

Wolfram syndrome UK family meeting Saturday 26th September 2020

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Liraglutide in a rat model of Wolfram syndrome

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This research group have made a rat model of Wolfram syndrome, by manipulating the rats' Wolfram gene. These rats have similar, but not the same, symptoms as people with Wolfram: these rats develop diabetes mellitus, lose weight as adults, and don't groom themselves as well as unaffected rats. By 15 months of age, they develop cataracts, then the optic nerves degenerate. Brain scans show brainstem shrinkage at 15 months. They have measured markers for endoplasmic reticulum stress (one of the mechanisms of disease in Wolfram), and they have shown these markers are present in rat brains by 7 months of age.

The group have done several studies of possible treatments: different drugs in the GLP-1 agonist family, called Exanatide, Dulaglutide, and Liraglutide. They have used their original mouse model, and their more recent rat model described above.

One consistent result has been an improvement in these animals' tolerance to glucose. This suggests that these treatments help the diabetes in these animal models.

They have treated their rat model with Liraglutide from ages 2 months (teenage rats) to 17 months (when the rats are elderly). The Wolfram rats that were not treated with Liraglutide, developed diabetes aged 9-10 months of age, then lost weight, and needed insulin treatment. In contrast, the Wolfram rats that were treated with Liraglutide, had milder diabetes, and did not lose weight. It appeared that treatment with Liraglutide slowed down the progression of the diabetes in these rats.

In this rat model, they also looked at the effects of liraglutide on vision. They showed that in the Wolfram rat model, vision became worse with age. This was associated with development of cataracts as well as degeneration of the optic nerve. In the rats that were treated with lifelong Liraglutide, the vision loss was slowed, and this was associated with less severe cataract formation. It is not clear whether liraglutide treatment slowed the optic nerve degeneration, or just slowed the cataract development.

The Liraglutide treated rats, seemed to have delayed hearing loss, but hearing loss was not prevented.

The brain imaging studies did not show differences between the size of the brains between Liraglutide treated or untreated rats; however, there was a reduction in the fluid-filled spaces in the Liraglutide treated rats; this may suggest that Liraglutide is working to preserve brain volume.

Overall, Liraglutide was well tolerated in the Wolfram rats, and seemed safe. However, about 7% of the Liraglutide treated rats developed cancer.

Overall, this is an exciting and scientifically excellent series of studies. They provide animal evidence that GLP-1 agonist medicines may slow the disease progression in Wolfram syndrome; and suggest that we do need careful randomised controlled trials in people, to check these medicines are safe; do not cause cancer in patients; and are effective in humans. The first study has started, in St Louis, USA, to see if Liraglutide is safe and can treat the diabetes in Wolfram. Long term studies will be needed to see if it can also slow the neurodegeneration.

Until these safety and effectiveness studies have been done, we do not recommend that people with Wolfram take Liraglutide or other GLP-1 agonists.