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JAK1 inhibition with abrocitinib decreases allergen-specific basophil and T-cell activation in pediatric peanut allergy

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Abstract

Background: JAK1 is a signaling molecule downstream of cytokine receptors, including IL-4 receptor α. Abrocitinib is an oral JAK1 inhibitor; it is a safe and effective US Food and Drug Administration–approved treatment for adults with moderate-to-severe atopic dermatitis.

Objective: Our objective was to investigate the effect of abrocitinib on basophil activation and T-cell activation in patients with peanut allergy to determine the potential for use of JAK1 inhibitors as a monotherapy or an adjuvant to peanut oral immunotherapy.

Methods: Basophil activation in whole blood was measured by detection of CD63 expression using flow cytometry. Activation of $CD4^+$ effector and regulatory T cells was determined by the upregulation of CD154 and CD137, respectively, on anti-CD3/CD28– or peanut-stimulated PBMCs. For the quantification of peanut-induced cytokines, PBMCs were stimulated with peanut for 5 days before harvesting supernatant.

Results: Abrocitinib decreased the allergen-specific activation of basophils in response to peanut. We showed suppression of effector T-cell activation when stimulated by CD3/CD28 beads in the presence of 10 ng of abrocitinib, whereas activation of regulatory T-cell populations was preserved in the presence of abrocitinib. Abrocitinib induced statistically significant dose-dependent inhibition in IL-5, IL-13, IL-10, IL-9, and TNF-α in the presence of peanut stimulation.

Conclusion: These results support our hypothesis that JAK1 inhibition decreases basophil activation and T_H2 cytokine signaling, reducing *in vitro* allergic responses in subjects with peanut allergy. Abrocitinib may be an effective adjunctive immune modulator in conjunction with peanut oral immunotherapy or as a monotherapy for individuals with food allergy.

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Keywords

Abrocitinib; allergen-specific T cell; JAK1; basophil activation; peanut allergy

INTRODUCTION

Patients with food allergy have 1 approved treatment (peanut oral immunotherapy under the brand name Palforzia [Aimmune Therapeutics, Brisbane, Calif]), 1 treatment that is being considered by the US Food and Drug Administration (FDA) (epicutaneous immunotherapy with the Viaskin patch [DBV Technologies, Montrouge, France]), and many treatments that are in various stages of development.[1]

Janus kinase 1 (JAK1) is a signaling molecule downstream of IL-4 receptor α (IL-4Rα) and cytokines that are key in the allergic response, including IL-4,IL-13, IL-9, and TSLP (see Fig E1 in the Online Repository at www.jaci-global.org). Simultaneous inhibition of signaling from these key cytokines involved in IgE class switch, mast cell expansion, and T_H2 cell induction may effectively suppress manifestations of food allergy more than is achieved by biologics targeting single cytokines or receptors. Abrocitinib is an oral biologic medication that inhibits JAK1 selectively, and it is a safe and effective FDA-approved option for treatment of moderate-to-severe atopic dermatitis in adults.[2]

There is growing evidence of an altered intestinal allergic milieu in IgE-mediated food allergy that may be restored with JAK inhibition. IL-9–producing mast cell subsets are downstream of T_H2 cells, and their numbers are increased in the duodenum of patients with IgE-mediated food allergy.[3] Mast cell numbers in the intestine are correlated with anaphylaxis severity in a food allergy model in mice.[4] Individuals with peanut allergy have poly-functional pathogenic T_H2 cells (T_H2A cells) that produce IL-9 in addition to IL-4 and IL-13.[5,6] Basophil activation is also a key immunologic process that is correlated with clinical reactivity and tolerance in patients with food allergy.[7]

In mouse models, the FDA-approved JAK inhibitor ruxolitinib, which blocks JAK1 and JAK2, prevented mast cell hyperplasia in the intestine, inhibited mast cell activation and symptoms, and decreased IL-4 and IL-9 production from the spleen.[8] Treatment of mice with ruxolitinib given as a therapeutic for 18 days together with intermittent allergen challenge (not with allergen immunotherapy) also significantly reduced anaphylaxis severity. Abrocitinib was used in this study instead of ruxolitinib because of a more desirable side effect profile associated with systemic administration.[9] We tested whether abrocitinib treatment of blood or PBMCs from individuals with peanut allergy could similarly suppress basophil and T-cell activation in a dose-dependent manner.

