PI3K pathway activation in severe asthma is linked to steroid insensitivity and adverse outcomes

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Background: Patients with severe asthma may demonstrate reduced sensitivity to steroid treatment. However, the implications of this reduced responsiveness for clinical outcomes and the underlying mechanisms remain unclear.
Objective: The aim of this study was to investigate whether steroid sensitivity in patients with asthma is related to severity and clinical outcomes and to elucidate the role of inflammatory pathways in reducing steroid sensitivity.
Methods: This observational study of 169 asthma patients, with 161 followed for 1 year, involved isolation of peripheral blood mononuclear cells. These cells were treated with dexamethasone, and the mRNA expression of *FKBP5,* which is a marker of steroid sensitivity, was measured. To explore the mechanism underlying the reduced steroid sensitivity, cells were exposed to PI3K and MAPK inhibitors in combination with dexamethasone.
Results: A total of 53 patients diagnosed with severe asthma exhibited markedly diminished sensitivity to steroids compared with those with nonsevere asthma. Reduced steroid sensitivity has emerged as a critical risk factor for failure to experience clinical remission and exacerbation. This relationship between reduced steroid sensitivity and disease severity and adverse outcomes was confirmed at the 1-year follow-up. Mechanistic investigations revealed that the degree of recovery from steroid sensitivity after PI3Kδ/γ inhibitor treatment was significantly greater in patients with severe asthma than in those with nonsevere asthma, a finding confirmed at the 1-year follow-up.
Conclusions: Patients with severe asthma demonstrate reduced steroid sensitivity, which results in unfavorable clinical outcomes. Conversely, inhibition of the PI3K pathway significantly improves steroid sensitivity. (J Allergy Clin Immunol Global 2025;4:100439.)

Key words: *Asthma, clinical remission, inflammatory pathway, steroid sensitivity*

Asthma is a heterogeneous disease with various clinical phenotypes.[1] Despite the use of inhaled corticosteroids (ICSs) as the primary treatment approach, some patients with asthma do not experience adequate therapeutic benefits. This group of patients with severe asthma, who present with difficult-to-treat asthmatic symptoms, constitutes 4% to 10% of all asthma patients.[2,3] Recent advances in biologics have demonstrated their efficacy in the treatment of severe asthma.[4] Moreover, the identification of biomarkers that can predict the effectiveness of these biologics has been the focus of several studies. Conversely, biomarkers that reflect the effects of steroid treatment have not yet been fully elucidated,[5] which makes identifying patients with disease that is unlikely to respond to steroids in clinical practice challenging. This may result in delays in optimal treatment. To obtain clinical remission in cases of severe asthma, providing effective treatment at an early disease stage is crucial.[6] Therefore, accurately assessing not only the efficacy of biologics but also sensitivity to steroid treatment is important.

In more than half of patients with asthma, type 2 inflammation represents the predominant pathophysiology, as evidenced by elevated blood eosinophil counts and fractional exhaled nitric oxide (FENO) levels.[7] Additionally, non–type 2 inflammation, including neutrophilic and T_H17-related inflammation, has been demonstrated to play a role in the pathogenesis of asthma.[8] Non–type 2 inflammation is associated with a lack of responsiveness to steroid treatment, whereas steroid treatment is believed to be effective for treating type 2 inflammation.[9] Nevertheless, despite the administration of high-dose ICSs, the disease of a subset of patients continues to exhibit residual type 2 inflammation.[10] The activation of inflammatory pathways due to inflammation and oxidative stress may alter the efficacy of steroids.[11,12] The activation of the p38 mitogen-activated protein kinase (MAPK) pathway has been proposed to inhibit the nuclear translocation of glucocorticoid receptors,[13,14] whereas the activation of the phosphatidylinositol 3-kinase (PI3K) pathway has been linked to a reduction in histone deacetylase 2 (HDAC2) activity.[11] Nevertheless, the reasons for the inadequate response to steroids remain unclear.

