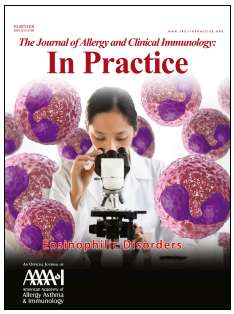

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Baricitinib treatment in children with COPA syndrome

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Clinical Implications box:

Baricitinib seems safe and effective in reducing the articular flares, controlling the systemic inflammation and lung disease progression of COPA patients. The drug dosage should be adjusted according to patient's age and weight in order to prevent disease flares.

Keywords: COPA syndrome, baricitinib, jak inhibitors, type I interferon

COPA syndrome is a rare inborn error of immunity, characterised by features of autoinflammation, immune dysregulation and autoimmunity. The disease has an onset in early childhood and is characterised by pulmonary manifestations (diffuse alveolar haemorrhages and interstitial lung disease) associated with destructive polyarthritis, and glomerular disease[1]. Almost 80% of patients present positive antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies, high levels of Rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA). The disease is transmitted in an autosomal dominant pattern with incomplete penetrance, with asymptomatic carriers described.

COPA syndrome is caused by heterozygous mutations of the *COPA* gene, which encodes for the COatomer Protein subunit alpha (COPα), a subunit of the coatomer complex-I involved in the transportation from the Golgi to the endoplasmic reticulum[1].

An enhanced activation of the type 1 interferon pathway in COPA syndrome has been described[2].

Up to now, no therapeutic guidelines exist for the treatment of COPA syndrome. Janus kinases inhibitors (JAKi) have been reported to be efficacious in few COPA cases[3,4].

Herein, we present the medium and long term follow up (12-48 months) of 3 COPA cases treated with the JAKi baricitinib.

Case presentation (see Table 1): All patients were females and had a disease onset before 3 years of age. P1 was Caucasian and carried the p.Arg233His mutation[2], while the 2 other unrelated patients (P2 and P3) were of African ancestry and carried the p.Arg281Trp mutation. P1 and P2 mothers' were asymptomatic carriers, while P2 has an elder brother and a sister affected. P3's father carries the same mutation and is diagnosed with end stage renal disease.

All patients presented an early onset polyarthritis (deforming in P1 and P2), and with a pulmonary involvement, characterized by an interstitial lung disease and by multiple pulmonary cysts on CT scan. P1 and P3 also presented ground glass opacities and bronchiectasias, while no pulmonary haemorrhages were reported. P3 presented bilateral renal dysplasia with hypoplasic kidneys and small cysts bilaterally. No kidney disease was present in the two other patients. Due to the young age, spirometry was performed at disease onset only in P1, showing a severe reduction of the forced vital capacity (FVC 70%) and of the DLCO (57%), and the 6-minute walking test (6MWT) resulted pathologic with a minimal SaO2 of 85%.

In all patients, a peripheral blood six-genes-based type I IFN signature was assessed (as previously reported with minor modifications[2]), at disease onset and at different timepoints of the disease. All the patients presented a positive type I IFN signature and were ANA and RF positive. P1 and P3 had also positive anti-citrullinated peptide antibodies.

Before baricitinib was started, P1- who had a disease onset seven years before COPA was described- underwent several immunosuppressive therapies (Table 1), as did P2 for one year before the diagnosis was made, while P3 was started on baricitinib at disease onset. All patients were started on baricitinib 2 mg twice a day. After the beginning of the therapy, a reduction of the inflammatory biomarkers was evident in all patients, and corticosteroids could be stopped in P1 and P2 (never used in P3). In P1 a marked improvement of the 6MWT was achieved (minimal SaO2 96%), while CT scan and spirometry showed no disease progression over the years (DLCO increased to 84%), and no intraarticular injections were needed for 36 months (before the start of baricitinib, 1-2 intra-articular injections/year). However, after a SARS-CoV-2 infection, P1 presented a monoarticular disease relapse associated with an elevation of ESR and CRP, treated with intra-articular injections and with an increased baricitinib dose (3mg twice/day), with only partial disease control. No modification of the lung disease on the CT scan was detected, even if the patient presented a worsening of the DLCO (58%). Also, P2, after 36 months of wellbeing, experienced an articular flare after which the dose was increased to 3 mg bid with resolution of the arthritis (see **Figure1**). P3 didn't experience any disease relapse since the start of the therapy. Both P1 and P2 have a current follow-up of 48 months, and P3 of 12 months on baricitinib. No patient experienced any severe infectious complication during treatment.