RESULTS AND DISCUSSION

The JAK1 inhibitor abrocitinib decreased peanut-specific basophil activation in a dose-dependent manner at 100 ng/mL ($P < .01$ [Fig 1] but not at 10 ng/mL). At higher doses, abrocitinib may suppress JAK2, which could potentially affect IgE-mediated basophil activation through inhibition of signaling downstream of IL-3. The concentration that

inhibits 50% for JAK1 is 29 nM (9.4 ng/mL), whereas that of JAK2 is 803 nM (260 ng/mL[9]), which is 2.6 times the highest dose used in these studies. There was no significant effect of abrocitinib on N-formylmethionyl-leucyl-phenylalanine or anti-FcεR1–induced basophil activation.

To address the impact of abrocitinib on peanut-induced effector and regulatory T (Treg) cell activation, PBMCs were stimulated with anti-CD3/CD28 or N-formylmethionyl-leucyl-phenylalanine purified peanut protein (PN) and CD154 and CD137 expression was examined at 24 hours, as measures of effector T-cell and Treg cell activation, respectively. CD154 was gated on $CD3^+CD4^+CD45RA^-$ memory T cells, whereas CD137 was gated on $CD3^+CD4^+CD25^-CD127^{low}$ cells. In response to polyclonal activation with anti-CD3/CD28, abrocitinib (10 ng/mL) significantly suppressed effector cell activation while having no significant impact on Treg cell activation (Fig 2). In response to PN stimulation, there was no significant decrease in effector cell activation and no decrease in $CD137^+$ Treg cells in the 4 of 7 subjects with a detectable peanut-specific CD137 response. JAK inhibition would not be expected to interfere with signaling downstream of the T-cell receptor, but it would impair cytokine-mediated expansion of the T-cell response in T-cell cultures. We have shown that Treg cells in peanut allergy are activated in an IL-2–dependentmanner,[10] but JAK inhibition spared the activation of Treg cells. The impact of abrocitinib on Treg cell inhibition of PN-induced effector memory responses should be investigated further.

We performed recall assays to examine T_H2 cell–derived cytokine production after 5 days of stimulation with PN. PN stimulation of PBMCs increased the concentration of IL-5, IL-13, IL-10, IL-9, TNF-α, and IL-17. The IL-4 content was below the level of detection in our assay. At 2 concentrations of abrocitinib, 10 and 100 ng/mL, the levels of each of these cytokines were relatively decreased in the presence of peanut protein and were no longer statistically different from the levels of unstimulated cells (Fig 3).

These data demonstrate the capacity for abrocitinib to inhibit IgE-mediated basophil activation and T_H2 cells while simultaneously preserving essential Treg cells. Although IL-10 concentration is inhibited by abrocitinib after 5 days of incubation, the preservation of Treg cell activation suggests that the primary source of IL-10 in this experiment is T_H2 cells. The requirement for higher doses of abrocitinib to inhibit basophil activation than for inhibition of T cells suggests that *in vivo* effects of abrocitinib may be more effective on T cells; however, whether *in vivo* administration of abrocitinib can suppress the activation of basophils in individuals with peanut allergy remains to be determined.

JAK1 inhibition may be an efficacious mechanism for treatment of patients with food allergy as a monotherapy or as an adjunct to food oral immunotherapy. These results with basophil activation support the potential role for abrocitinib as a monotherapy in patients with food allergy, whereas the inhibition of T_H2 cytokines and T-cell activation support the role of abrocitinib as a potential adjuvant to food oral immunotherapy.

