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Efficacy of baricitinib in the treatment of chilblains associated with Aicardi-Goutières syndrome, a type I interferonopathy

Aicardi-Goutières syndrome (AGS) is a rare, juvenile-onset autoinflammatory disease characterized by basal ganglia calcification, chronic cerebrospinal fluid (CSF) lymphocytosis, and elevated type I interferon (IFN) levels in the CSF (1,2). Typical clinical manifestations include developmental delay, intellectual impairment, chilblains, panniculitis, glaucoma, and autoimmunity overlapping with systemic lupus erythematosus (SLE) (1,3).

AGS is classified as a monogenic type I interferonopathy with autoinflammation resulting from constitutive up-regulation of type I IFN signaling (3). IFN-stimulated genes (ISGs) are constantly overexpressed in peripheral blood cells from AGS patients, and measurement of ISGs in these cells is a useful marker for disease activity (4,5). At least 7 distinct gene mutations have been reported for AGS, including mutations in *SAMHD1* (1). *SAMHD1* loss-of-function mutations are associated with dysfunctional cytosolic dNTP metabolism and overproduction of type I IFNs (1).

JAK/STAT activation is present in various autoimmune diseases, and treatment with specific JAK inhibitors in immune-mediated diseases has been increasingly reported (6). Recently, the oral JAK1/2 inhibitor baricitinib was approved for the treatment of active rheumatoid arthritis and was also found to be effective in the treatment of a patient with a *STAT1* gain-of-function mutation (7). In this report, we describe an AGS patient treated with baricitinib and demonstrate its potential clinical applications for the treatment of type I interferonopathies.

The patient, a 22-year-old Caucasian woman with a consanguineous family history, was diagnosed as having AGS at age 19 years based on a homozygous nonsense mutation in exon 4 of *SAMHD1* (c.490C>T [p.Arg164Ter]). This mutation has been described previously in AGS (8). Her medical history included subclinical hypothyroidism, basal ganglia calcifications, and mild intellectual disability. The most prominent clinical feature was severe chilblains, which had been active over many years. Scaly and crusted ulcers from chilblains persisted on both hands and feet (Figure 1A). Inflammation and pain were typically exacerbated after cold exposure.

Baricitinib treatment was initiated at a daily dose of 2 mg/kg. At the start of baricitinib therapy, the patient experienced active chilblains of the hands and feet. After 6 weeks of treatment, the lesions completely resolved. To date, there has been no recurrence of chilblains after 18 months of treatment (Figure 1A). Lesions also did not reappear during winter, when the disease was usually more active. No occurrences of viral infections, opportunistic infections, or other complications were reported during treatment.

Peripheral blood samples were collected from the patient 4 weeks prior to the start of baricitinib therapy and after 2 and 6 weeks of treatment. Expression levels of 5 ISGs (*IFI44*, *IFI44L*, *IFIT3*, *LY6E*, and *MX1*) representing the gene signature for type I IFN activity (9) were measured in isolated CD14+ monocytes by quantitative reverse transcription–polymerase chain reaction and compared to the expression levels in 54 healthy controls. Prior to baricitinib therapy, monocytes from the patient displayed higher expression of all tested ISGs compared to healthy controls (Figure 1B). Expression of all 5 ISGs declined remarkably after initiation of baricitinib treatment (Figure 1B).

Furthermore, we measured total *STAT1* and phosphorylated *STAT1* in peripheral blood T lymphocytes by flow cytometry (7). Before and during treatment, T lymphocytes from the patient expressed higher levels of total *STAT1* than those observed in 2 age-, sex-, and race-matched healthy controls (Figure 1C). As shown in Figures 1D and E, T lymphocytes from the patient before and during baricitinib therapy displayed baseline levels of phosphorylated *STAT1* comparable to those in the healthy controls. However, T lymphocytes obtained from the patient before treatment displayed much higher levels of phosphorylated *STAT1* upon IFNα stimulation than healthy control T lymphocytes. The enhanced level of phosphorylated *STAT1* observed in patient T lymphocytes before baricitinib treatment was strongly reduced during treatment.

