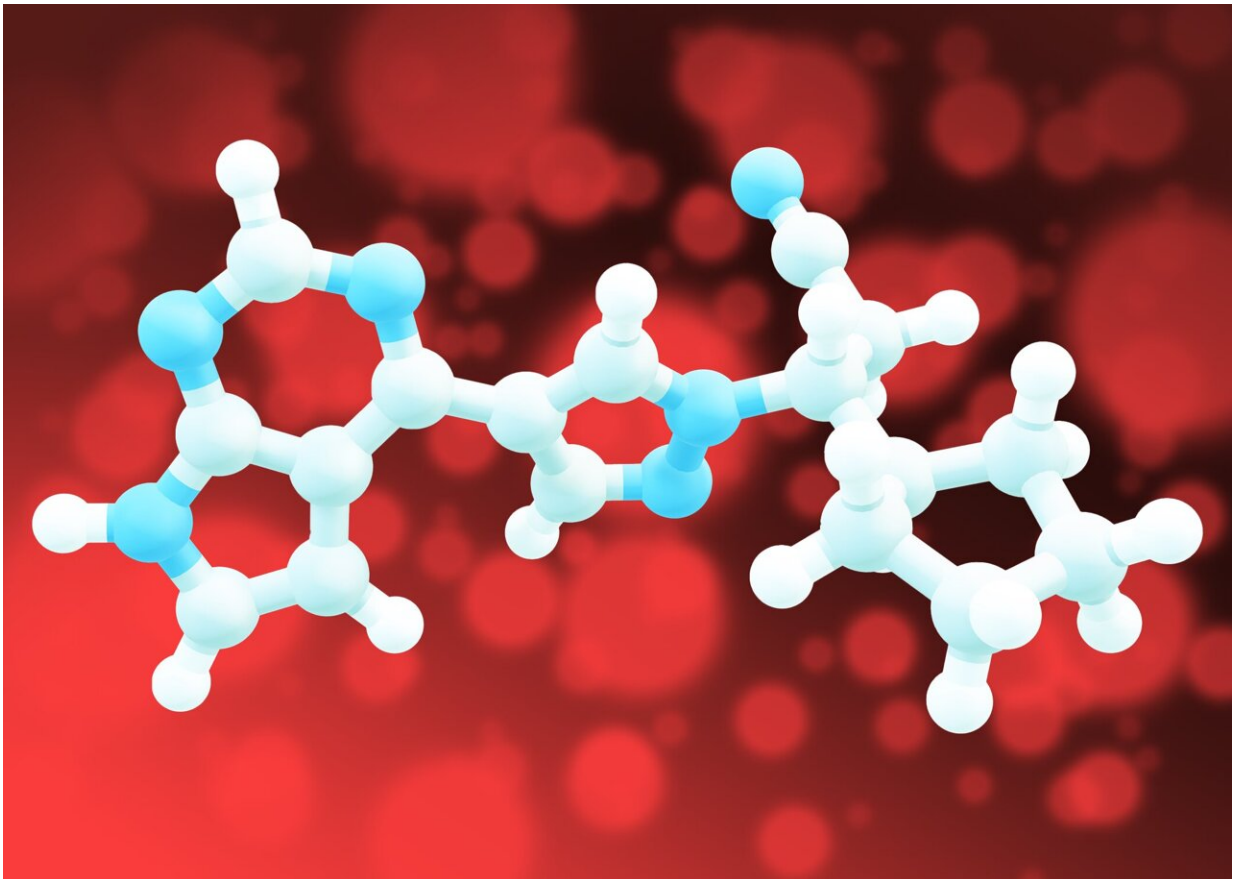


# Existing drug shows promise as treatment for rare genetic disorder

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3D model of the drug ruxolitinib. Credit: NIAID

A drug approved to treat certain autoimmune diseases and cancers successfully alleviated symptoms of a rare genetic syndrome called

autoimmune polyendocrine syndrome type 1 (APS-1). Researchers identified the treatment based on their discovery that the syndrome is linked to elevated levels of interferon-gamma (IFN-gamma), a protein involved in immune system responses, providing new insights into the role of IFN-gamma in autoimmunity.

The study, led by researchers at the National Institutes of Health's National Institute of Allergy and Infectious Diseases, was [published](#) in the *New England Journal of Medicine*.

In a three-stage study, conducted in mice and people, the researchers examined how APS-1 causes autoimmune disease. The syndrome is marked by dysfunction of multiple organs, usually beginning in childhood, and is fatal in more than 30% of cases.

This inherited syndrome is caused by a deficiency in a gene that keeps the immune system's T cells from attacking cells of the body, leading to autoimmunity; chronic yeast infections in the skin, nails, and [mucous membranes](#); and insufficient production of hormones from endocrine organs, such as the adrenal glands. Symptoms include stomach irritation, liver inflammation, lung irritation, hair loss, loss of skin coloring, [tissue damage](#), and organ failure.

In the first stage of this study, researchers led by scientists in NIAID's Laboratory of Clinical Immunology and Microbiology examined the natural history of APS-1 in 110 adults and children. Blood and tissues were analyzed to compare gene and protein expression in people with and without APS-1.

They found elevated IFN-gamma responses in the blood and tissues of people with APS-1, indicating that IFN-gamma may play an important role in the disease and providing a pathway to target for treatment.

In the second stage of the study, the scientists examined mice with the same gene deficiency that causes APS-1 in people, finding that the animals also experienced autoimmune tissue damage and elevated IFN-gamma levels. Mice also deficient in the gene for IFN-gamma did not have autoimmune tissue damage, which showed a direct link between IFN-gamma and APS-1 symptoms.

With this understanding, the researchers looked for a drug that could be used to lower IFN-gamma activity in people. They selected ruxolitinib, a Janus kinase inhibitor, because it acts by shutting down the pathway driven by IFN-gamma. When ruxolitinib was administered to the mice with the gene deficiency that causes APS-1, IFN-gamma responses were normalized and T cells were prevented from infiltrating tissues and damaging organs.

These results showed that ruxolitinib could alleviate effects of the gene deficiency, suggesting that it could be effective for treatment of APS-1 in people.

The researchers administered ruxolitinib, which was supplied by the NIH Clinical Center, to five people—two adults and three children—with APS-1 in the third stage of the study. The dosing and regimens were tailored to the individuals, and the treatments were continued for over a year. The drug was safe and tolerated well, and improvement in symptoms was seen in all study participants.

Blood and tissue analyses revealed decreased production of IFN-gamma from T cells, as well as normalized levels of IFN-gamma in the blood. Many APS-1-related symptoms were reduced, including [hair loss](#), oral yeast infections, stomach and bowel irritation, hives, and thyroid inflammation.

The results revealed that normalizing IFN-gamma levels using ruxolitinib

could reduce the damaging effects of APS-1 in people. The scientists note that a study with a larger and more diverse group of patients is needed to determine whether ruxolitinib and similar drugs are suitable treatments for individuals with APS-1.

They write that understanding the role of IFN-gamma in autoimmunity may lead to the development of treatments for related diseases. This research highlights the importance of finding the causes of and treatments for rare diseases.

APS-1 is also known as polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in the literature.

**More information:** Vasileios Oikonomou et al, The Role of Interferon- $\gamma$  in Autoimmune Polyendocrine Syndrome Type 1, *New England Journal of Medicine* (2024). [DOI: 10.1056/NEJMoa2312665](https://doi.org/10.1056/NEJMoa2312665)

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