# Ruxolitinib in Aicardi-Goutières Syndrome

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**Short Report**

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# Abstract

Aicardi Goutières Syndrome (AGS) is a monogenic leukodystrophy with pediatric onset, clinically characterized by a variable degree of neurologic impairment. It belongs to a group of condition called type I interferonopathies that are characterized by abnormal overproduction of interferon alpha, an inflammatory cytokine which action is mediated by the activation of 2 of the four human Janus Kinases. Thanks to an ever-increasing knowledge of the molecular basis and pathogenetic mechanisms of the disease, Janus Kinase inhibitors (JAKIs) have been proposed as a treatment for interferonopathies. We described the 24 months follow-up of the fifth AGS patient treated with ruxolitinib. Treatment was globally well tolerated; clinical and radiological picture demonstrated a progressively improving course. It is however to note that patients presenting mild and spontaneously improving picture have been reported. Large natural history studies on AGS spectrum are urgently needed in order to help the interpretation of the results of therapeutic trials.


# Introduction

Aicardi-Goutières Syndrome (AGS) is a monogenic leukodystrophy with pediatric onset, clinically characterized by a variable degree of neurologic impairment (Adang et al. 2020a). It is due to mutations in genes involved in the intracellular nucleic acid sensing machinery (*TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, IFIH1, LSM11* or *RNU7-1*) that result in an abnormal overproduction of interferon alpha (IFN alpha), a mechanism shared by a group of condition now called type I interferonopathies (Livingston and Crow 2016; Uggenti et al. 2020). IFN alpha is an inflammatory cytokine which action is mediated by the activation of 2 of the four human Janus Kinases (JAK): JAK1 and TYK2 (Fragoulis et al. 2019; Melki and Frémond 2020). Thanks to an ever-increasing knowledge of the molecular basis and pathogenetic mechanisms of the disease, Janus Kinase inhibitors (JAKIs) have been proposed as a treatment for interferonopathies (Fragoulis et al. 2019; Tonduti et al. 2020). Specifically considering AGS, promising results from a clinical trial investigating efficacy of baricitinib, a JAK1 and JAK2 inhibitor, have been recently published (Vanderver et al. 2020), as also the favorable outcome of 3 patients treated by ruxolitinib which is a JAK1, JAK2 and TYK2 inhibitor (Kothur et al. 2018; Tüngler et al. 2016). 2 out of them (both *RNASEH2B*-mutated AGS) were treated with dosage of 0.25 mg/kg increased to 0.5 mg/kg over a week (Tüngler et al. 2016) while the third (*IFIH1*- mutated AGS) took 2.5 mg twice daily from 16 months of age, increased to 5 mg twice daily 6 weeks later (Kothur et al. 2018). A fourth child carrying biallelic *RNASEH2B* mutations treated before symptoms onset with ruxolitinib has been recently described. In this case the dose of 1 mg/kg/day didn't prevent disease onset at 15 months of age but twice period of 3 days of treatment discontinuation at 14 months are reported (Neven et al. 2020).

# Patient And Methods

We recently admitted to our Center for Leukodystrophies (C.O.A.L.A.) a boy aged 12 months because, concomitantly to an intercurrent infection of upper airways, he presented with irritability, sleep

disturbances, followed by language regression (loss of babbling), loss of postural control, axial hypotonia, extrapyramidal signs (facial grimacing, persistent neonatal reflexes, fluctuating tone, exaggerated startle reactions), microcephaly (42 cm, < 3° percentile). Lumbar puncture revealed slight lymphocytosis (17 cells/$mm^3$), CSF interferon-alpha was normal, MRI showed diffuse brain atrophy associated with T2 hyperintensity of frontal white matter, more evident in anterior regions (Fig. 1), without detectable calcification on CT scan. On the suspicion of Aicardi-Goutières Syndrome, Interferon Score (Rice et al. 2017) was tested and resulted positive (6.862). Genetic analysis finally confirmed the diagnosis revealing double compound heterozygous mutations on *RNASEH2B*: c.253C > G inherited from the Italian father and c.65-13G > A from the Indian mother.

