

Targeting the roots of Sjögren's syndrome ^[1]

Patient Perspectives ^[2]

Author: Elizabeth Dougherty

Rheumatologist Benjamin Fisher sympathizes with patients suffering from Sjögren's syndrome, who he says are often misunderstood. They have dry eyes, and doctors prescribe eye drops. But drops aren't enough. In Sjögren's, the immune system can go haywire, causing swollen joints, lung and kidney disease, lymphoma and crippling fatigue.

"This is a very neglected patient group," says Fisher, principal investigator for a recent clinical trial of a molecule from Novartis for Sjögren's syndrome.

In the small early stage trial, the research team tested the molecule – called CFZ533 – in patients with severe primary Sjögren's syndrome. This molecule takes aim at the roots of Sjögren's rather than treating symptoms such as dry eyes, and follows a Novartis strategy of seeking to influence the underlying biology of disease. Patients were given one of two doses of the experimental drug. Those who took the higher dose on average showed a reduction of 5.6 points from a baseline mean of about 11 on a clinical score that summarizes the effects of the disease on the body as a whole.

The results were presented by Fisher on November 6 at the American College of Rheumatology Annual Meeting. The safety and efficacy of CFZ533 are yet to be confirmed in larger clinical trials.

"If this is repeated in a much larger study, we have potentially found a way to alter the effects of Sjögren's on patients," says Fisher, who is on the faculty of the University of Birmingham in the UK, and is a rheumatologist at Queen Elizabeth Hospital Birmingham, one of the trial's sites.

Opportunity meets preparation

Sjögren's syndrome affects an estimated 0.2-4% of the population worldwide.¹ In the US, approximately 2 to 4 million people have the disease, though only a million have been definitively diagnosed.²

Diagnosis is challenging because the disease can affect not only the eyes and mouth, but also a dozen other organ systems. Patients experience a range of symptoms, so they typically visit a range of specialists.

"[Patients] are scattered, going to the general practitioner, the rheumatologist, the dentist, even the neurologist," says Peter Gergely, a rheumatologist at the Novartis Institutes for BioMedical Research (NIBR) who led the team to design the trial. "These doctors don't always

recognize Sjögren's."

Even with a diagnosis, Sjögren's patients suffer because there are no approved therapies for the underlying causes of the disease. NIBR researchers recognized this unmet need, but they had to learn more to develop a drug discovery and development strategy, so they partnered with the few medical centers that specialize in treating Sjögren's. They talked to patients and launched a series of studies on tissue samples from them, which pointed to a role for a specific interaction between T-cells and B-cells of the immune system in driving the disease.

The NIBR team decided to attempt to stop Sjögren's where it starts by blocking this interaction. They also happened to have a compound, CFZ533, with the potential to interrupt the interaction.

"This was one of those lucky moments when two things came together: our understanding of Sjögren's and our compounds that target B-cells," says Guido Junge, who leads Sjögren's programs in Novartis Global Drug Development.

Testing an idea

The NIBR research suggested that blocking this interaction could potentially slow Sjögren's, but testing this hypothesis in people presented a challenge. "There had only been a few clinical trials before, none positive, so we had many question marks," says Gergely.

A key question was how to measure improvement in patients with such varied symptoms. The team chose a recently established measure called the EULAR Sjögren's syndrome disease activity index, or ESSDAI. The ESSDAI rolls up all of a patient's symptoms into one score reflecting the disease's influence on the body as a whole. If a compound slows the disease process, the score should drop as symptoms across the body abate.

Gergely and his team decided to enroll only severe Sjögren's patients with ESSDAI scores over 6 – high enough to detect a change. The medical community had agreed that a change of 3 points would be considered meaningful for Sjögren's patients. However, that bar had never been tested because no one had ever before used the ESSDAI score in a randomized clinical trial with positive results.

The NIBR team decided to set a goal for the compound to reduce scores by 5 points. In the trial, the scores of patients taking the higher dose of CFZ533 reduced by a mean of 5.6 from a baseline mean of about 11 compared to those taking a placebo. According to Fisher, score changes reflected improvements in swollen glands, night sweats, fevers, and swollen and painful joints. "These results are fascinating," he says.

In an interim analysis of data from this ongoing study, the side effects the investigators observed were mostly mild or moderate and were balanced across the CFZ533 and placebo groups. One case of conjunctivitis (pink eye) was deemed to be unrelated to the experimental drug. The trial enrolled 44 people, all of whom eventually received the drug.

With these results, the team is moving forward with additional clinical testing of CFZ533 and another compound that also targets B-cells. "We are understanding the processes that drive Sjögren's better and better," says Junge. "And we're looking at all of our compounds that could interrupt the disease process. The scientific and medical community is working to fill this

blank spot on the treatment map for patients with Sjögren's."

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Main image: B-cells normally produce antibodies to destroy invaders, but in Sjögren's syndrome, the antibodies attack healthy tissue. Image: Juan Gaertner/Shutterstock

1. Pierce JL et al; "Swallowing Disorders in Sjögren's Syndrome: Prevalence, Risk Factors, and Effects on Quality of Life." *Dysphagia*; V.31; No.1; 02/16; p49.
2. Kassan SS et al; "Clinical Manifestations and Early Diagnosis of Sjögren Syndrome." *Archives of Internal Medicine*; V.164; 6/28/04; p1275

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