A mechanistic pilot trial (ClinicalTrials.gov identifier NCT05069831) using abrocitinib as a monotherapy is currently recruiting[11] and will address the *in vivo* impact of JAK1 inhibition. The doses used in an ongoing clinical trial (100–200 mg) do correspond to the

concentrations used in these *in vitro* studies. Bauman et al noted that after a 200-mg dose of abrocitinib, the maximum concentration in plasma after 30 minutes is 778 ng/mL.[12] Clinically, we anticipate that there may be some impact on skin testing results or on the tolerated amount of peanut that would correlate with the decrease in basophil activation at 100 ng/mL seen *in vitro*; given that complete abrogation of activation did not occur, we do not expect to see absence of a skin test response or sustained unresponsiveness after monotherapy with abrocitinib.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

CD154	CD40 ligand
FDA	US Food and Drug Administration
IL-4Rα	IL-4 receptor α
JAK	Janus kinase
PN	Purified peanut protein
T reg	Regulatory T

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Clinical implications:

Ex vivo inhibition of JAK1, a clinically relevant target in food allergy, led to inhibition of allergen-specific basophil activation, dose-dependent inhibition of T_H2 cytokine levels, and spared Treg cell activation.

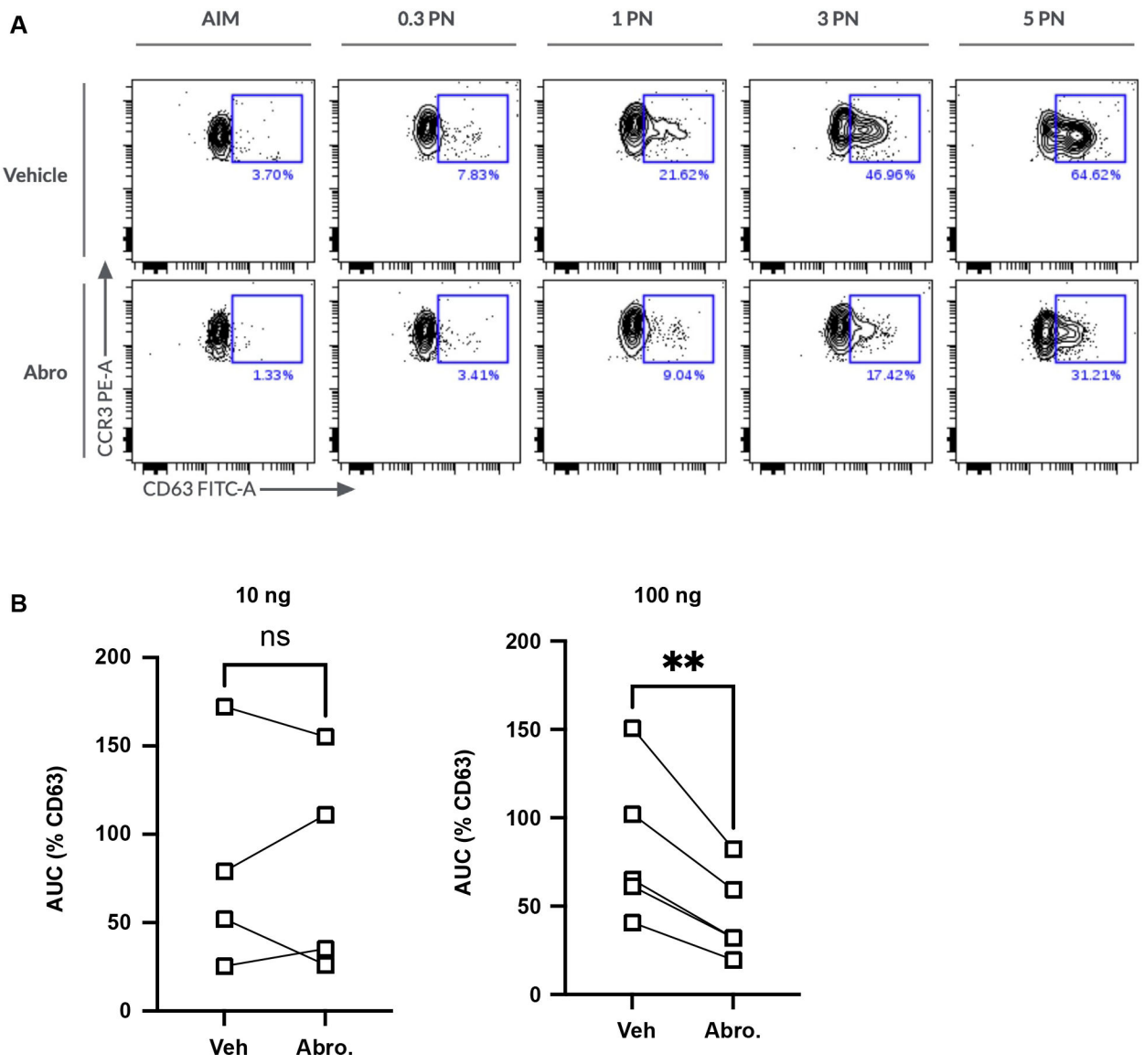

FIG 1.