Based on data from literature (Kothur et al. 2018; Tüngler et al. 2016; Vanderver et al. 2020) we decided to start JAK inhibitor. Between baricitinib and ruxolitinib we preferred the latter because of its effect on both Janus Kinases activated by interferon alpha (JAK1 and TYK2) (Fragoulis et al. 2019) and because of its proven capacity to cross blood brain barrier (Kothur et al. 2018). It was started at 18 months of age at a dosage of 0.8 mg/kg divided in 2 daily doses. Monthly IVIG (1 mg/kg) was associated since the boy had not received chickenpox vaccination. At that time startle reactions and irritability were already improved, sleep disturbances were partially attenuated by niaprazine. Neurological examination was unchanged. Lumbar puncture confirmed lymphocytosis (64 cells/$mm^3$), interferon-alpha was not tested.

# Results

During the 24 months follow-up we observed a progressive reduction of extrapyramidal signs and the neurological picture finally stabilized to spastic diplegia. Improvement on neuromotor and language skills was also observed. At 24 months of age, he regained head control and he acquired the ability to pronounce single words. At 31 months he was able to stand and maintain sitting position with support and at 43 months he sat without support, he pronounced 2–3 words sentences. Startle reactions, irritability and sleep disturbances progressively disappeared, niaprazine was stopped at 40 months of age. Control MRI, performed at the time of treatment initiation, revealed a spontaneous reduction of T2 white matter hyperintensity with no longer signs of brain atrophy; it was repeated at 31 and 43 months showing progressive normalization of the neuroradiological picture (Fig. 1) without appearance of cerebral calcification even on last CT performed at 31 months of age. Electroencephalographic registration (EEG) revealed a progressive reduction of diffuse centro-occipital delta waves initially evidenced.

Progressive clinical improvement was confirmed on standardized evaluation including Griffiths-III neurodevelopmental scale (Green et al. 2020), Gross Motor Function Measure 88 (Palisano et al. 2000), Functional Classification System Scales (EDACS, CFCS, MACS, GMFCS) (Paulson and Vargus-Adams 2017) and AGS severity score (Adang et al. 2020b) (Fig. 2).

Knowing that AGS usually behaves as a biphasic disease with an initially active phase followed by a chronic stable one which can lead to a misdiagnose of cerebral palsy (Galli et al. 2018), we compared the

clinical evolution of our patient to the one expected in children at the same GMFCS initial level. Figure 2c shows that during follow up the GMFM-88 score improved more than expected from children starting from the same GMFCS disability level.

Disease available biomarkers were in line with clinical findings showing progressive normalization: Interferon Score resulted negative starting from 1 month after ruxolitinib initiation. Lumbar puncture was repeated at 12 months from treatment start, IFN alpha and CSF cell count were both normal.

Ruxolitinib was well tolerated, only slight serum CPK fluctuations (max 356 U/l) were detected as also slight hypercholesterolemia (max 252 mg/dl) and hypertriglyceridemia (max 153 mg/dl), both rapidly controlled by dietary management.

Considering the positive response to treatment and recent suggestions about possible neurological regression soon after JAK inhibitors discontinuation, the patient is still on treatment.

## Conclusions

We described the 24 months follow-up of the fifth AGS patient treated with ruxolitinib at a dosage of 0.8 mg/kg/day. Treatment was globally well tolerated; while positive effect of JAKIs on systemic symptoms of AGS seems to be clear, the demonstration of neurological improvement is more complex (Vanderver et al. 2020). In our case, clinical and radiological picture demonstrated a progressively improving course, it is however to note that patients presenting mild and spontaneously improving picture have been reported (Tonduti et al. 2019). Large natural history studies on AGS spectrum are urgently needed in order to help the interpretation of the results of therapeutic trials.

## Declarations


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the authors have no conflicts of interest to declare that are relevant to the content of this article.

# Availability of data and material (data transparency):

all data generated or analyzed during this study are included in this published article

# Code availability (software application or custom code):

not applicable

# Author's Contribution:

EM, SM: study concept and design, neurological data collection and analysis, manuscript preparation; CA: functional scale application, manuscript revision; CP, GI: neuroimaging evaluation, manuscript revision; JG, DS, CC: genetic and interferon signature analysis, manuscript revision; SO, PV, GZ: study concept and design, manuscript revision; DD, FP: general pediatric follow-up and data collection, manuscript preparation; DT: study concept and design, neurological data collection and analysis, manuscript revision.