The primary objective of this study was to evaluate the steroid sensitivity of peripheral blood mononuclear cells (PBMCs) in patients with asthma by measuring the mRNA levels of *FKBP5,* a marker of steroid sensitivity, and to investigate the relationship between sensitivity and clinical outcomes. Furthermore, this study aimed to elucidate the role of the MAPK and PI3K signaling pathways in reducing steroid sensitivity.

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Abbreviations used
FENO: Fractional exhaled nitric oxide
FEV_1: Forced expiratory volume in 1 second
FVC: Forced vital capacity
GILZ: Glucocorticoid-induced leucine zipper
HDAC2: Histone deacetylase 2
ICS: Inhaled corticosteroid
MAPK: Mitogen-activated protein kinase
NLR: Neutrophil–lymphocyte ratio
PBMC: Peripheral blood mononuclear cell
PI3K: Phosphatidylinositol 3-kinase
TSLP: Thymic stromal lymphopoietin

METHODS

Study design

This was a single-center prospective observational study with 1-year follow-up of patients with asthma at Shizuoka General Hospital, Japan, from December 2021 to March 2024. We enrolled Japanese patients with asthma using the following inclusion criteria: patients aged 20 years or older with no asthma exacerbations within the 4 weeks before enrollment. Asthma was diagnosed according to the Global Initiative for Asthma and Japanese guidelines.[15] Two study visits were performed for each subject at the beginning of the study (visit 1) and at the 1-year follow-up (visit 2), and patients continued to receive routine clinical care during the 1-year period. The Shizuoka General Hospital research ethical committee approved the study protocol (approval no. 2021013). Written informed consent was obtained from all subjects.

Measurements and clinical outcomes

At each study visit, the subjects underwent peripheral blood sampling, pulmonary function testing, FENO level testing, and asthma symptom assessment. The lower limits of normal for forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio were calculated via the reference equation.[16] The Asthma Control Test and the Asthma Control Questionnaire were used to assess asthma symptoms. Patients with severe asthma were defined as those requiring treatment with high-dose ICSs (≥1000 μg/d fluticasone propionate or equivalent) plus long-acting β_2-agonists or long-acting muscarinic antagonists, leukotriene receptor antagonists, theophylline, oral corticosteroids, or biologics to prevent poor control, in accordance with European Respiratory Society/American Thoracic Society guidelines.[17] Asthma exacerbations, defined as worsening symptoms requiring oral or intravenous corticosteroids for 3 days or more or an emergency department visit or hospitalization due to asthma, were identified from 1 year before visit 1 to visit 2. In addition, clinical remission was defined as long-term control of asthma, as evidenced by the absence of oral corticosteroid therapy for disease control, the absence of exacerbations, an Asthma Control Test score of ≥20, and percentage predicted FEV_1 of ≥80% over the past 12 months.[18]

Measurements of steroid sensitivity

PBMCs isolated from each patient were treated with 1 μmol dexamethasone and cultured with control wells for 24 hours. The mRNA levels of *FKBP5* and *TSC22D3,* which are known to be induced by dexamethasone, were then determined via a qPCR assay. Steroid sensitivity was defined as the degree of induction of gene expression by dexamethasone treatment relative to that of control. The involvement of inflammatory pathways was also identified by simultaneously exposing PBMCs to each inhibitor (1 μmol) and dexamethasone (1 μmol), and the sensitivity to steroids was evaluated after 24 hours. The alteration in steroid sensitivity with inhibitors was quantified by comparing the gene expression induced by the inhibitor plus dexamethasone to that induced by dexamethasone alone. The selected inhibitors included a PI3Kδ/γ inhibitor (IPI-145, duvelisib), a PI3Kδ inhibitor (CAL-101, idelalisib), and a p38 MAPK inhibitor (BIRB796, doramapimod).

Details of the measurement methods we used are provided in the Methods section in this article's Online Repository available at www.jaci-global.org.

Statistical analysis

Categorical variables were compared by the Fisher exact test, whereas the Kruskal-Wallis or Wilcoxon rank-sum test was used to evaluate continuous variables. Logistic regression analysis was conducted to calculate the odds ratio of steroid sensitivity with clinical outcomes as objective variables. Analyses were performed by R v 4.4.0 software (R Project; www.r-project.org), with statistical significance set at $P < .05$.