Impact of abrocitinib on basophil activation. **A**, Representative flow cytometry showing activation of basophils with different doses of peanut (PN) extract or media control (AIM) in the presence of abrocitinib (Abro) (10 or 100 ng/mL) or vehicle control. **B**, Area under the curve of percentage of $CD63^+$ basophils for doses of 0.3 to 5 ng of peanut subtracting media (AIM) control. $^{**}P < .01$; paired *t* test. *Ns*, Not significant.

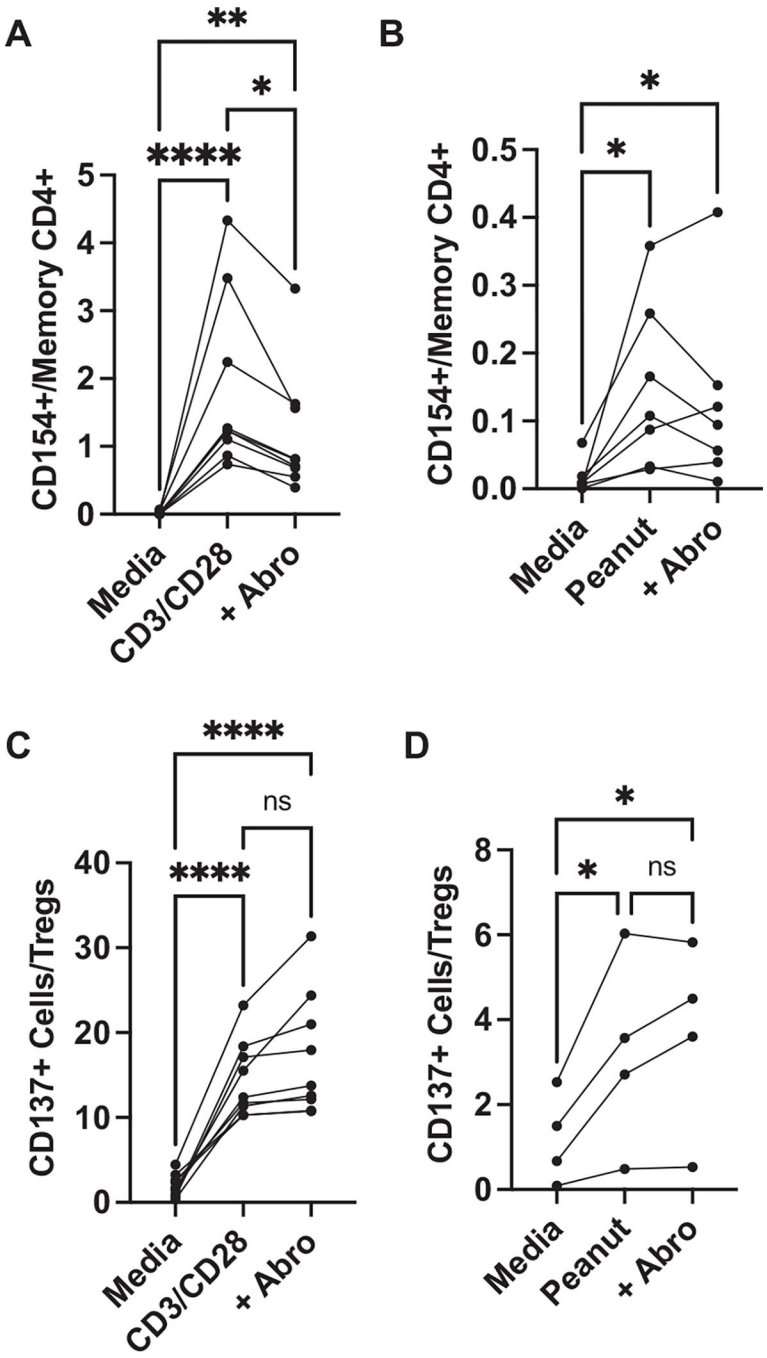

FIG 2.

