BRIEF COMMUNICATION
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Add-on Baricitinib in Omalizumab-refractory Chronic Rhinosinusitis with Nasal Polyps as a Dual-pathway Strategy

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ABSTRACT

A subset of patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) remains refractory to omalizumab, necessitating alternative therapeutic strategies. Blocking downstream interleukin (IL)-4 and IL-13 signaling via Janus kinase (JAK) inhibition represents a plausible approach, particularly in settings where the IL-4/IL-13 receptor blocker dupilumab is unavailable. This study aimed to evaluate the efficacy and safety of add-on baricitinib, an oral JAK1/2 inhibitor, in patients with severe, omalizumab-refractory CRSwNP.

In this open-label pilot case series, 10 adults with severe, refractory CRSwNP despite standard medical treatment and at least 1 endoscopic sinus surgery, who demonstrated poor control after a 6-month trial of omalizumab, received add-on baricitinib (4 mg daily) for 6 months while continuing omalizumab. Outcomes included the 22-item Sinonasal Outcome Test (SNOT-22), Lund-Mackay (LMK) CT score, lung function (forced expiratory volume in 1 second [FEV_1]% predicted), and safety monitoring.

The addition of baricitinib was associated with clinically meaningful improvements from baseline in all patients. Mean SNOT-22 scores decreased from 41.7 to 25.9, LMK scores improved from 14.5 to 11.5, and FEV_1% predicted increased from 77.1% to 79.7%. The combination was well tolerated; adverse events included transient hypercholesterolemia (n=3) and 1 self-limited oral herpes simplex recurrence, with no thromboembolic events observed.

This first-in-human case series provides preliminary evidence that dual-pathway blockade with add-on baricitinib may be a viable and well-tolerated therapeutic strategy for patients with omalizumab-refractory CRSwNP, especially in resource-constrained environments. These findings warrant further investigation in controlled trials.

Keywords: Baricitinib; Biologic therapy; Chronic rhinosinusitis with nasal polyps (CRSwNP); JAK-STAT pathway; Omalizumab; Refractory

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INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a debilitating type 2 (T2) inflammatory disease. While biologics targeting immunoglobulin E (IgE; omalizumab) or the interleukin (IL)-4/IL-13 receptor (dupilumab) have revolutionized care, a significant proportion of patients exhibit an inadequate response to single-pathway inhibition.[1] The pathogenesis of T2 inflammation is driven by cytokines, including IL-4, IL-5, and IL-13, whose signaling is centrally mediated through the Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway.[2] Consequently, JAK inhibition offers a strategic downstream blockade of multiple T2 cytokines.

In clinical contexts where the most effective biologic, dupilumab, is unavailable,[1] targeting the shared JAK-STAT pathway downstream of the IL-4/IL-13 receptor represents a rational therapeutic alternative. Baricitinib, an oral JAK1/2 inhibitor, blocks signaling of these key cytokines.[3] We hypothesized that in patient's refractory to omalizumab, adding baricitinib to simultaneously target IgE (upstream) and intracellular T2 cytokine signaling (downstream) could enhance clinical efficacy. We present, to our knowledge, the first case series evaluating add-on baricitinib in omalizumab-refractory CRSwNP.

MATERIALS AND METHODS

We enrolled 10 consecutive adult patients with severe, refractory CRSwNP (70% female, mean age 50.2 years, 70% with nonsteroidal anti-inflammatory drug–exacerbated respiratory disease [NERD]) from our tertiary allergy clinic. All had failed standard medical therapy and at least 1 standard sinus surgery during the preceding 5 years. Following a 6-month trial of weight- and IgE-adjusted omalizumab, all met the European Position Paper on Rhinosinusitis and Nasal Polyps–European Forum for Research and Education in Allergy and Airway Diseases (EPOS-EUPHOREA) criteria for "uncontrolled" disease.[4] Baricitinib (4 mg daily) was then added to their ongoing omalizumab regimen for an additional 6 months. All cases continued both omalizumab and baricitinib without changing the dose.

The study was approved by the Institutional Review Board of Iran University of Medical Sciences (IR.IUMS.REC.1404.358) and registered with the Iranian Registry of Clinical Trials (IRCT20181230042174N3). All participants provided written informed consent. Pretreatment screening included evaluation for tuberculosis and hepatitis B and C viruses. Safety monitoring comprised monthly complete blood counts, liver function tests, and lipid profiles for the first 3 months, then quarterly, with all adverse reactions recorded.

