THERAPY

An extended-release form of cysteamine bitartrate for cystinosis

Treatment of cystinosis necessitates that the cysteamine bitartrate Cystagon® (Mylan Pharmaceuticals, Morgantown, WV, USA) is taken every 6 h. New research, however, has shown that a novel, delayed-release formulation of cysteamine bitartrate, called RP103, which can be taken every 12 h, is noninferior to Cystagon® for maintaining cystine at levels associated with optimal outcomes for patients with this disease.

Cystinosis is a rare systemic disease caused by mutations in the gene that encodes cystinosin. Dysfunctional cystinosin leads to an intralysosomal accumulation of cystine crystals, resulting in damage to various organs, including the kidney. “Treatment has been with agents used to deplete the intralysosomal accumulation of cystine crystals”, explains researcher Craig Langman. “The only approved product ... must be taken every 6 h around the clock ... thus, it is virtually

impossible to sustain that dosing for a lifetime.”

To compare the efficacy of RP103 with Cystagon®, Langman and colleagues performed an open-label, randomized, controlled, crossover study, in which they randomly assigned 43 patients to receive either RP103 or Cystagon® for 3 weeks. The primary end point was based on the comparison of peak reduced cystine ($\frac{1}{2}$ cystine) levels in peripheral white blood cells (WBCs). “We demonstrated that when used on a 12 h basis, RP103 was not inferior to Cystagon® for the ability to keep WBC $\frac{1}{2}$ cystine levels equivalently low”, notes Langman. “Importantly, we did this at a total daily dose of the active agent, cysteamine bitartrate, with RP103 that was only 82% of the total daily dose of Cystagon®.”

The researchers did not observe any adverse effects with RP103 that they considered unexpected, given the side effect profile of Cystagon®. A greater number of gastrointestinal adverse effects

occurred in the RP103 arm but as Langman points out, “...we asked patients to discontinue cytoprotective therapy, largely protein-pump-inhibitor (PPI) use, during the RP103 phase to minimize pH interaction with the delayed release ... in doing that patients were exposed to PPI rebound symptoms and to a maximal side effect profile.”

The researchers will continue to monitor these patients in an ongoing extension study. They also hope to investigate the effects of RP103 in treatment-naïve patients and in kidney transplant recipients.

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Original article Langman, C. B. et al. A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety. *Clin. J. Am. Soc. Nephrol.* doi:10.2215/CJN.12321211