Repurposing Valganciclovir to Treat Cytomegalovirus-Induced Hearing Loss

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SUMMARY STATEMENT

Clinical trial repurposing valganciclovir (VGC), an antiviral drug used in organ transplantation, to improve hearing outcomes in newborns infected with cytomegalovirus

DISEASE/CONDITION

Almost 400 children die each year from congenital cytomegalovirus (cCMV) infections, and 35% of affected infants develop permanent disabilities, including hearing loss. cCMV is a leading cause of childhood sensorineural hearing loss (SNHL), a condition where the inner ear is unable to convert sound into nerve impulses to the brain. Hearing loss can occur in both symptomatic and asymptomatic cCMV infected infants.

The resulting hearing loss has extreme detrimental effects on language development and quality of life, and it incurs the major cost associated with cCMV infection, which has been estimated to be $4 billion a year.

CURRENT TREATMENT

Currently, there is no approved drug to treat CMV induced hearing loss. VGC is used off-label but exhibits a narrow therapeutic window and high variability.

Additionally, healthcare costs for a cCMV infected infant with speech / language delays are $1.3 million across lifespan, compared to $3,492 for a 6 month course of VGC.

PROPOSED TREATMENT

Repurposing valganciclovir (VGC), an orally available pro-drug of the antiviral drug ganciclovir (GCV), in cCMV infected infants with hearing loss.

We have demonstrated previously that GCV improved hearing outcomes and reduced viral counts in a mouse neonatal model of CMV-mediated hearing loss. VGC is a pro-drug of GCV, meaning it is metabolized into GCV once in the body. While VGC is already used off-label to treat cCMV hearing loss and has been shown to modestly improve hearing outcomes in symptomatic cCMV infants, the drug exhibits a narrow therapeutic window and high variability. Prior research has not addressed the role of VGC in asymptomatic, hearing loss-only cCMV infants.

This proposal will address a critical unmet need: the value of drug monitoring – the association between patient's drug exposure and the drug's efficacy and safety – for hearing loss in asymptomatic cCMV infected infants. Our group will leverage our ongoing, NIH-funded cCMV ValEAR clinical trial to obtain pharmacokinetic data, in addition to viral titers, hearing outcomes, and safety data, in infants treated with VGC.

Identifying this association could directly benefit the health of the more than 3,600 children who develop isolated hearing loss from this infection annually.

PROJECT

A multi-center, double-blinded, randomized, placebo-controlled clinical trial to investigate the safety and effectiveness of VGC treatment in asymptomatic, isolated hearing loss cCMV infected infants.

The trial will enroll 52 asymptomatic cCMV infected infants with isolated hearing loss between the ages of 1 – 12 months through a collaborative group of over 30 institutions. Overall safety and effectiveness will be evaluated as part of the parent NIH-funded ValEAR study. Additional funding will allow us to:

- Determine if higher VGC/GCV exposures lead to improvements in hearing thresholds
- Identify the VGC/GCV exposure that leads to increased incidence of neutropenia, a potential adverse effect
- Define VGC dosing that is both safe and effective for cCMV infected infants with isolated hearing loss

Future studies would build upon these results to develop an algorithm for drug monitoring that could optimize a patient's dosing to achieve safe and effective VGC/GCV exposure.

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