Outcomes

Efficacy was assessed by SNOT-22, LMK CT scores, and spirometry (FEV_1% predicted) at 3 time points: T0 (pre-omalizumab, only standard medical treatment), T1 (post-omalizumab/pre-baricitinib, standard medical treatment plus omalizumab), and T2 (after 6 months of combination therapy, standard treatment plus omalizumab plus baricitinib). Safety was assessed via adverse event monitoring, including blood cell cytopenias, lipid, liver, and renal profiles, viral infections (such as herpes simplex virus), and thromboembolic events.

RESULTS

Clinical Efficacy

The addition of baricitinib was associated with consistent improvement across all measured outcomes in all 10 patients (Table 1). From the omalizumab-refractory baseline (T1) to the end of combination therapy (T2), mean SNOT-22 scores improved from T0: 46.4 (standard therapy alone) and T1: 41.7 (standard therapy plus omalizumab) to T2: 25.9 (standard therapy plus omalizumab plus baricitinib), reflecting a clinically significant reduction in symptom burden. Radiologic inflammation decreased, with mean LMK scores improving from T0: 15.6 and T1: 14.5 to T2: 11.5. Lung function also improved, with mean FEV_1% predicted increasing from T0: 67.6% and T1: 77.1% to T2: 79.7% (Figure 1).

Safety and Tolerability

The combination therapy was generally well tolerated. Adverse events were manageable and included transient, mild hypercholesterolemia (<10% elevation from baseline) in 3 patients, which did not require treatment discontinuation. One patient with a prior history of oral herpes simplex virus experienced a mild recurrence that resolved with standard episodic treatment without interrupting baricitinib therapy. No serious adverse events, thrombotic events, or significant cytopenias were observed.

Table 1. Patient characteristics and clinical outcomes

Pt	Age /sex	NERD	Prior surgeries, No.	IgE, IU/mL	Blood Eos, cells/µL	SNOT-22 score (T0/T1/T2)[a]	LMK score (T0/T1/T2)[a]	FEV_1, % predicted (T0/T1/T2)[a]	Adverse events
1	27/M	+	1	177	1748	89/80/51	18/17/14	65/73/78	Hyperchol
2	51/F	−	1	216	376	34/28/11	16/14/10	59/79/78	None
3	45/M	+	2	362	281	44/38/21	18/17/17	46/65/78	None
4	44/F	+	2	108	250	49/43/37	12/10/7	75/79/85	Hyperchol.
5	55/F	+	1	188	273	43/35/21	15/12/9	65/72/79	None
6	64/M	+	4	132	801	40/42/28	16/14/13	81/88/89	None
7	55/F	−	1	1385	130	52/50/11	17/15/11	65/78/82	None
8	65/F	+	1	79	440	43/48/42	19/21/18	71/73/76	Hyperchol.
9	46/F	+	3	250	372	38/21/17	14/13/9	80/85/83	Oral HSV
10	49/F	−	3	376	385	31/32/20	11/12/8	69/79/88	None
Mean	50.2	NA	1.9	329.3	545.6	46.4/41.7/25.9	15.6/14.5/11.5	67.6/77.1/79.7	NA

[a]Time points: T0 (pre-omalizumab; standard medical treatment only), T1 (post-omalizumab/pre-baricitinib; after 6 months of omalizumab monotherapy), and T2 (post-baricitinib combination therapy; after 6 months of omalizumab plus baricitinib combination therapy). [b]Eos: eosinophils; F: female; FEV_1: forced expiratory volume in 1 second; HSV: herpes simplex virus; Hyperchol.: hypercholesterolemia; IgE: immunoglobulin E; IU: international units; LMK: Lund-Mackay; M: male; NA: not applicable; NERD: NSAID-exacerbated respiratory disease; NSAID: nonsteroidal anti-inflammatory drug; Pt: patient; SNOT-22: 22-item Sinonasal Outcome Test.

