RHEUMATOLOGY

# Letter to the Editor (Case report)

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## Efficacy of baricitinib on chronic pericardial effusion in a patient with Aicardi–Goutières syndrome

**Rheumatology key message**

- Baricitinib administration was highly effective for treating pericardial effusion in a patient with Aicardi–Goutières syndrome.

Dear Editor, Aicardi–Goutières syndrome (AGS) was initially described as an early-onset progressive encephalopathy with severe neurological symptoms, acquired microcephaly, basal ganglia calcification, leukoencephalopathy, cerebral atrophy and chronic cerebrospinal fluid (CSF) pleocytosis [1]. Subsequently, autoinflammatory systemic manifestations (e.g. recurrent sterile fevers, chilblain-like lesions, hepatitis) and elevated CSF IFN-α activity were also reported [1].

Nine genes that encode proteins involved in nucleotide metabolism and/or sensing (*TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR1*, *IFIH1, LSM11* and *RNU7-1*) have been associated to AGS [2]. Mutations in these genes result in constitutive induction of type I IFN and upregulation of IFN-stimulated genes (ISGs) [3]. The IFN signature (IS) measures the expression of ISG in peripheral blood and is a useful marker for disease activity [3].

Janus kinase (JAK) inhibitors may be effective in blocking IFN activation in patients with AGS [4, 5]. In one patient with AGS and an *IFIH1* mutation, an open-label trial of ruxolitinib, a JAK 1/2 blocker, resulted in substantial developmental gains against a background of previous regression, combined with a decrease in IS [4]. An open-label trial of baricitinib, another JAK 1/2 blocker, in 35 patients with genetically confirmed AGS (including 8 patients with *IFIH1* mutations), showed overall clinical improvement (including a likely improvement in neurologic function) and a decrease in IS [5]. In this report we describe an AGS patient with *IFIH1* mutation treated with baricitinib and show new potential clinical benefits.

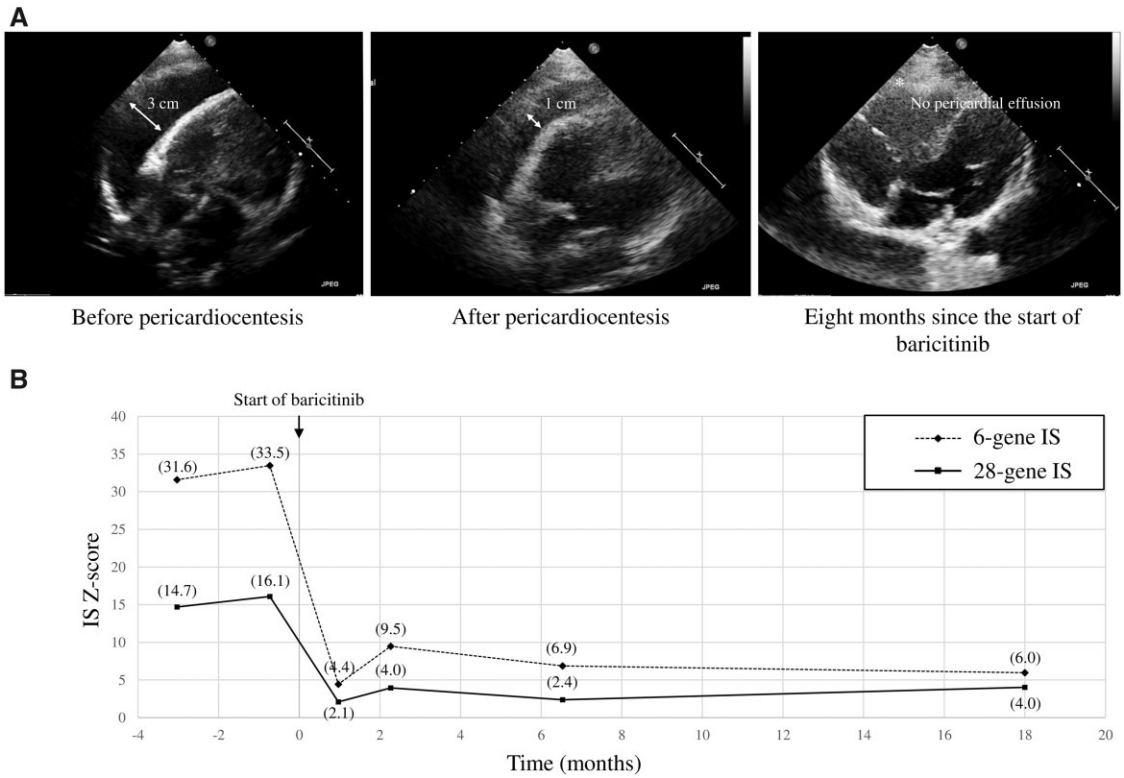
The patient was the only child of healthy non-consanguineous parents, born after an uneventful pregnancy and delivery. The child had normal development until 12 months, when he presented with neurological regression leading to spastic-dystonic tetraparesis that required intrathecal baclofen, intellectual disability and progressive microcephaly. Neuroimaging showed bilateral calcifications in the basal ganglia, subcortical white matter and cerebellar folia. Over the course of the disease he developed recurrent episodes of fever, sometimes associated with an isolated and self-limited blister-like ear lesion. He also developed chronic hypertension and chronic pericardial effusion refractory to standard treatment with aspirin, ibuprofen and colchicine. A *de novo* heterozygous missense mutation in the *IFIH1* gene (NM_022168, c.1009C>G, p.Arg337Gly) that has previously been reported as a pathogenic variant was identified [3].