RESULTS

Patient information

The study included 169 patients with asthma, of whom 53 (31.4%) had severe asthma at visit 1. Table I presents a comparative analysis of the clinical characteristics of patients with severe and nonsevere asthma. Patients with severe asthma were significantly younger than those with nonsevere asthma. No significant differences were observed in the distributions of sex, body mass index, or smoking history between the two groups. Patients with severe asthma resented significantly lower respiratory function, as evidenced by significantly lower predicted FEV_1 and predicted FVC values and a significantly greater proportion of patients with actual FVC, FEV_1, and FEV_1/FVC values below the lower limits of normal. There were no significant differences in FENO levels, total serum IgE levels, or peripheral blood eosinophil counts; however, neutrophil counts and the neutrophil–lymphocyte ratio (NLR) were significantly greater in the group with severe asthma.

At the 1-year follow-up visit (visit 2), 161 patients (95.3%) were reevaluated. At this visit, 52 patients were diagnosed with severe asthma (see Table E1 in the Online Repository available at www.jaci-global.org), of whom 50 were followed up at visit 1 and two were newly diagnosed. Like those at visit 1, patients with severe asthma at visit 2 were significantly younger and had lower respiratory function than those with nonsevere asthma.

Steroid sensitivity and clinical outcomes

First, we assessed the steroid sensitivity of each patient's PBMCs by measuring the mRNA levels of *FKBP5,* a marker of steroid sensitivity. At visit 1, patients with severe asthma had significantly lower steroid sensitivity than did those with

TABLE I. Demographic and clinical characteristics of asthma patients at visit 1

Characteristic	Severe asthma	Nonsevere asthma	*P* value
No. of patients	53	116	
Age (years), median (IQR)	61 (51, 73)	72 (61, 77)	.006
Sex, M/F (no.)	27/26	65/51	.618
BMI (kg/m^2), median (IQR)	23.4 (20.8, 25.4)	24.3 (21.2, 27.5)	.140
Current/ex-smoker (no.)	1/29	6/54	.495
Smoking pack years, median (IQR)	5.5 (0.0, 33.0)	0.9 (0.0, 31.0)	.597
GINA step 1/2/3/4/5 (no.)	0/0/0/17/36	8/7/9/92/0	<.001
FENO (ppb), median (IQR)	29 (17, 63)	31 (21, 50)	1.000
Total serum IgE (IU/mL), median (IQR)	186 (23.4, 1170)	250 (112, 618)	.465
Peripheral blood cells (/μL), median (IQR)			
Neutrophil	4076 (3213, 5716)	3817 (2975, 4497)	.035
Lymphocyte	1558 (1159, 2128)	1636 (1286, 2060)	.448
Monocyte	380 (297, 491)	354 (284, 430)	.212
Eosinophil	205 (40, 539)	272 (138, 410)	.296
Basophil	49 (29, 71)	47 (29, 59)	.356
NLR, median (IQR)	2.60 (1.97, 3.79)	2.30 (1.59, 3.12)	.039
FVC (L), median (IQR)	2.87 (2.22, 3.50)	2.99 (2.50, 3.64)	.238
FVC (% predicted), median (IQR)	98.4 (80.1, 106.3)	102.0 (91.5, 110.8)	.013
FVC (L) <LLN, no. (%)	15 (28.3)	11 (9.5)	.003
FEV_1 (L), median (IQR)	1.83 (1.41, 2.45)	2.09 (1.60, 2.62)	.050
FEV_1 (% predicted), median (IQR)	77.9 (56.8, 96.1)	89.6 (70.2, 101.8)	.008
FEV_1 (L) <LLN, no. (%)	29 (54.7)	40 (34.5)	.018
FEV_1/FVC, median (IQR)	67.0 (56.4, 77.8)	7.3 (61.0, 77.6)	.283
FEV_1/FVC <LLN, no. (%)	32 (60.4)	48 (41.4)	.030
ACT, mean (SD)	20.8 (4.5)	23.0 (2.8)	<.001
ACQ, mean (SD)	0.9 (1.1)	0.5 (0.7)	.001
Exacerbation, no. (%)	17 (32.1)	4 (3.4)	<.001
Clinical remission, no. (%)	11 (20.8)	63 (54.3)	<.001
ICS dose (μg/d), median (IQR)	1000 (500, 1000)	500 (500, 500)	<.001
Medication, no. (%)			
ICS	51 (96.2)	108 (93.1)	.726
LABA	51 (96.2)	106 (91.4)	.344
LAMA	34 (64.2)	38 (32.8)	<.001
LTRA	31 (58.5)	26 (22.4)	<.001
Theophylline	7 (13.2)	5 (4.3)	.052
OCS	11 (20.8)	0	<.001
Biologics	30 (56.6)	0	<.001

