Key Summary of Published Article

Erythrocyte Ion Content and Dehydration Modulate Maximal Gardos Channel Activity in KCNN4 V282M/+ Hereditary Xerocytosis (HX) Red Cells

Background

- Hereditary xerocytosis (HX) is a rare form of hemolytic anemia that is caused by a heterozygous missense mutation in the gene *PIEZO1* or the gene *KCNN4*. *KCNN4* encodes a Ca^{2+}-activated K^{+} channel known as the Gardos channel.[1]
- The compound senicapoc is a Gardos-channel blocker and is being studied as a potential treatment for HX.
- To date, all Gardos channel mutants have been associated with gain-of-function phenotypes: higher current magnitude and higher red blood cell dehydration than wild-type cells.[1] During further characterization of the V282M mutation, investigators found some loss-of-function phenotypes that could affect the use of senicapoc.
- **Objective:** In this study, the investigators further examined the characteristics of red blood cells from patients with HX who were heterozygous for *KCNN4* V282M (V282M/+).

Methods

- Blood specimens were obtained from 6 related HX patients who were V282M/+.
- Specimens were analyzed for red blood cell KCNN4-mediated changes.
  - Baseline and stimulated activity were measured by influx of a rubidium isotope. Stimulated activity was provoked by a calcium ionophore (A23187) or a plasma membrane calcium ATPase inhibitor (orthovanadate).
  - Other characteristics of the red blood cells were also assessed, including number, size, hemoglobin content, deformability, sodium content, and potassium content.
- Results were compared to those of 6 specimens from apparently healthy (WT) individuals.

Results

- Baseline channel activity was higher in cells from HX V282M/+ patients than those from WT individuals. This phenotype was expected gain-of-function.
- Stimulated channel activity was lower in cells from HX V282M/+ patients than those from WT individuals. This phenotype was loss-of-function.
  - Loss-of-function was unrelated to altered intracellular Ca^{2+}, Ca^{2+} sensitivity, senicapoc sensitivity, or altered Ca^{2+} handling.
- Compared to red blood cells from WT individuals, red blood cells from HX V282M/+ patients were fewer, but had a higher proportion of macrocytic (larger) cells, a higher proportion of hyperchromic (high hemoglobin, >41 /dL) cells, lower deformability, higher intracellular sodium content, and much lower potassium content.

Conclusions

- The results of this study indicate that the V282M mutation causes both gain-of-function and loss-of-function phenotypes, including lower stimulated channel activity.
- Such results may have clinical implications for the treatment of HX patients with senicapoc.

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Webpage

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