In summary, our findings suggest that baricitinib is a novel drug for the treatment of chilblains in AGS patients with a *SAMHD1* mutation and consequent up-regulation of type I IFN activity. The immunologic effects of JAK inhibitors depend on their selectivity and inhibitory capacity for the several JAK subtypes. Baricitinib displays a stronger inhibitory effect on cytokine-induced phosphorylated *STAT1* than ruxolitinib, which had been previously reported as successful in the treatment of STING-associated type I interferonopathy (6,10). Therefore, more in-depth research is warranted to evaluate baricitinib in the treatment of type I interferonopathies.

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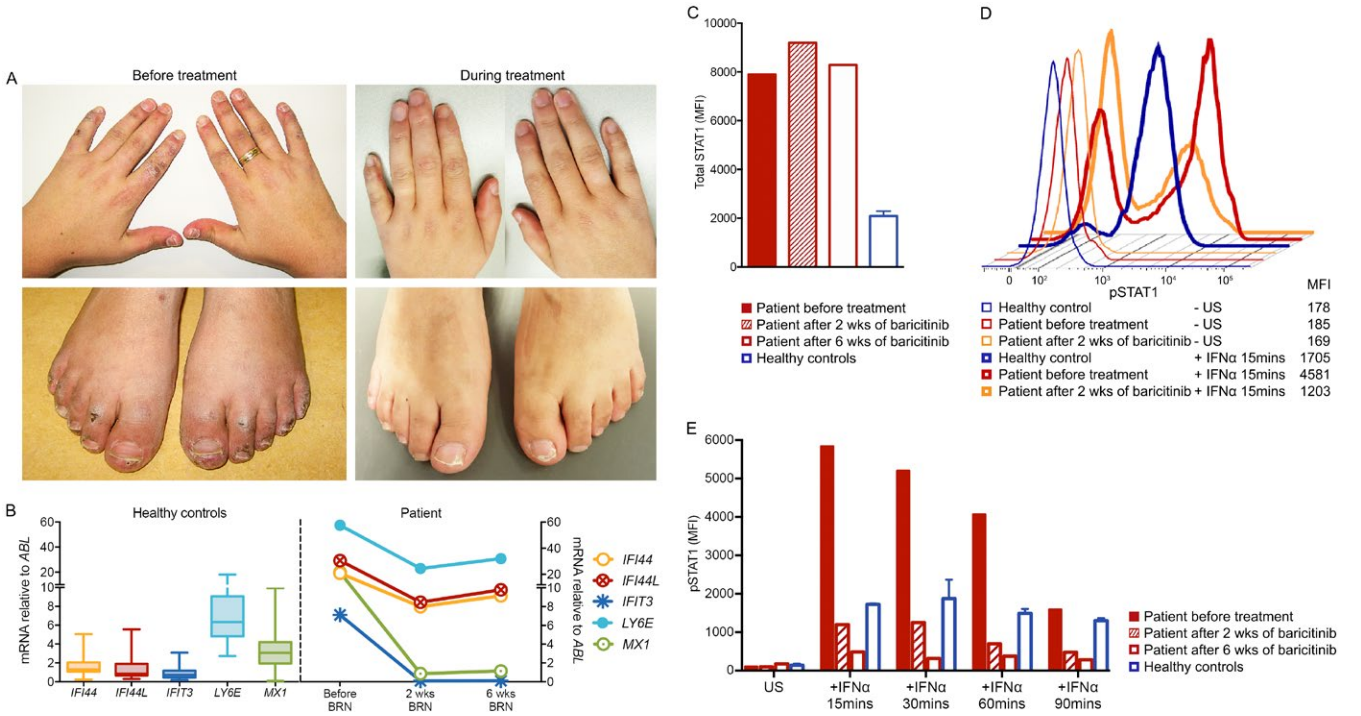

