Ruxolitinib in Aicardi-Goutières syndrome

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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 two 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 option for selected interferonopathies. Here we reported the 24 months follow-up of the fifth AGS patient treated with ruxolitinib described so far in literature. The treatment was globally well tolerated; clinical examinations and radiological images demonstrated a progressively improving course. It is however to note that patients presenting with mild and spontaneously improving course have been reported. Large natural history studies on AGS spectrum are strongly required in order to get a better understanding of the results emerging from ongoing therapeutic trials on such rare disease.

Keywords Aicardi-Goutières syndrome · Leukodystrophy · Interferonopathy · Treatment · Janus Kinase inhibitor · Ruxolitinib

Introduction

Aicardi-Goutières Syndrome (AGS) is a monogenic leukodystrophy with pediatric onset, clinically characterized by a variable degree of neurologic impairment (Adang et al. 2020). 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), which result in an abnormal overproduction of interferon alpha (IFN alpha), a mechanism shared by a group of condition currently 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 two of the four human Janus Kinases (JAK): JAK1 and TYK2 (Melki and Frémond 2020; Fragoulis et al. 2019). 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 option for selected interferonopathies (Fragoulis et al. 2019; Tonduti et al. 2020). Specifically considering AGS, promising results from a clinical trial investigating the efficacy of baricitinib, a JAK1 and JAK2 inhibitor, have been recently...
reported (Vanderver et al. 2020). Similarly, favorable outcomes were observed in three patients treated by ruxolitinib, which is a JAK1, JAK2 and TYK2 inhibitor (Tüngler et al. 2016; Kothur et al. 2018). More in detail, two 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). Recently, a fourth case of a child carrying biallelic RNASEH2B mutations treated before symptoms onset with ruxolitinib has been described. In this case, the dose of 1 mg/kg/day was not able to prevent the onset of a clinically-evident disease at 15 months of age, even though two periods of 3 days of treatment discontinuation at 14 months were reported (Neven et al. 2020). Here we reported the clinical course of the fifth AGS patient treated with ruxolitinib described so far in literature.

**Patient and methods**

A 12-months patient who presented neurological symptoms concomitantly to an intercurrent infection of upper airways was admitted to the tertiary-care referral Center for Leukodystrophies (C.O.A.L.A.). 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/mm³), while cerebrospinal fluid (CSF) interferon-alpha level was normal. The 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. In the suspect 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) a JAK inhibitor therapy was started. Considering the reports on baricitinib and ruxolitinib, we selected ruxolitinib because of its effect on both Janus Kinases activated by interferon alpha (JAK1 and TYK2) (Fragoulis et al. 2019) and its proven capacity to cross the blood brain barrier (Kothur et al. 2018). The treatment was started at 18 months of age at a dosage of 0.8 mg/kg divided in two daily doses. Monthly intravenous immunoglobulin (IVIG, 1 mg/kg) was administered since the boy had not received chickenpox vaccination. At baseline of treatment, startle reactions and irritability were already improved, sleep disturbances were partially attenuated by niaprazine, while neurological examination was unchanged compared to the onset of the disease. Lumbar puncture confirmed lymphocytosis (64 cells/mm³), interferon-alpha was not tested. During treatment, the patient was evaluated every month for clinical assessment and control blood tests. Standardized functional evaluations were administered every 6 months during the first year of treatment, then every 12 months; particularly Griffiths-III neurodevelopmental scale (Green et al. 2020), Gross Motor Function Measure 88 (GMFM-88) (Palisano et al. 2000), Functional Classification System Scales (EDACS, CFCS, MACS, GMFCS) (Paulson and Vargus-Adams 2017) and AGS severity score were assessed (Adang et al. 2020). Brain MRI was repeated at 12 and 24 months after treatment initiation.

