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Upadacitinib-induced remission of allergic asthma: A case report"

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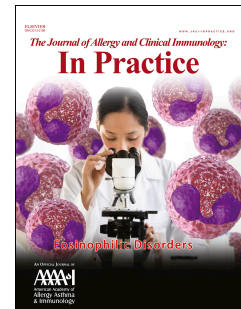
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Long title: Upadacitinib-induced remission of allergic asthma: A case report"

Short title: Upadacitinib for asthma treatment

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Sastre J reports having served as a consultant to Thermofisher, MEDA, Novartis, Sanofi, Leti, Faes Farma, Mundipharma, and GSK; having been paid lecture fees by Novartis, GSK, Stallergenes, Leti, and Faes Farma; as well as having received grant support for research from Thermofisher, Sanofi, and ALK. Betancor D is supported by a Rio Hortega Research Contract from Instituto Carlos III, Ministry of Science.

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Clinical Implications: We report a patient with severe AD , rhinitis, and asthma who, after initiating treatment with upadacitinib, experienced improvement in AD and remission of allergic rhinitis and asthma symptoms.

Upadacitinib is an oral, reversible, selective Janus kinase (JAK) inhibitor that has demonstrated higher selectivity for JAK1 compared to JAK2, JAK3, and tyrosine kinase (TYK2) in cellular assays (1). JAK1 plays an essential role in the expression of IL-4, IL-5, IL-13, and IL-31, all associated with pro-inflammatory signaling pathways in atopic dermatitis (AD) (2).

In 2019, the United States Food and Drug Administration and the European Medicines Agency approved the use of upadacitinib in adult patients with moderate-severe rheumatoid arthritis that is refractory to biologic disease-modifying antirheumatic drugs. The results of phase III clinical studies of upadacitinib in patients with moderate to severe AD refractory to topical treatment have been highly promising (3).

Allergic asthma is characterized by airway inflammation due to the generation of key cytokines (interleukin (IL)-4, IL-5, and IL-13) released by Th2 cells on activation of IL-13-dependent genes (4). Therefore, inhibition of these pathways is likely to reduce the activation of Th2 cells, hence improving asthma symptoms and promoting asthma control. Disruption of JAK1 signaling also targets the Th2-dependent JAK-STAT activation pathway, inhibiting differentiation of Th2 cells. A study by Ashino S. et al. (5) demonstrated this inhibiting effect in vitro and showed prevention of airway hyperresponsiveness and Th2 cytokine production through an in vivo animal model with allergen challenges (5).

We present a 45-year-old male non-smoker with a history of atopy since childhood consistent with mild AD, seasonal rhino-conjunctivitis, and mild-to-well-controlled asthma with multiple sensitizations to aeroallergens (pollen, dust mites, mold, and pet

danders). In 2017, due to asthma exacerbation and worsening of his rhinitis, he reported to the allergy department of the Fundación Jimenez Diaz University Hospital in Madrid, Spain. A complete work-up was performed, including blood eosinophil test (600 cells/ μ l), baseline spirometry evidencing mild obstruction (FVC: 116%, FEV1: 95%, FEV1/FVC: 66%) with a negative bronchodilator test (FEV1+8.8% and 370 ml), and exhaled fraction of nitric oxide showing elevated levels (251.3 ppb). A methacholine challenge revealed mild bronchial hyperresponsiveness (PC20 3.93 mg/ml). Treatment with salmeterol/fluticasone propionate 50/250 mg twice daily over 6 months led to controlled symptoms and improvement in spirometry findings (FVC 115%, FEV1: 103%, FEV1/FVC: 72%, MMEF75/25 73.2%), though the results of a bronchodilator test were still negative (FEV1 +6% and 280 ml) and FeNO was elevated (115 ppb). His IgE was > 2500 UI/L and blood eosinophil count of 500/ μ L

At the same time, the patient complained of worsening AD with recurrent eczematous plaques on his arms, legs, and face, followed by the dermatology department of the 12 de Octubre University Hospital, also in Madrid. He required daily topical treatment with clobetasol propionate and tacrolimus but due to uncontrolled eczema with these topical treatments 3-5 prednisone burst per year were prescribed with partial improvement. In April 2019, due to presence of severe AD refractory to topical treatments with a corticosteroid-dependent phenotype, the patient enrolled in a phase III, placebo-controlled clinical trial with oral daily upadacitinib (6). His EASI at that time was 21, scorad 58 and an IGA of 4.