Figure 1. Clinical and immunologic response to baricitinib (BRN) treatment in a patient with Aicardi-Goutières syndrome (AGS). **A**, Dermatologic manifestations in the hands and feet before treatment (left), and clinical improvement during the fifth month of therapy (right). **B**, Expression of mRNA for interferon (IFN)–stimulated genes (ISGs) in monocytes from healthy controls (left) and from the patient before and during the treatment (right). Data were normalized to the housekeeping gene *ABL*. Data in the left panel are shown as box plots. Each box represents the 25th to 75th percentiles. Lines inside the boxes represent the median. Lines outside the boxes represent the 10th and 90th percentiles. **C**, Total *STAT1* levels in T lymphocytes from the patient and healthy controls. **D**, Phosphorylated *STAT1* levels in T lymphocytes upon IFNα induction. **E**, Kinetics of phosphorylated *STAT1* levels in T lymphocytes upon stimulation with IFNα for the indicated time periods. Values in **C** and **E** are the mean ± SEM. MFI = mean fluorescence intensity; US = unstimulated.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Meesilpavikkai had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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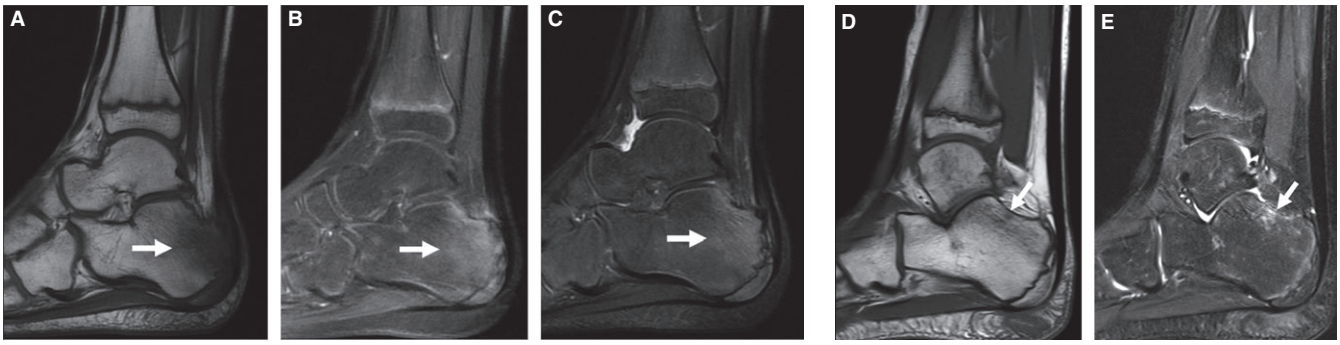
Clinical Images: Heel pain in a young patient—calcaneal involvement in juvenile spondyloarthritis



The patient, an 11-year-old boy, presented with left heel pain and mild fever. He had recently experienced diffuse arthralgias of the right knee, costochondral junctions, and both ankles. Laboratory findings were normal except for a slightly increased erythrocyte sedimentation rate. Magnetic resonance imaging (MRI) of the left heel was performed. On T1-weighted and fat-suppressed T2-weighted MRI sequences, bone marrow edema with indistinct margins was seen at the posterior margin of the calcaneus, above the growth plate, and below its posterior and superior cortex (**A** and **B**) (**arrows**). The shape of the apophysis was preserved. Enhancement was seen in the area of the bone marrow edema after gadolinium injection (**C**) (**arrow**), and the calcaneal bursa was also enhanced. This pattern of marrow changes differed from the thin high-signal-intensity strip normally seen along the growth plate at this age and from the normal variant of scattered patchy areas sometimes present in the posterior calcaneus (**D** and **E**) (**arrows**) (1). Sever's disease was ruled out as it mainly affects the secondary ossification center. Spondyloarthritis was diagnosed based on the calcaneal bone marrow edema and the involvement of the adjacent soft tissues below the Achilles tendon in a clinical context of diffuse arthralgias. This case illustrates calcaneal involvement in juvenile spondyloarthritis, which consisted of bone marrow edema and gadolinium enhancement involving the superior area of the posterior calcaneus above the secondary ossification center as well as the calcaneal bursa. Interestingly, in this patient, bone marrow changes predominated in the superior part of the posterior calcaneus at the level of the periosteal fibrocartilage located above the secondary ossification center and the Achilles enthesis (2).

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