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Oral N-acetylcysteine Trial for RYR1-related Myopathies

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Investigators from NIH, Hyperion Biotechnology Inc., and Hospital for Sick Children studied the effect of oral N-acetylcysteine (NAC) on decreasing oxidative stress and increasing physical endurance in individuals with ryanodine receptor 1-related myopathies (RYR1-RM).

The trial design included a selection of 37 genetically confirmed ambulatory individuals (adult and pediatric) with mild to moderate RYR1-RM phenotype. They were tracked as a part of natural history for six months, after which 33 of them were subsequently randomized (1:1) to a double-blinded, placebo-controlled trial. They either received a placebo (n = 17) or oral NAC (n=16) for six months. Primary endpoints were the evaluation of oxidative stress as measured by urine 15-F2t isoprostane concentration and physical endurance by the 6-minute walk test (6MWT) distance.

At baseline, individuals with RYR1-RM, in comparison to the general population, had a significantly ($p<0.001$) elevated mean 15-F2t isoprostane level (3.2 ± 1.5 vs 1.1 ± 1.7 ng/mg creatinine) and a decreased 6MWT distance (468 ± 134 vs 600 ± 58 m). Trial results showed no significant change of either 15-F2t isoprostane levels (($p = 0.98$) or 6MWT distance ($p = 0.61$) during the 6-month natural history interval. Furthermore, in the NAC treatment group, there was no significant change in the 15-F2t isoprostane levels ($p = 0.88$) or 6MWT distance ($p = 0.11$). NAC had no substantial safety concerns, and it was well tolerated at the doses administered. [1]

COMMENTARY. RYR1-RM is the most frequently diagnosed of all the congenital myopathies, with an estimated US point prevalence of 1:90,000. The RYR1 gene is responsible for calcium channel stability, mutations of which lead to channel hyper- or hyposensitivity and chronic Ca2+ leak. There are no FDA-approved treatments for RYR1-RM. As of 2018, the following were some of the therapeutic approaches postulated for RYR1-RM based on the pathomechanism of disease and potential targets: RyR1 channel stabilization using Rycal ®, chaperones such as Sodium 4-phenylbutyrate, enhancing sarco-endoplasmic reticulum Ca2+ ATPase expression by 5-Aminoimidazole-4-carboxamide ribonucleoside, dantrolene as a RyR1 channel antagonist, carvedilol (a beta-blocker) and an acetylcholinesterase inhibitor such as pyridostigmine. A gene-based approach using adenovirus-mediated therapy was not possible, as the RYR1 gene is 159 kb long and exceeds the ~5 kb packaging capacity [2].

This study used NAC as an approach as it was readily available and had been FDA approved for acetaminophen overdose and other pulmonary conditions. NAC is a precursor to glutathione and is known to reduce oxidative stress. NAC was also shown to have a beneficial effect on muscle function and structure in both zebrafish and mouse models of RYR1-RM.

The following seemed to be some of the reasons that NAC may not have shown benefit in this study: the oral route of NAC administration may have undergone extensive first-pass metabolism and therefore decreased the overall drug availability, the low sample size may not have permitted detection of a clinically meaningful difference, the 6MWT distance was based on Duchenne muscular dystrophy minimum clinically important difference and not on RYR1-RM specifically, and finally the 15-F2t isoprostane levels could have been influenced by diet and exercise and were not corrected for [1].

This was a well-designed and executed study that was based on sound preclinical evidence. This study provides Class I evidence that treatment with oral NAC does not decrease oxidative stress as measured by 15-F2t isoprostane. This study for RYR1-RM will certainly benefit the design for future trials.

Disclosures

The author has declared that no competing interests exist.

References

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