Investigating the Impact of NLRP3 inhibitor, Usnoflast, on Interstitial Cystitis/Bladder Pain Syndrome

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Background and Hypothesis:

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pelvic pain condition that is highly prevalent in the US population (~5%), particularly in those 50 years of age or older and women. IC/BPS is characterized by symptoms of urinary frequency, dysuria, hematuria, and significant pain. Inflammation is a major contributor to the development and progression of IC/BPS. The NLRP3/caspase1 inflammasome pathway is a major contributor that drives IC/BPS pathophysiology. The purpose of this pre-clinical study was to evaluate the therapeutic effect of an NLRP3 inhibitor, Usnoflast (ZYIL1), in an IC/BPS mouse model.

Methods:

A vascular endothelial growth factor A (VEGFa) bladder instillation IC/BPS mouse model was used to assess the effect of Usnoflast. Male and female caspase-1 bioluminescence reporter mice were transurethrally instilled with VEGFa 3x once every other day for one week. They are then subjected to in vivo imaging, pain testing to evaluate spontaneous grimace behaviors, and evoked pain Von Frey testing. Their micturition behaviors were assessed via Void Spot Assay.

Results:

We found that Usnoflast treatment significantly reduced IC/BPS-associated caspase-1 inflammasome activation in vivo and ex vivo tissue of both the brain and bladder. Furthermore, we found Usnoflast significantly improved voiding dysfunction and Von Frey behaviors in female mice compared to males. Finally, we found minimal changes in male grimace pain scores.

Conclusion:

In conclusion, modulating NLRP3/Caspase 1 activation with Usnoflast significantly attenuates IC/BPS-associated inflammatory response. This reduction in inflammation correlates with a decrease in voiding frequency and pain responses in females, but not much in males. It's interesting to see how IC/BPS, a women-dominant disease, manifests in a mouse model.

Potential Impact:

Our preliminary study provides the first insights into Usnoflast's effectiveness for IC/BPS, and we aim to advance it to clinical trials as a potential novel therapy.