See Annex A).

Council of Patient Advocates

This year's COPA meeting was very well attended with over 100 people in the room representing a mix of patient support groups and patient advocacy and other staff from various companies. The meeting this year was designed to allocate themes to each table of around 10 people who were tasked to a) define an unmet need, b) hypothesise a solution and then c) create a short pitch for research funding.

Presentations

There were many presentations across all LSDs, several were dedicated to Pompe disease, below the abstracts from the equivalent posers are added as they are possibly more informative and accurate than my scribbled notes:

Manuela Corti, University of Florida, Gainesville, FL, United States,
"Enabling re-dosing of AAV by immune management in Pompe disease: preclinical to clinical studies"

A rAAV9 vector carrying a transgene that expresses codon optimized human acid alpha-glucosidase driven by a human desmin promoter (rAAV9-DES-hGAA) has been generated as a clinical candidate vector for Pompe disease. In young patients, the therapy may need to be re-administered to maintain therapeutic levels of GAA. In LOPD anti-AAV antibodies may require a similar strategy. To establish the basis for re-administration of AAV vectors we have completed IND-enabling pre-clinical studies testing immune reactions after the concomitant use of immune modulation with local and systemic delivery of AAV9. Both mouse and NHP data were obtained to establish the safety of this approach. $GAA^{-/-}$ mice were engineered to express human CD20 and therefore amenable to use of

human anti-CD20 antibody treatment. The immune modulation regimen is based on B-cell ablation with rituximab and sirolimus immediately prior to vector exposure. Data from the NHP study showed that 1) Clearance of AAV is influenced by antibody formation; 2) Protection from anti-AAV antibodies allows for re-administration of AAV9 given IM; 3) Screening for naïve status requires the assessment of both total antibody titer by ELISA as well as neutralizing Ab titer; 4) Immune modulation completely block anti-human transgene immune response in NHPs, and 5) In the setting of pre-immunity, high-titer anti-AAV antibodies lead severe infusion reactions after IV AAV delivery. Findings from human CD-20+/KO mice confirmed the above findings and showed that repeated IV dosing leads to augmentation of GAA activity above wildtype levels without increased anti-GAA or anti-AAV9 antibodies from baseline. In conclusion, co-administration of rituximab and sirolimus with AAV vectors is safe in non-human primates. In naïve animals, blockade of humoral immunity prevents anti-AAV and anti-transgene antibodies which enhances safety and allow for repeated AAV dosing. A study in LOPD has been initiated to further develop this strategy for all Pompe patients

Nina Raben, National Institutes of Health, Bethesda, MD, United States,
"A major advance in the search for more effective therapy for Pompe disease"

Current treatment with enzyme replacement therapy (ERT) is very effective in restoring cardiac function and extending the life span of infants, but skeletal muscle abnormalities have proven to be notoriously difficult to correct. The pathological mechanisms of muscle damage involve lysosomal glycogen accumulation, lysosomal swelling and dysfunction, and a major secondary abnormality - impairment of autophagy. Build-up of autophagic debris greatly contributes to skeletal muscle resistance to ERT. Here, we report that a new experimental drug (a proprietary recombinant human GAA, designated as ATB200, with an optimized N-glycan profile for enhanced biodistribution and lysosomal uptake) clears lysosomal glycogen far more efficiently than the current standard of care, as shown by biochemical and histochemical analyses of muscle samples from *Gaa* knockout mice. Following two biweekly administrations of ATB200 at a dose of 20 mg/kg, immunostaining of single fibers with lysosomal and autophagosomal markers, and second harmonic imaging of muscle bundles showed a complete or near complete reversal of lysosomal pathology in most fibers. Furthermore, remarkably, autophagic buildup was resolved or significantly reduced in the diseased muscle - an outcome not seen with the current standard of care even at higher doses and longer treatment durations.

