Overview of Initial Findings

June 2015
Overview of study and initial conclusion

Chaperone therapy for neuronopathic Gaucher disease

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Background

- Chaperone therapy is expected to make contributions to alleviating neurological symptoms in lysosomal storage disorders, since small molecules can cross the blood-brain barrier. Gaucher disease (GD) is characterized by a deficiency of the lysosomal enzyme, glucocerebrosidase (GBA), Ambroxol (ABX), a commonly used expectorant, has been reported to have chaperone activity on mutant GBA. We aimed to investigate the effect of ABX on neurological manifestations of GD

Methods

- We enroll 3 patients with Type 3 GD. The genotypes were N188S/G193W and N188S/?. Before inclusion in the study, written informed consent was obtained; and the study was approved by the institutional review board. They received ABX combined with ERT. ABX treatment began with 3 mg/kg/day, with doses escalating over time to 25 mg/kg/day. The evaluation of efficacy included changes in neurological or neurophysiological assessments, activities of daily living (ADLs), hematological and clinical laboratory assessments, and safety evaluations

Results

- The median (range) exposure to ABX was 12 (12-31) months. No clinical or biochemical adverse effects were found. ABX enhanced GBA activity in lymphocytes to normal levels with a serum concentration of more than 1 μM. ABX was detected in the cerebrospinal fluid, at approximately 14% of serum levels. As ABX dose increased, persistent myoclonus and seizures were ameliorated, and oculomotor deficits were improved. Improvement of the neurological symptoms also correlated with recovery of the patients’ ADLs

Initial conclusions

- ABX improves or stabilizes neurological symptoms in Type 3 GD. Combination therapy with high-dose ABX and ERT may be beneficial for neuronopathic GD patients with specific mutations, and the early clinical application should be explored