At 16 years of age, the neurological symptoms were stable, although the patient experienced daily low-grade fever and chronic hypertension requiring treatment with enalapril and carvedilol. Despite receiving steroids, the echocardiography showed an anterior echo-free space of 30 mm (Fig. 1A). Pericardiocentesis was performed that reduced the anterior echo-free space to 10 mm (Fig. 1A).

With the aim of treating the comorbidities associated with the systemic inflammatory manifestations, we prescribed baricitinib under a compassionate use protocol after obtaining informed consent from the parents. Oral baricitinib was initiated at 2 mg twice a day. After the first week of therapy the patient remained afebrile and enalapril was discontinued <1 month later due to normalization of arterial tension. The pericardial effusion decreased significantly until it resolved completely (Fig. 1A). The carvedilol has also been discontinued and the improvements in systemic manifestations have been maintained 18 months after treatment initiation. No neurological changes were seen and no adverse effects have occurred to date.

Peripheral blood samples were collected using PAXgene Blood RNA Tubes (Qiagen, Venlo, The Netherlands) before starting baricitinib therapy and after 1, 2, 6 and 18 months of treatment (Fig. 1B). Total RNA was extracted using the PAXgene Blood RNA Kit (Qiagen). RNA samples were quantified using Qubit 2.0 Fluorometer (Life Technologies, Carlsbad, CA, USA) and RNA integrity was checked with a 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). Expression levels of 28 ISGs (*CXCL10*, *DDX60*, *EPSTI1*, *BGP1*, *HERC5*, *HERC6*, *IFI27*, *IFI44*, *IFI44L*, *IFI6*, *IFIT1*, *IFIT2*, *IFIT3*, *IFIT5*, *ISG15*, *LAMP3*, *LY6E*, *MX1*, *OAS1*, *OAS2*, *OAS3*, *OASL*, *RSAD2*, *RTP4*, *SIGLEC1*, *SOCS1*, *SPATS2L* and *USP18*) and 4 housekeeping genes (*ALAS1*, *HPRT1*, *TBP* and *TUBB*) were measured using the nCounter Digital Analyzer (NanoString, Seattle, WA, USA) [6]. The type I IS was calculated using the median of the Z scores [7] of the six genes mainly involved in AGS previously reported

Fig. 1 Echocardiograms and IFN signature before and after baricitinib treatment




(**A**) Echocardiograms showing the evolution of pericardial effusion before pericardiocentesis, after pericardiocentesis and after 8 months of treatment with baricitinib. (**B**) IS before starting baricitinib therapy and after 1, 2, 6 and 18 months of treatment.

by Rice *et al.* [3] and the median of the Z scores [7] of the 28 genes described by Kim *et al.* [6]; both were considered positive if >1.96 (S.D. 2) [7]. Expression of all ISs was highly elevated and declined markedly after initiation of baricitinib (Fig. 1B).

In conclusion, baricitinib administration in a patient with AGS and an *IFIH1* mutation was well tolerated and had a beneficial effect on several inflammation-mediated comorbidities, including pericardial effusion. Further studies in large series of patients are needed to confirm these findings. It would be particularly interesting to investigate whether early treatment with JAK inhibitors in patients with AGS could modify neurological outcomes. The IS was a useful marker for disease activity and a decrease in IS correlated with clinical response to treatment.

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## Data availability statement

The data that support this article are available from the corresponding author upon reasonable request.

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