Andrew Baik, Regeneron Pharmaceuticals, Tarrytown, NY, United States,
"Next-generation antibody-guided enzyme replacement therapy in Pompe disease mice"

Here, we present an antibody-guided enzyme replacement therapy where antibodies are fused to hGAA and guide hGAA to skeletal muscle by targeting cell-surface internalizers that have a more favorable biodistribution and internalization kinetics than the cation-independent mannose 6-phosphate receptor (CI-MPR). Antibodies against broadly-expressed or skeletal muscle-specific internalizers were fused to hGAA and were able re-direct hGAA independently of CI-MPR *in vitro.* AAV-mediated liver depot gene therapy using an antibody::hGAA against the broadly expressed tetraspanin CD63 cleared glycogen in cardiac and skeletal muscles in Pompe mice to wild-type levels, while hGAA alone was only able to reduce 50% of muscle glycogen at the same dose. Markers for autophagy and lysosomal over-proliferation were significantly improved. Antibody::hGAA treated mice show improved performance on Rotarod and grip strength within 2 months of treatment, performing similarly to wild-type mice, while hGAA treated mice only stabilized or declined their strength.

Kelly George, Sanofi Genzyme, Framingham, MA, United States,

“Comprehensive exploratory study to identify novel biomarkers of Pompe disease”

Alglucosidase alfa is an enzyme replacement therapy (ERT) for the treatment of Pompe disease that provides patients with exogenous recombinant human GAA. The second generation of ERT, neoGAA, is currently in Phase III trials. The biomarkers being used clinically, including glycogen content via muscle biopsy, CRIM status, ACE polymorphism, urinary Hex4, and MRI, are either invasive, technically challenging, or more useful for the infantile form of the disease. Therefore, there is a great need for a sensitive, non-invasive, and reliable biomarker that can aid in prognostic monitoring of disease progression in symptomatic and asymptomatic patients, and to measure response to treatment. To identify novel biomarkers, an unbiased approach was taken using samples from late-onset Pompe disease patients enrolled in the EMBASSY or neoGAA Phase I/II trials. Normal control donors that were similar in age, gender, race, and BMI were also included. A comprehensive discovery program that included proteomics, metabolomics, and multi-analyte profiling was used to identify potential biomarkers in urine and plasma samples. These analyses identified candidates at both the protein and metabolite level that are being investigated further in targeted mass spectrometry assays. Further investigation linked identified biomarkers to a number of pathways that are altered in Pompe patients. As expected, intermediates in glycogen metabolism were significantly upregulated. However, changes in other metabolic pathways suggest that there is a decrease in overall energy production with preferential utilization of fatty acids over glucose in Pompe disease. This is the first multi-omic approach to identify biomarkers in late-onset Pompe disease for the development of targeted assays with potential clinical utility.

Taszeen Mozaffer, Amicus Therapeutics, Inc., Cranbury, NJ, United States,
“First-in-human preliminary pharmacokinetic data on a novel recombinant acid α-glucosidase, ATB200, co-administered with the pharmacological chaperone, AT2221, in patients with late-onset Pompe disease”