On follow-up consultation in 2020, the patient reported substantial improvement in AD with some remaining patches of eczema which were easily controlled with topical corticosteroids. He had achieved total remission of his rhinitis and asthma symptoms,

though he remained on daily treatment with salmeterol/fluticasone propionate (50/250 mg). His spirometry results improved (FVC: 117.6%, FEV1: 112%, FEV1/FVC: 77.04) bronchodilator test was negative (FEV1 +3.4% and 160 ml) and his FeNO levels decreased (54.1 ppb). Tapering of inhaler therapy was performed under our supervision. After one year of follow-up, the patient discontinued inhaler therapy and remained completely asymptomatic for asthma and rhinitis. Baseline spirometry was normal (FVC: 119%, FEV1: 109%, FEV1/FVC: 74.31, MMEF75/25 80.1%); therefore, we performed both direct and indirect bronchial challenges, revealing no bronchial hyperresponsiveness to methacholine nor adenosine (7) (methacholine: PC20 >16 mg/ml and adenosine challenge: PC20 > 520 mg/ml) (7). Induced sputum showed no eosinophils (7). Blood eosinophil count remained 500 cells/ μ L. Clinical characteristics of the patient are summarized in Table 1.

Unblinding in May 2021 confirmed that the patient was in the active treatment group. (Actually, the study has since been extended and the patient continues to receive daily upadacitinib). Under this treatment, not only has he experienced an improvement in AD (current EASI of 7, SCORAD of 29 and IGA of 1), but he also experienced an improvement in lung function tests (spirometry, FeNO), and remission of bronchial hyperresponsiveness (negative methacholine and adenosine) and symptoms of asthma and rhinitis. Clinical findings are summarized in table 1.

His clinical phenotype is consistent with atopic march, which defines a subset of subjects with an increased risk of developing asthma and/or allergic rhinitis after the onset of AD characterized by allergen-specific type 2 (including Th2) responses (8). The mechanism of action of upadacitinib, by which JAK1 and is inhibited and Th2

differentiation of cells is disrupted, may explain the clinical improvement in asthma and rhinitis observed in our patient. Other drugs in development abrocitinib (JAK1 specific) and Baricitinib (JAK1/2 specific) also are in development for AD but have not as of yet had a report of improvement in atopic asthma to date (9).

In conclusion, we report a patient with severe AD, rhinitis, and asthma who, after initiating treatment with upadacitinib, experienced improvement in AD and remission of rhinitis and asthma symptoms, including improved lung function tests and a negative response to methacholine and adenosine tests. To our knowledge, this is the first case describing improvement in asthma under treatment with upadacitinib, a JAK1 inhibitor. This case report could provide initial evidence for continued research aiming to treat allergic asthma with upadacitinib.

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	Prior upadacitinib	Two years after upadacitinib
Atopic Dermatitis		
EASI	21	7
SCORAD	58	29
IGA	4	1
Asthma/Allergic Rhinitis		
Frecuency of respiratory symptoms	2-3 episodes per week of nocturnal wheezing and chest tightness Moderate rhinitis symptoms	Asymptomatic
Peripheral blood eosinophil count (cells/ μ l)	600	500
FeNO	251.3ppb	54.1ppb
Spirometry	FEV1: 95%, FEV1/FVC: 66%	FEV1: 109%, FEV1/FVC: 74.31
Methacholine challenge	Mild (3.93 mg/ml PC20)	Negative (>16mg/ml PC20)
Adenosine challenge	Not done	Negative (<520 mg/ml PC15)

191 Table 1: Clinical characteristic of the patient before and after treatment with
 192 upadacitinib