Impact of abrocitinib on T-cell activation. PBMCs were stimulated with anti-CD3/CD28 (**A** and **C**) and peanut extract (**B** and **D**) for 24 hours in the presence or absence of abrocitinib (10 ng/mL) before measurement of CD154 on memory $CD4^+$ T cells (**A** and **B**) and CD137 on Treg cells. $*P < .05$; $**P < .01$; $****P < .0001$.

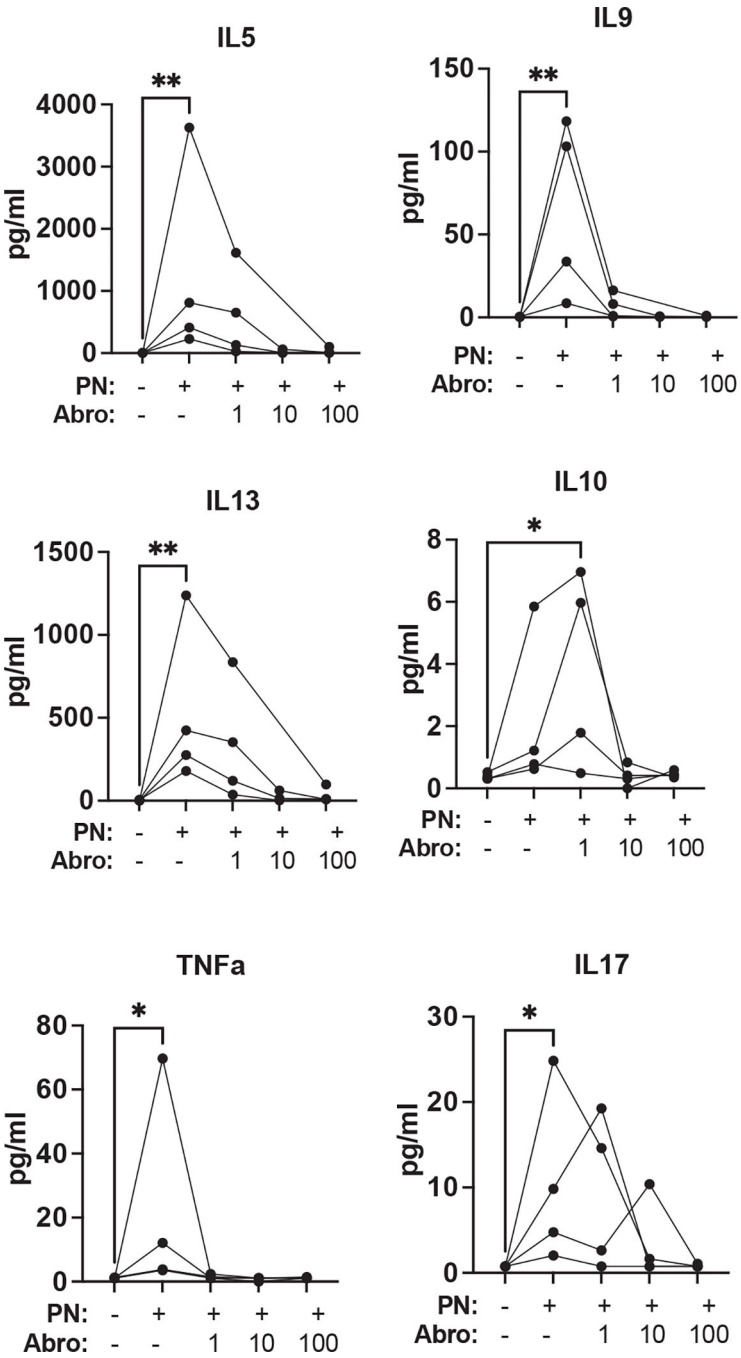

FIG 3.

Impact of abrocitinib on cytokine production by peanut-stimulated PBMCs. PBMCs from individuals with peanut allergy were stimulated with 100 ug/mL of peanut extract in the presence or absence of abrocitinib at doses from 1 to 100 ng/mL. After 5 days, supernatants were harvested for analysis of secreted cytokines. *$P < .05$ and **$P < .01$ compared with unstimulated control.