Baricitinib is a selective JAK 1/2 inhibitor approved for the treatment of moderate-severe rheumatoid arthritis. JAK1 and JAK2 mediate the signalling of key cytokines, including IL-6, IL-23, IL-7, IL-2, IL-12, and interferons (type I and II). Up to now, therapy with JAKi was reported in 4 COPA cases: one with baricitinib[3], one with ruxolitinib[4], and two that correspond to our P2 and P3, previously reported after 6 and 3 months of follow-up respectively[5,6]. In our cohort, baricitinib was effective in controlling the systemic inflammation, in reducing the articular flares, the need for intrarticular injections and in blocking the lung disease progression in medium-term follow-up. However, it is worth noting that two patients experienced a disease flare after 36 months. As shown in Figure 1, the relapse in both P1 and P2 occurred with a baricitinib dosage of 0.14 mg/kg/day (started at 0.2 mg/kg/day). Baricitinib dosages according to weight for interferonopathies have been proposed by Kim et al.[7] In our 3 patients, we observed a good response at a dosage of 0.2 mg/kg/day in two doses without infectious complications. We would therefore advise to follow Kim's et al. indications[7], evaluating a dose escalation according to the clinical tolerance and disease activity.

Also, the possibility of performing baricitinib blood concentration analysis should be considered, in order to perform an early dose adjustment[8].

No current guidelines for the treatment and follow-up of COPA syndrome exist. However, since systemic inflammation can be present, and a discordance of ESR and CRP has also been described, CRP and ESR levels should be periodically assessed[9]. Also, due to the risk of BK virus reactivation in patients treated with JAKI, serum and urine BK viral titres should be closely monitored. Although the IFN signature of the reported COPA cases never became negative during the treatment, an evident elevation was present during disease flares. We therefore propose to assess IFN signature routinely as part of COPA patients clinical care, especially if there is the suspicion of disease flare.

In conclusion, this represents the largest cohort of patients with COPA treated with JAK-inhibitors with a medium and long-term follow-up (1 to 4 years). Baricitinib seems safe and effective in controlling the disease and should be considered as a therapeutic option in these patients. Further studies are needed to assess the optimal treating dose and prevent disease relapse.

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Figure 1. Baricitinib dosages/kg , ESR levels , CRP levels, IFN signature , and treatment modifications related to disease flare (D). Yellow arrow: disease flare. Patient 1 blue lines, Patient 2 orange lines, Patient 3 grey lines. Dashed line: normal values cut-off: ESR <10mm/h, CRP < 1 g/L, IFN signature < 0.7

Table 1. Clinical and serological characteristic of the 3 COPA patients

	P1	**P2**	**P3**
Mutation	c.698G>A (p.Arg233His)	c.841C>T (p.Arg281Trp)	c.841C>T (p.Arg281Trp)
Sex	F	F	F
Ethnicity	Caucasian	African	African
Age at disease onset	3	3	2
Age at diagnosis	9	3	2
CRP at diagnosis	1.1 mg/L	5.7 mg/L	5.1 mg/L
ESR at diagnosis	57 mm/h	68 mm/h	40 mm/h
Arthritis	+	+	+
N° affected joints	30	6	2
Articular deformations	+	+	-
Respiratory symptoms at disease onset (tachypnea/cough/hemoptysis)	-	+ (cough)	-
ILD	+	+	+
Pulmonary hemorrhages	-	-	-
Bronchiectasis	+	-	+
GGO on CT scan	+	-	+
Cysts on CT scan	+	+	+
Renal disease	-	-	-
Proteinuria	-	-	-
Hypertension	-	-	-
IFN SIGNATURE	Positive	Positive	Positive
ANA	1:160 speckled	1:640 speckled	1:640 speckled
Rheumatoid Factor	534 U/ml	+	574 UI/ml
ACPA	169AU/ml	ND	> 340 U/ml
Previous treatments	Oral corticosteroids, intra-articular corticosteroids, abatacept, methotrexate, mycophenolate, rituximab	Oral corticosteroids, methotrexate, mycophenolate, hydroxychloroquine	NSAIDS
Age baricitinib started (years);	12	5	2
Baricitinib dose	2mg BID → 3mg BID	2mg BID → 3mg BID	2mg BID
Months of follow-up at present	48	48	12

ANA AntiNuclear Antibodies, ACPA Anti-Citrullinated Peptide Antibodies, CT Computerized Tomography, GGO Ground Glass Opacities, IFN Interferon, ILD Interstitial Lung Disease, ND not done, BID twice per day

FIGURE 1