ACQ, Asthma Control Questionnaire; *ACT,* Asthma Control Test; *BMI,* body mass index; *GINA,* Global Initiative for Asthma; *IQR,* interquartile range; *LABA,* long-acting β_2-agonist; *LAMA,* long-acting muscarinic antagonist; *LLN,* lower limit of normal; *LTRA,* leukotriene receptor antagonist; *OCS,* oral corticosteroid; *SD,* standard deviation.

nonsevere asthma (Fig 1, *A*). This reduced sensitivity persisted at visit 2 (Fig 1, *B*). Of the 169 patients, 21 had exacerbations, 17 of whom had severe asthma. Moreover, steroid sensitivity at visit 1 was significantly lower in patients with exacerbations than in those without exacerbations (Fig 1, *A*), and this trend continued at visit 2 (Fig 1, *B*). At visit 1, 43.8% (74/169) of all patients experienced clinical remission, whereas only 20.8% (11/53) of patients with severe asthma experienced clinical remission. Patients in the nonremission group had significantly reduced steroid sensitivity compared with those in the remission group (Fig 1, *A*). At visit 2, 46.6% (75/161) of all patients and 23.1% (12/52) of patients with severe asthma experienced remission, with nonremission patients showing disease with significantly reduced steroid sensitivity (Fig 1, *B*).

Next, *TSC22D3* mRNA expression was evaluated as a marker of steroid sensitivity. Although *TSC22D3* mRNA expression induced by dexamethasone was lower in patients with severe asthma than in those with nonsevere asthma, the difference was not statistically significant (Fig 1, *C* and *D*). Similar trends were observed for other clinical outcomes, including exacerbation and remission (Fig 1, *C* and *D*). Consequently, only *FKBP5* expression was used as a marker of steroid sensitivity in subsequent studies.

Associations of clinical and molecular features with steroid sensitivity

The subjects were stratified by tertiles at visit 1 into high (≥66.67th percentile), medium (33.33-66.67th percentile), and low (<33.33rd percentile) steroid sensitivity groups according to their *FKPB5* induction levels. A comparison of the patient characteristics among the 3 groups is presented in Table E2 in the Online Repository at www.jaci-global.org. The prevalence of severe asthma was highest among patients in the low steroidal sensitivity group, with 24 (42.9%) of 56 patients exhibiting severe asthma. No significant differences were observed in the proportions of the high- and medium-sensitivity groups. Patients with low steroid sensitivity had a significantly greater risk of severe asthma, exacerbations, and failure to obtain clinical remission (Fig 2). This group was younger and had a higher NLR; however, no

