Enzyme Therapy for ABCC6 Deficiency/Pseudoxanthoma Elasticum: from Bench to Bedside

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Introduction: Pseudoxanthoma elasticum (PXE) is a rare mineralization disorder caused by mutations in the ABCC6 gene. ABCC6 is a critical protein involved in the metabolic pathway that produces inorganic pyrophosphate (PPi), an inhibitor of mineralization, and adenosine, an inhibitor of vascular intimal proliferation. PXE is associated with reduced levels of PPi and adenosine leading to ectopic calcification and artery lumen narrowing. Adults with PXE experience progressive dermatologic, ocular, and cardiovascular morbidities, and there are no therapies that target the underlying disease process. INZ-701 is an investigational product comprised of an ENPP1-Fc fusion protein designed to increase PPi and adenosine levels.
Methods: Subcutaneous (SC) INZ-701 was tested in ABCC6 deficient mouse models, and in a dose escalating phase 1/2 study in adults with ABCC6 Deficiency manifesting as PXE (NCT05030831).
Results: Abcc6−/− mice were injected with INZ-701 at 2 or 10 mg/kg SC for 8 weeks. Both doses increased plasma ENPP1 activity and PPi levels, and histopathology and calcium quantification revealed significantly reduced calcification in the muzzle skin of treated mice. In adults with PXE, INZ-701 was well-tolerated with no serious or severe (> grade 2) adverse events. A rapid increase in mean PPi from baseline of 969±62 nM was noted in 8/9 patients after a single dose of INZ-701, with sustained elevation through week 48 in the highest (1.8 mg/kg twice weekly) dosing cohort. Improvements in vascular and retinal pathology were observed from baseline to week 48, with preservation and improvement of visual function in 4/6 evaluable patients (Global Visual Function Questionnaire). In addition, clinician (9/9) and patient (7/9) reported outcomes improved from baseline to week 48 (Global Impression of Change).
Conclusions: Across preclinical and clinical testing, INZ-701 demonstrated benefit in ABCC6 Deficiency, and was well-tolerated with evidence of efficacy in adults with PXE.

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