The Use of Serum Markers to Determine Therapeutic Dosing of Chaperones TUDCA and 4PBA for the Treatment of Collagen 4A1 and 4A2 Mutations in Gould Syndrome Patients

**Abstract:**
This proposal for clinical trial outlines a plan for using chaperones TUDCA and 4PBA to alleviate endoplasmic reticulum (ER) stress in patients with Gould Syndrome (having collagen 4A1 and 4A2 mutations) by adjusting their chaperone dosage based on markers found in the serum of these patients. Collagen misfolding or improperly processed proteins in the ER can induce the unfolded protein response (UPR), leading to ER stress, which can cause oxidative stress, inflammation, decreased cell energy and function, weak and degenerative basement membranes, and cell death. In preclinical studies, chaperones like TUDCA and 4PBA have been shown to alleviate ER stress by helping with protein folding and transport in the ER. Lowering ER stress and production of functional proteins corresponds to normalizing UPR, inflammation, and cytokine markers (1,2). We plan to use markers in the serum to find a safe, therapeutic dose range for TUDCA and 4PBA.

**Introduction:**
Gould Syndrome is a rare genetic disorder that results from mutations in the COL4A1 and COL4A2 genes, which encode collagen IV alpha chains responsible for basement membranes. Patients with Gould Syndrome can develop small vessel disease in the brain, resulting in ischemic and hemorrhagic strokes and other symptoms, including muscle spasms, fatigue, tics, eye malformations, kidney disease, and seizures. Chaperone therapy using TUDCA and 4PBA has been proposed as a potential therapy for Gould syndrome patients due to their ability to help with protein folding, alleviate ER stress, and usually form stronger, healthier basement membranes in mice. But safety is a concern (1,2,3). Knowing serum lab values for various markers can help find a therapeutic dose range and lower safety concerns.

**Objective:**
Gould Syndrome is a rare genetic disorder that results from mutations in the COL4A1 and COL4A2 genes, which encode collagen IV alpha chains responsible for basement membranes. Patients with Gould Syndrome can develop small vessel disease in the brain, resulting in ischemic and hemorrhagic strokes and other symptoms, including muscle spasms, fatigue, tics, eye malformations, kidney disease, and seizures. Chaperone therapy using TUDCA and 4PBA has been proposed as a potential therapy for Gould syndrome patients due to their ability to help with protein folding, alleviate ER stress, and usually form stronger, healthier basement membranes in mice. But safety is a concern (1,2,3). Knowing serum lab values for various markers can help find a therapeutic dose range and lower safety concerns.

**Methods and Data Collection:**
Patients with Gould Syndrome will undergo physical exams to determine affected organ systems and complete standardized questionnaires for pain, depression, quality of life, and other disease severity indicators. Regular and regular testing laboratories will obtain serum baseline values for GRP78/BIP, CHOP, caspases 3, 6, 9, 12, TNF alpha, interleukins, as well as urine albumin, GFR, and CPK. Low, medium, and high doses of TUDCA and 4PBA will be administered over a week each, with serum samples collected at the end of each week to correlate laboratory results with physical exams and questionnaires. Clinicians will use the data to determine the appropriate chaperone therapy and dosage for each patient.

**Conclusion:**
It is essential to take care when dosing with chaperones, as high dosages of 4PBA may produce a weakened basement membrane (see video). The lab panel with serum markers will help to find a safe, therapeutic dose range for both chaperones, contributing to the better understanding and treatment of protein-folding diseases such as Gould Syndrome.

**References for this poster:**
2. TUDCA and 4PBA: http://www.chaperonethrapy.com
3. Human Equivalent Dose calculations: WebMD
4. Endoplasmic Reticulum (ER) Stress and Chaperone Therapy: ER Stress is gone.
5. Treatment of diseases: ER Stress gone. All UPR markers are expected to be normalized. The quality control ER-associated Degradation (ERAD) system is intact. This keeps malformed collagen Recycled to the proteasome and out of the BM
6. Too High: ER Stress is gone. Serum markers are normal or low. BM thickens. ERAD system may be lacking, allowing malformed collagen to be sent to the BM
7. Too Low: ER Stress is gone. Serum markers are normal or low. BM thin. ERAD system is intact. This keeps malformed collagen Recycled to the proteasome and out of the BM
8. Sudan Staining: BM thick. Sudan Staining: BM thin