**Fig. 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 supratentorial brain parenchima, with diffuse enlargement of CSF 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 (white arrows); 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 (white arrows). Brain trophism is substantially normal.
Results and discussion

During the 24 months of follow-up, we observed a progressive reduction of extrapyramidal signs and a stabilization of pyramidal signs in a spastic diplegia. Improvements on neuromotor and language skills were also noticed. At 31 months of age, the patient regained head control and he acquired the ability to pronounce single words. At 31 months of age, he was able to stand and maintain sitting position with support while at 43 months he sat without support, he pronounced 2–3 words sentences. Startle reactions, irritability and sleep disturbances progressively disappeared so that 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 then repeated at 31 and 43 months showing progressive normalization of neuroradiological parameters (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, which were initially evidenced.

Progressive clinical improvements were confirmed on standardized evaluations (Fig. 2). Griffiths-III Developmental Scale 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 improvements on the gross motor scores were observed by Griffiths Developmental Scale, while the GMFM-88 seemed to be more sensitive in showing progressive improvement of the gross motor function. Such improvement obtained during treatment allowed to upgrade the level in the Gross Motor Function Classification System (GMFCS) from V to IV. The functional performances of the patient were assessed using the Functional Classification System Scales, where lower scores correspond to a better clinical condition. In details, 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), he improved in manual dexterity (MACS, Level II), he was able to sit, to crawl on his stomach (GMFCS, Level IV) and to

Fig. 2 Result of functional scales; assessments were done at 12 months of age, time of disease onset, 18 months of age, time of ruxolitinib initiation, and at 6, 13 and 25 months from ruxolitinib initiation (respectively 24, 31 and 43 months of age). a Griffiths-III Developmental Scale. b AGS severity scores. c Gross Motor Function Measure (GMFM-88). d Classification according with Functional Classification System Scales: EDACS (Eating and Drinking Classification System), MACS (Manual Ability Classification System), GMFCS (Gross Motor Function Classification System), CFCS (Communication Function Classification System). Note that CFCS is not applicable (NA) under 24 months. Abbreviations: NA, Not Applicable; DO, Disease Onset; RI, Ruxolitinib Initiation
communicate effectively with known partners (CFCS, Level III – note that this scale is not applicable under 24 months of age). AGS severity score also progressively improved during the treatment. Taking into account the usual AGS biphasic disease course, with an initially active phase followed by a chronic stable one, which can lead to a misdiagnosis of cerebral palsy (Galli et al. 2018), we compared the clinical evolution of our patient to that expected in children at the same GMFCS initial level. Figure 2c shows that, during the follow-up, the GMFM-88 score improved more than what was expected from children starting from the same GMFCS disability level.

The currently available disease biomarkers were in line with clinical findings, showing progressive normalization during the follow-up: Interferon Score resulted negative starting from 1 month after ruxolitinib initiation; IFN alpha and CSF cell count were both normal on the lumbar puncture performed 12 months after the treatment start. Ruxolitinib was well tolerated, only slight serum CPK fluctuations (max 356 U/l) were detected as well as slight hypercholesterolemia (max 252 mg/dl) and hypertriglyceridemia (max 153 mg/dl), both rapidly controlled by dietary management.

At present, considering the positive response to treatment and recent evidences about possible neurological regression soon after JAK inhibitors discontinuation, the patient is still on treatment.

Conclusions

The results emerging after 24 months of treatment with ruxolitinib at a dosage of 0.8 mg/kg/day in a child affected by AGS are encouraging. The treatment was globally well tolerated; although the 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, progressive improvements both on clinical and neuroradiological viewpoint were obtained. However, it is to note that patients presenting with mild and spontaneously improving course have been reported in literature (Tonduti et al. 2019), even if it seems uncommon compared to the typical neuroradiological evolution described in the majority of AGS cases (Uggetti et al. 2009; La Piana et al. 2016). Large natural history studies on AGS spectrum are urgently needed in order to help the interpretation of the results of therapeutic trials.

Author contributions 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; 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.

Data availability All data generated or analyzed during this study are included in this published article.

Code availability Not applicable.

Declarations

Conflicts of interest/Competing interests The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval All procedures were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from the parents of the patient described in this study.

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

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