All authors read and approved the final manuscript.

# Ethics approval (include appropriate approvals or waivers):

all procedures were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

# Consent to participate (include appropriate statements):

informed consent was obtained from the parents of the patient described in this study.

# Consent for publication (include appropriate statements):

not applicable. Information is anonymized and the submission does not include images that may identify the person.

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# Figures

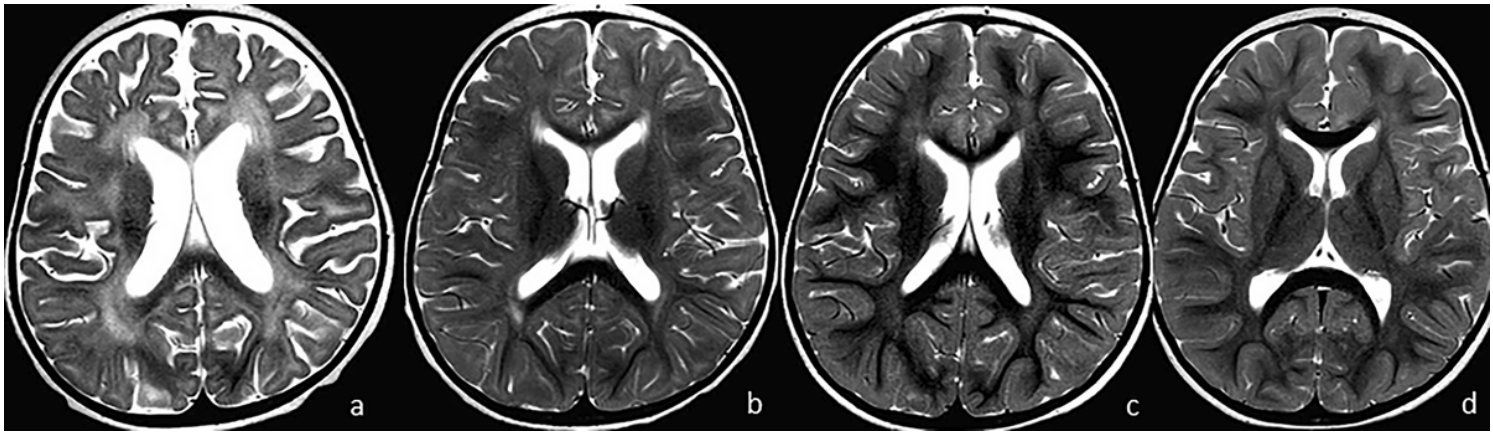


**Figure 1**

T2-weighted axial images at 12 (a), 18 (b), 31 (c) and 43 (d) months. In (a), a bilateral signal hyperintensity with a patchy appearance of fronto-central white matter is evident; also note a moderate atrophy of sovratentorial brain parenchima, with diffuse enlargement of liquoral spaces and lateral ventricles. The MRI control before starting treatment (b) already shows a spontaneous improvement of signal alterations, exclusively persisting along the periventricular white matter; a concomitant brain atrophy reduction is present. The following two controls performed during follow-up (c, d) demonstrates a further reduction of periventricular signal alterations, just faintly appreciable in the frontal regions. Brain trophism is substancially normal