ATB200-02 is a first-in-human, Phase 1/2 trial to evaluate ATB200, a next-generation rhGAA ERT, co-administered with AT2221, an oral pharmacological chaperone, in adults with LOPD. This open-label, single-ascending-dose study assessed the safety/tolerability, pharmacokinetics/pharmacodynamics, and efficacy of ATB200/AT2221. Twenty patients were enrolled: ERT-switch ambulatory (n=11; Cohort 1), ERT-switch nonambulatory (n=4; Cohort 2), and ERT-naive ambulatory (n=5; Cohort 3). The most common treatment-related adverse events were nausea, tremor, headache, and fatigue (n=3 each). Three events of infusion-associated reactions occurred in 400+ infusions. ATB200/AT2221 therapy was associated with reductions in markers of muscle damage (CK, ALT, AST) and substrate accumulation (Hex4). At months 6 and 9, muscle function improvements were observed in 16/18 and 10/10 patients, respectively. Mean [SD] 6-minute walk test increased from baseline for both ERT-switch and ERT-naive patients at month 6 (cohort 1 [n=9], +35.3 [40.1]; cohort 3 [n=5], +41.8 [29.4] meters) and month 9 (cohort 1 [n=8], +37.2 [33.8]; cohort 3 [n=2], +74.9 [4.0] meters); other motor function tests were consistent with these results. At month 6, increases were observed in elbow and shoulder strength in non-ambulatory ERT-switch patients. Forced vital capacity (% predicted) increased in ERT-naive patients (cohort 3: month 6 [n=5], +4.2; month 9 [n=2], +5.0) and was generally stable in ambulatory ERT-switch patients (cohort 1: month 6 [n=8], -1.0; month 9 [n=7], -2.0). Preliminary data indicate that next-generation ATB200/AT2221 has the potential to be an important treatment option for patients with Pompe disease.

Satellite Symposia

Responding to the Challenge of Pompe Disease

CME Satellite Symposium. Supported by an independent educational grant from Sanofi Genzyme. The main speaker in this session was Priya Kishnani who spoke of emerging new phenotypes of Pompe disease as a result of new-born screening in the USA. For example the atypical Infantile Onset children who are diagnosed under the age of one year and have no cardiomyopathy.

Creating Hope for the Unreachable, Unprofitable and Unthinkable Patient

Sponsored by Care Beyond Diagnosis Foundation, in conjunction with the MPS Society UK and the European Gaucher Alliance.
Supported via unrestricted educational grants from Chiesi Farmaceutici, Shire and FYMCA Medical Ltd.

FYMCA Medical is a new organisation formed by Chris Hendriksz and his family. Chris was, until recently, the clinical lead at the adult LSD specialist centre in Salford, UK. They work to improve the care of people with rare diseases in areas of the globe where high standards of medical care do not exist.

Early treatment of lysosomal disorders: a closer look at Fabry and Pompe disease

Supported by Amicus Therapeutics, Inc.
Mark Patterson gave an interesting talk about the need for early diagnosis across all diseases, and Priya Kishnani gave examples from the New-born Screening programme in the USA.

Sanofi Genzyme's 6th Annual Forum for patient advocates

This was a small meeting designed to introduce the global patient advocacy team and the support they can provide, and to inform Patient groups of grants available and the process for making grant applications. Groups are advised to submit applications at least 16 weeks before the funds are required and, particularly in the US, year-end reports are required to show how the funds were used.
An extremely successful art exhibition, "Beyond the Diagnosis" by Patricia Weltin was highlighted as a successful way of raising awareness of rare diseases.

Annex A. Poster Presentations

Over 30 posters were presented with Pompe in the title. Many other posters had some relevance to Pompe although the research concentrated on other LSDs or LSDs in general.

Abstracts of all these posters are published in the Journal of Molecular Genetics and Metabolism, February 2018, Volume 123, Issue 2.

