Substrate Reduction Therapy (SRT)

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Translated from German – except English quotes – with www.DeepL.com/Translator,
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Along with the information we have provided on Enzyme Replacement Therapy (ERT) and the gene therapy, we would like to advise you of clinical trials of Substate Reduction Therapy (SRT) for Pompe. This is similar to that currently being used in other Lysosomal diseases (miglustat/eliglustat for the treatment of Gaucher disease type 1 and Miglustat for Niemann-Pick type C):

Substrate reduction therapy offers an approach to treatment of certain metabolic disorders, especially glycogen storage diseases and lysosomal storage disorders. In a storage disorder, a critical failure in a metabolic pathway prevents cellular breakdown and disposal of some large molecule. If residual breakdown through other pathways is insufficient to prevent harmful accumulation, the molecule accumulates in the cell and eventually interferes with normal biological processes. … In a metabolic or genetic pathway, enzymes catalyse a series of reactions. Each enzyme is regulated or mediated by one gene through its RNA and protein products. At each phase in the pathway, enzyme activity catalyses a reaction in which a precursor molecule (the substrate) is transformed into its next intermediate state. Failure of the metabolic pathway leads to accumulation of the substrate, with possible harmful effects. Substrate reduction therapy addresses this failure by reducing the level of the substrate to a point where residual degradative activity is sufficient to prevent substrate accumulation.
[Source: https://en.wikipedia.org/wiki/Substrate_reduction_therapy (Wikipedia)]

A novel SRT for Pompe disease proposed by a U.S. biotechnology company *Maze Therapeutics* (https://mazetx.com/) is designed to prevent the excessive build-up of glycogen in muscle cells typical of Pompe by inhibiting the action of the gene GYS1; the gene controlling glycogen synthesis in muscle cells.

A graphic (https://mazetx.com/wp-content/themes/maze/images/pipeline/pipeline-img2.jpg) under the menu item "pipeline" on the website of *Maze Therapeutics* clearly explains the mode of action of SRT (Note: We have not requested permission from Maze Therapeutics to use the graphic; therefore, the graphic is not embedded here, but only linked):

1. The muscle cells (more precisely: the lysosomes) are symbolized by a vessel filled by a tap. The "water" is in the case of Pompe the glycogen; it "flows" normally in full stream into the vessel due to the glycogen synthesis. The "drain", i.e. the breakdown of the stored glycogen, occurs in healthy individuals due to the action of the enzyme alpha-glucosidase, so that no glycogen can accumulate in the vessel.
2. In Pompe disease, the degradation of stored glycogen is impaired; it cannot "flow out" to a sufficient extent, so that it accumulates in the vessel. This glycogen storage in the lysosomes leads to the destruction of the lysosomes and muscle cells with the well-known Pompe symptoms.

3. SRT, i.e. inhibition of the gene GYS1, which is responsible for glycogen synthesis, reduces the "influx" of glycogen into the vessel, so that glycogen can no longer accumulate to such an extent and cause destruction.

In addition to SRT, the use of ERT together with SRT is possible. Referring to the graphic, ERT increases the outflow from the vessel such that the reduced inflow and increased outflow are matched, and result in a "healthy" fill level.

Results reported by *Maze Therapeutics* are predominantly from the preclinical phase (studies in animal models) and give rise to hope that SRT alone or in combination with ERT could also work in humans. Corresponding clinical studies have already begun and others are in preparation. The January 2022 corporate presentation available on *Maze Therapeutics'* website under "news & press" indicates that the clinical trials will work towards oral SRT as a monotherapy or in combination with ERT.

As with any therapy, the possibility of side-effects must be considered with SRT. For other lysosomal storage diseases, experience is already available on the tolerability of other SRTs and on their possible effects on human metabolism. It remains to be seen whether comparable effects can also occur with SRT for Pompe disease. Information on possible side effects is expected to be provided by a phase-1 clinical trial that started in February 2022:

A Randomized Phase 1 Single and Multiple Ascending Dose Study of MZE001 (https://clinicaltrials.gov/ct2/show/NCT05249621). A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study of MZE001 to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in Healthy Subjects. MZE001 is a small molecule inhibitor of muscle glycogen synthase for the potential treatment of Pompe disease.

Links for further reading

- February 22, 2022 First Healthy Volunteers Dosed in Trial of Oral Therapy MZE001
- February 17, 2022 Press Release: Maze Therapeutics Announces Phase 1 Trial Initiation Evaluating MZE001 as a Potential Oral Treatment for Pompe Disease
- February 10, 2022 Press Release: Maze Therapeutics Presents New Preclinical Data Supporting Advancement of MZE001 as a Potential Treatment for Pompe Disease

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