August 24, 2024

Dear Friends,

I hope you had a wonderful summer. As the number of patients referred to us continues to grow, our team feels an even greater urgency to develop safe and effective treatments for Wolfram syndrome. I'm pleased to share the latest updates with you:

Ongoing Clinical Trial of AMX0035 in patients with Wolfram Syndrome
https://clinicaltrials.gov/study/NCT05676034

We have been collaborating with Amylyx Pharmaceuticals to advance the development of AMX0035, a novel oral medication with the potential to halt or delay the progression of Wolfram syndrome, based on its mechanisms of action and pre-clinical studies. The trial began in April 2023, and the interim results were announced in April 2024. According to Amylyx, the interim analysis of the ongoing Phase 2 clinical trial of AMX0035 for Wolfram syndrome, which involved eight participants assessed at Week 24, revealed encouraging outcomes. Participants demonstrated improvements in pancreatic function and glycemic control, as indicated by C-peptide levels and other markers of glucose metabolism. This contrasts with the typical disease progression expected in Wolfram syndrome. All eight participants met the prespecified responder criteria, showing either improvement or stabilization of their condition, as assessed by both the Patient Global Impression of Change (PGIC) and Clinician Global Impression of Change (CGIC) scales. Furthermore, the majority of participants reported some improvement in vision. Importantly, AMX0035 was generally well-tolerated by all participants, supporting its potential as a therapeutic option for this rare and devastating disorder.
For further information, please refer to the following link: Amylyx Pharmaceuticals Press Release.
We plan to announce additional data in the autumn of this year. The next steps are currently under discussion with Amylyx and the US FDA. While nothing is finalized yet, we appreciate your patience as we continue to move forward.

Gene-Editing Therapy

We're making steady progress in developing gene-editing therapies. The root cause of Wolfram syndrome and related disorders lies in mutations in the WFS1 gene. Correcting these genetic changes offers the best hope for a lasting treatment. Our current efforts focus on second- and third-generation gene-editing technologies: base-editing (second-generation) and prime editing (third-generation). These advanced techniques offer the most precise and efficient gene correction available today. We are testing base-editing in combination with engineered DNA-free virus-like particles (eVLPs), which enhance the effectiveness of editing in different tissues. To ensure these methods work effectively, we've developed brain cells from patient-derived induced pluripotent stem cells (iPSCs) and created rodent models with Wfs1 mutations akin to those seen in our patients. Our ultimate goal is to bring this promising therapy to our patients within the next 5-10 years.

Regenerative Therapy for Optic Nerve Atrophy

We are dedicated to tackling vision loss due to optic nerve atrophy, which is a major challenge for patients with Wolfram syndrome. Our approach centers on regenerative medicine, particularly by introducing a neurotrophic factor called MANF directly into the eyes. MANF is unique in its ability to protect against ER stress—a crucial factor in Wolfram syndrome—and to support the survival and function of stressed cells. Early preclinical studies, including those using humanized mouse models, have shown encouraging results. We are currently exploring various methods to effectively deliver MANF into the eye. This innovative approach holds promise not only for Wolfram syndrome patients but also for individuals with other causes of low vision. We aim to initiate clinical trials for this regenerative therapy within the next 3 to 7 years

Wolfram Syndrome and Related Disorders Clinic

To further enhance the clinical care of patients with Wolfram syndrome and WFS1-related disorders, including WFS1-related deafness and optic nerve atrophy, we continue to operate the WFS1 Clinic at the Center for Advanced Medicine, Washington University Medical Center. This clinic has been a great success, and I have the privilege of seeing patients from across the country and around the world almost every week.

I want to extend my sincere thanks to the Snow Foundation, the Ellie White Foundation, Unravel Wolfram Syndrome, and the various Facebook groups related to Wolfram syndrome for their referrals. Our clinic offers comprehensive genetic evaluations, education, and counseling for patients and their families, as well as personalized management plans in collaboration with other specialists at our medical center and beyond. We welcome both international and out-of-state patients.

For more information, please visit our website: Wolfram Syndrome Clinic.

Conclusion

As we continue to advance our research and clinical efforts, I am filled with hope and determination to bring new and effective treatments to those living with Wolfram syndrome and related disorders. Our progress, though challenging, is a testament to the dedication of our research teams, the support of our partners, and the resilience of the patients and families who inspire us every day. While there is still much work to be done, each step forward brings us closer to our ultimate goal: a future where Wolfram syndrome is no longer a life-limiting condition. Thank you for your ongoing trust and support. Together, we will make a difference.

Sincerely,
Fumi

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