Poster #	First Author	Abstract Title
18	Stephanie Austin	Insight into the phenotype of infants with Pompe disease identified by newborn screening with the common c.-32-13T>G "late-onset" GAA variant
43	Irene Chang	Proteolytic immuno-SRM-MSMS in dried blood spots to determine immunogenicity in patients with infantile Pompe disease
71	Ankit Desai	An immune tolerance approach using methotrexate in the naïve setting of patients treated with a therapeutic protein: experience in infantile Pompe disease
72	Jordi Díaz-Manera	Anti-rh-GAA antibodies does not influence late onset Pompe disease progression
77	Alícia Dornelles	Enzyme replacement therapy for late-onset Pompe disease: a systematic review
98	Allison Foley	Planning, implementation, and initial results of newborn screening for Pompe disease and MPS I in Georgia
110	Kelly George	Comprehensive exploratory study to identify novel biomarkers of Pompe disease
123	John Gray	Establishing the optimal tissue target for alpha-glucosidase gene delivery in Pompe disease
124	Abhinav Grover	Optimization of CRISPR mediated genome correction of Pompe disease-specific GAA mutations in C2C12 mouse myoblasts
142	Mrudu Herbert	Cognition and brain involvement in infantile Pompe disease
150	Elise Holmes	Minnesota Department of Health long-term follow-up of newborn screening conditions: new applications for Pompe disease and MPS I
154	Jeffrey Huang	Characterization of CRISPR-Cas9 generated Pompe disease models
168	Franklin Johnson	First-in-human preliminary pharmacokinetic data on a novel recombinant acid α- glucosidase, ATB200, co-administered with the pharmacological chaperone, AT2221, in patients with late-onset Pompe disease
169	Harrison Jones	Lingual pathophysiology in late-onset Pompe disease
170	Harrison Jones	Respiratory muscle training in Pompe disease
182	Zoheb Kazi	A prediction model to identify infantile Pompe disease (IPD) patients at high-risk of developing significant anti-drug antibodies (ADA) utilizing acid α-glucosidase (GAA) variants and HLA-type
189	Virginia Kimonis	Variable clinical features and progression in 18 patients with Pompe disease
193	Dwight Koeberl	Correction of biochemical abnormalities and gene expression associated with improved muscle function in a phase I/II clinical trial of clenbuterol in Pompe disease patients stably treated with ERT
198	David Kronn	Response to omalizumab in a patient with Pompe disease

Poster #	First Author	Abstract Title
213	Jeong-A Lim	The pros and cons of manipulating different pathways to address defective autophagy in Pompe disease
228	M. Valerie Marrero-Stein	Diagnostic challenges for Pompe disease newborn screening in a pre-term infant
298	Nita Patel	The patient and clinician point of view: living with late-onset Pompe disease
323	Deborah Ramsdell	Treatment of Pompe disease with VAL-1221
330	Roberto Sandobal Pacheco	Description of a patient with infantile onset Pompe disease after 45 months of enzyme replacement therapy
364	David Stockton	Long-term study of growth and development outcomes in patients with infantile-onset Pompe disease receiving alglucosidase alfa: safety data update
385	Alfredo Uribe Ardila	Confirmatory assays for alpha-glucosidase enzymatic values using glycogen: an improving test for the diagnosis of Pompe disease
410	Chia-Feng Yang	Very early treatment for infantile-onset Pompe disease contributes to better outcomes: 10-year experience of nationwide NBS in Taiwan
416	Mindy Zhang	Transcriptome analysis in muscle biopsies of late-onset Pompe patients treated with alglucosidase alfa or neoGAA
LB-09	Pasqualina Colella	Whole-body rescue of Pompe disease with adeno-associated virus vector-mediated liver gene transfer of secretable acid alpha-glucosidase
LB-22	Nadene Henderson	Pompe and MPS I newborn screening in Pennsylvania - review of our experience
LB-30	Virginia Kimonis	Antisense oligonucleotide treatment targeting glycogen synthase (GYS1) in a mouse model of Pompe disease
LB-38	Tahseen Mozaffar	Updated results from ATB200-02: a first-in-human, open-label, phase 1/2 study of ATB200 co-administered with AT2221 in adults with Pompe disease
LB-45	Loren Pena	Neo1 and NEO-EXT: long-term safety of repeat neoGAA (avalglucosidase alfa) dosing in late-onset Pompe disease patients for 3.5 years
LB-49	Gerben Schaaf	Reactivation of muscle regeneration activity reverses muscle wasting phenotype in Pompe disease
LB-50	Kristen Skvorak	Improving ERTs with CodeEvolver® protein engineering technology to improve protein stability and in vivo half-life, as well as reduce immune response
LB-51	Barbara Smith	Coordination of breath and stimulator initiation in diaphragm-paced individuals with Pompe disease