

Clinical trial shows JAK inhibitor improves multiple autoimmune conditions in patients with Down syndrome

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Before



After



Acute results of clinical trial participant with alopecia areata after four months of treatment. Credit: Linda Crnic Institute for Down Syndrome Multi-organ autoimmunity and widespread autoantibody production in Down syndrome.

A [new study](#) published in *eLife* by researchers from the Linda Crnic Institute for Down Syndrome (Crnic Institute) at the University of Colorado Anschutz Medical Campus reports the initial results of a first-in-kind clinical trial testing the safety and efficacy of a JAK inhibitor to decrease the burden of autoimmune conditions in people with Down syndrome.

Drawing upon their [2016 discovery](#) that the interferon response is constantly activated in people with Down syndrome, the team designed the trial to focus on the autoimmune and inflammatory skin conditions that are very common in people with Down syndrome including [alopecia areata](#), psoriasis, atopic dermatitis, and hidradenitis suppurativa, and employed the JAK inhibitor tofacitinib (marketed as XELJANZ). The study also monitored effects on co-occurring [autoimmune conditions](#), such as autoimmune thyroid disease, celiac disease, and arthritis.

"Individuals with Down syndrome are at a high risk of developing autoimmune skin conditions, which are often hard to treat and cause significant discomfort and decrease their quality of life," explains Dr. Emily Gurnee, assistant professor of dermatology, one of the dermatologists involved in the study, and a principal investigator in the trial.

"Limited data exist to guide conversations about [treatment options](#) for skin conditions common to individuals with Down syndrome. The

findings from scientists at the Crnic Institute support the notion that JAK inhibitors are a valuable treatment not only for skin conditions but may benefit other autoimmune conditions prevalent in this population."

The study team observed important improvements in skin pathology, with the most striking results observed for those affected by alopecia areata, as well as improvements in arthritis and decreased biomarkers of autoimmune thyroid disease. Most study participants chose to remain on the medicine, often through off-label prescriptions, after completion of trial activities.

"Most importantly, we observed that major inflammatory markers elevated in Down syndrome that are known to cause autoimmunity were brought down to the normal range with this medicine, indicating that the immune system is being calmed down by this JAK inhibitor, while preserving strong immune function," explains Dr. Joaquín Espinosa, executive director of the Crnic Institute, professor of pharmacology, and one of the principal investigators in the clinical trial.

"More data will be needed to define the safety profile of JAK inhibitors in Down syndrome, and we look forward to the completion of the trial and analysis of the full dataset."

The study also reports the deepest characterization of the immune system dysregulation characteristic of Down syndrome to date through analysis of [clinical data](#) and biospecimens collected by the ongoing Human Trisome Project study.

The Crnic Institute team analyzed clinical data and blood samples to characterize the pattern of autoimmune conditions and accompanying inflammatory processes in hundreds of research participants in the Human Trisome Project using so-called multi-omics technologies. They observed that triplication of chromosome 21, or trisomy 21, the genetic

abnormality underlying Down syndrome, leads to rapid onset of diverse autoimmune conditions during childhood, along with increased levels of many inflammatory factors and strong dysregulation of multiple immune cell types.

"One key observation is that elevation of multiple inflammatory markers and dysregulation of all branches of the immune system occurs from a very early age, even before any clinical manifestations of autoimmunity," says Dr. Matthew Galbraith, assistant research professor of pharmacology, director of the Data Sciences Program of the Crnic Institute and co-author of the study. "This points to a constitutive state of immune dysregulation triggered by the extra chromosome that eventually leads to the appearance of multiple autoimmune conditions, with variations in timing and severity among individuals."

"Since 2016 we have been hypothesizing that the class of medicines known as JAK inhibitors will provide therapeutic benefits in this population," explains Dr. Angela Rachubinski, assistant research professor of pediatrics, director of the Clinical and Translational Sciences Program at the Crnic Institute, lead author of the paper, and one of the principal investigators in the trial.

"Although JAK inhibitors have been approved for a range of autoimmune and inflammatory conditions in the general population, this clinical trial, which started activities back in 2020, provides the first systematic investigation of the effects of a JAK inhibitor in people with Down syndrome."

The Crnic Institute study team is already overseeing a second trial testing the safety and efficacy of the JAK inhibitor relative to other medicines for treating the condition known as Down Syndrome Regression Disorder, and a third trial focused on children with Down syndrome is expected to start recruitment in late 2024.

"We are very grateful to the scientists and physicians at the Crnic Institute for their transformative research that is already translating into improved [medical care](#) and health outcomes for the amazing people with Down syndrome who we serve," says Michelle Sie Whitten, president & CEO of Global Down Syndrome Foundation, a partner and an affiliate organization of the Crnic Institute.

More information: Angela L Rachubinski et al, JAK inhibition decreases the autoimmune burden in Down syndrome, *eLife* (2024). [DOI: 10.7554/eLife.99323.1](https://doi.org/10.7554/eLife.99323.1)

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