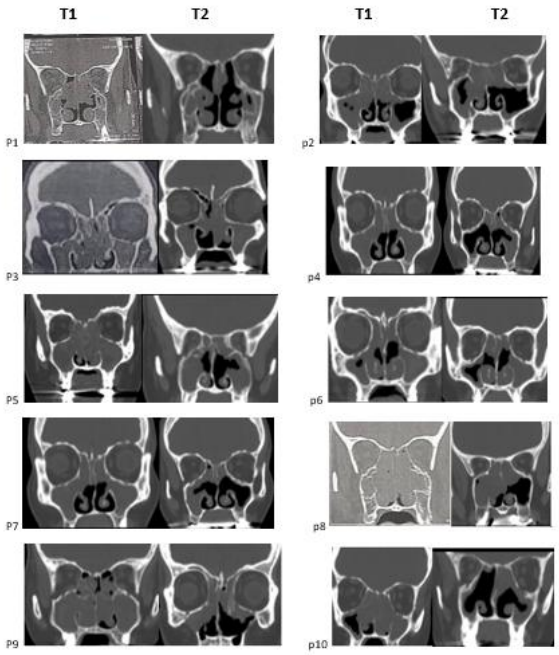

Figure 1. Conceptual diagram illustrating the dual-pathway therapeutic strategy: Omalizumab targets upstream IgE, while add-on baricitinib inhibits the downstream JAK-STAT signaling pathway shared by key T2 cytokines (IL-4, IL-13) implicated in CRSwNP pathogenesis.

DISCUSSION

This novel case series demonstrates the potential of dual-pathway immunomodulation using add-on baricitinib for patients with severe CRSwNP refractory to omalizumab. The observed improvements in patient-reported symptoms, radiographic findings, and lung function suggest that JAK inhibition can provide meaningful clinical benefit in this difficult-to-treat population by targeting the intracellular signaling of key T2 cytokines.

Our approach is supported by a strong mechanistic rationale. The immunological synergy of this dual-pathway strategy lies in coupling upstream IgE depletion with downstream receptor-level blockade; while omalizumab limits mast cell and basophil activation, add-on baricitinib—a selective JAK1/2 inhibitor—simultaneously blunts IL-4, IL-13, and epithelial-derived alarmin signaling (eg, thymic stromal lymphopoietin [TSLP], IL-33) that bypass IgE-mediated pathways to drive recalcitrant type 2 innate lymphoid cell (ILC2) and eosinophil activation. Omalizumab reduces free IgE and downregulates FcεRI receptors,[5] while baricitinib inhibits the JAK-STAT pathway, the final common signaling route for IL-4 and IL-13.[3] This synergistic upstream/downstream blockade may overcome the limitations of single-pathway therapy. Our findings align with the established efficacy of JAK inhibitors in other T2 diseases like atopic dermatitis[6] and emerging research in asthma.[7]

Clinical Implications and Limitations

In regions where dupilumab is inaccessible, our strategy offers a clinically feasible alternative. The oral administration of baricitinib may also be preferable for some patients. However, this study has inherent limitations: its open-label design, small sample size, and lack of a control group preclude definitive efficacy conclusions. The very small sample size precluded formal statistical analysis and therefore constitutes an important limitation of the present study. In addition, to the best of our knowledge, there are currently no published human studies evaluating baricitinib in patients with CRSwNP, which limited our ability to compare and contextualize our findings within the existing literature. Finally, at the time this study was conducted, baricitinib was the only JAK inhibitor available in our country, thereby limiting the opportunity to assess or compare other agents within the same therapeutic class. Larger randomized controlled trials are essential to validate these preliminary findings and to establish the long-term safety profile of this combination in CRSwNP.

This first report of add-on baricitinib in omalizumab-refractory CRSwNP provides promising preliminary evidence for its efficacy and tolerability. It highlights JAK inhibition as a viable therapeutic strategy for severe, multi-refractory CRSwNP and underscores the potential of precision, pathway-based therapy in respiratory allergy. These results urgently call for formal evaluation in controlled clinical trials. Finally, we acknowledge the various limitations of this study and recognize that, given its design and scope, definitive conclusions cannot be drawn and the findings cannot be generalized. Nevertheless, the clinical importance of this topic warrants further investigation in larger, well-designed studies.

STATEMENT OF ETHICS

The study was approved by the Institutional Review Board of Iran University of Medical Sciences (IR.IUMS.REC.1404.358) and registered with the Iranian Registry of Clinical Trials (IRCT20181230042174N3). All participants provided written informed consent.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

Researchers can access the study's documentation by emailing the corresponding author and stating their reasons

AI ASSISTANCE DISCLOSURE

AI was not used to assist in writing any part of the article.

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