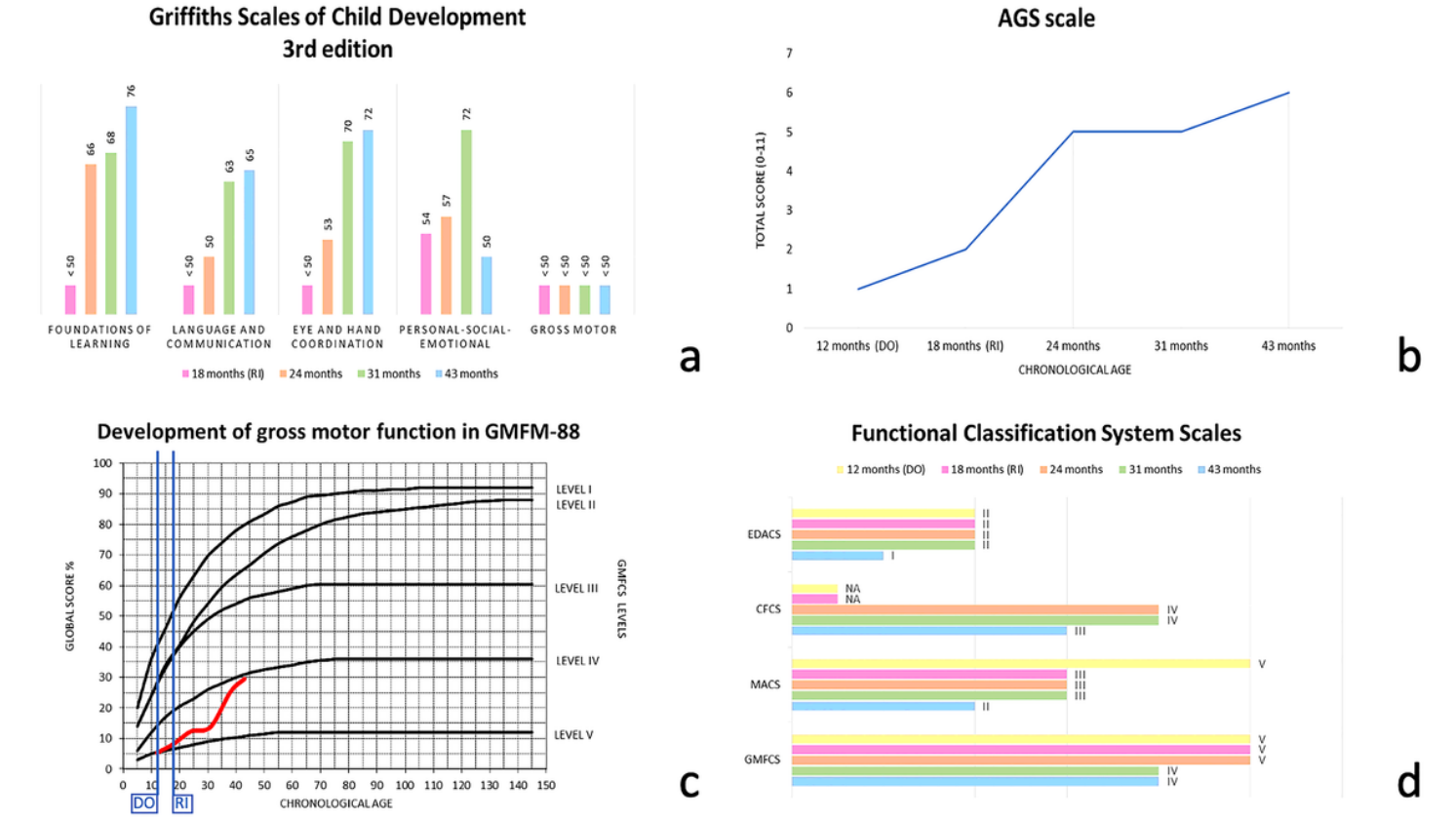


**Figure 2**

Result of functional assessment. a) Griffiths-III Developmental Subquotients. Scores showed improvements on learning (subscale A), language and communication (subscale B), eye and hand coordination (subscale C). Scores in personal, social and emotional development (subscale D) revealed an initial improvement followed by a collapse which was likely related to the growing incidence of motor abilities on the final score of this subscale. No significant improvement on the gross motor scores for Griffiths Developmental scale. b) AGS severity scores progressively improved during treatment. c) Gross Motor Function Measure (GMFM-88) was more sensible than Griffiths scale in showing progressive improvement in gross motor function. During treatment results made the boy change level in the Gross Motor Function Classification System (GMFCS) from Level V to IV. d) Functional performance of our patient described by the Functional Classification System Scales, where lower scores correspond to a better clinical condition: in our patient all scales revealed a progressive improvement, at the last evaluation (43 months) the patient was able to eat and drink independently in a safe and efficient way (EDACS, Level I), improved in manual dexterity (MACS, Level II), was able to sit, to crawl on his stomach (GMFCS, Level IV) and to communicate effectively with known partners (CFCS, Level III – note that this scale is not applicable (NA) under 24 months). Abbreviations: NA, Not Applicable; DO, Disease Onset; RI, Ruxolitinib Initiation