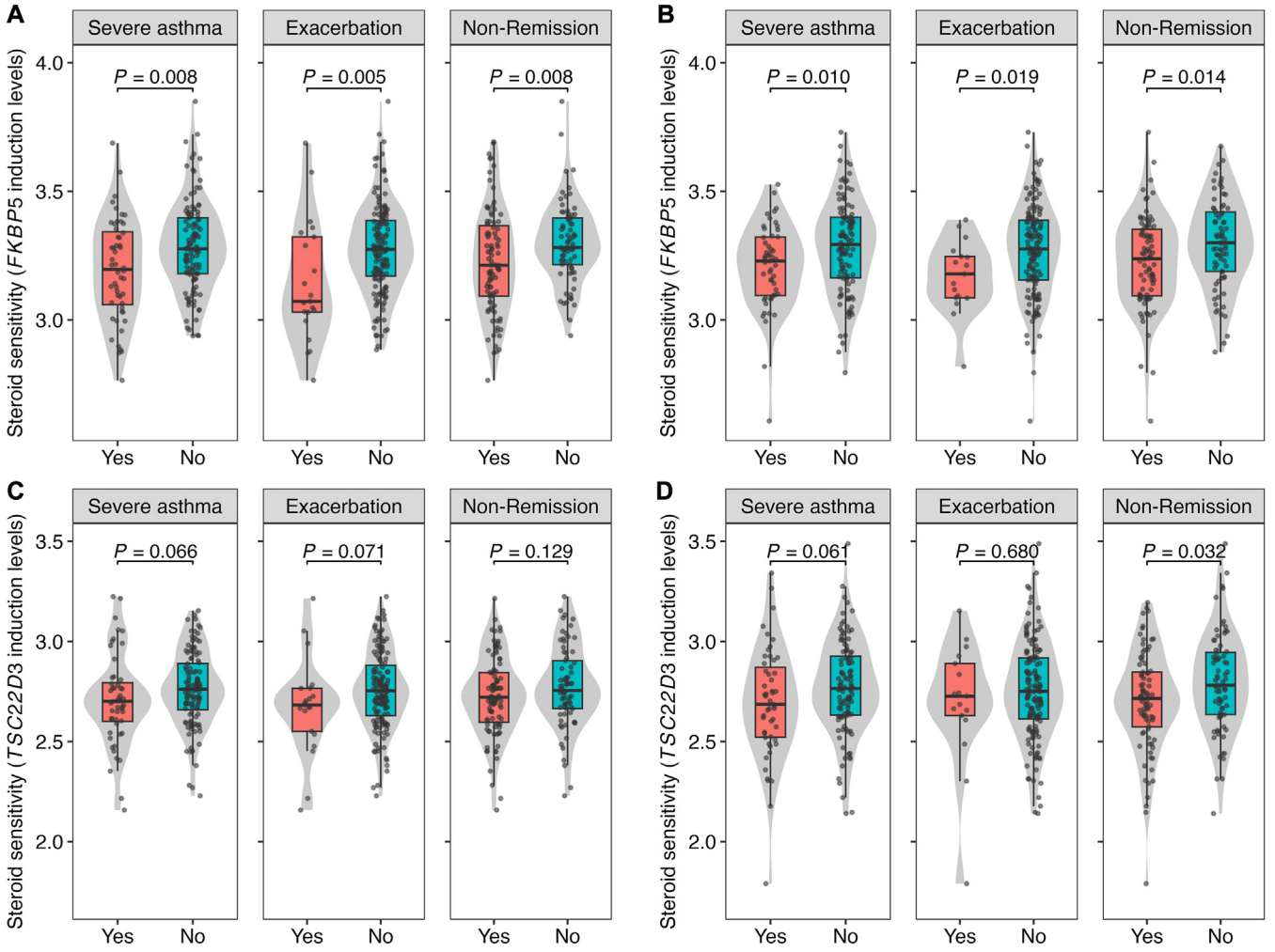

FIG 1. Associations of steroid sensitivity as reflected by *FKBP5* mRNA levels with severe asthma, asthma exacerbation, and clinical remission at beginning of study (visit 1) **(A)** and at 1-year follow-up (visit 2) **(B)**. Steroid sensitivity as reflected by *TSC22D3* mRNA levels at visit 1 **(C)** and visit 2 **(D)**. "Yes" classification is applicable to patients diagnosed with severe asthma, those who have experienced exacerbation, and those who have not experienced clinical remission. Steroid sensitivity was calculated as follows: $\log_2$(*FKBP5* or *TSC22D3* mRNA level in dexamethasone-treated well) − $\log_2$(*FKBP5* or *TSC22D3* mRNA level in control well).

associations were found with the eosinophil count or FENO level (Table E2). In addition, we evaluated the expression levels of epithelial cell–derived cytokine receptors and transcription factors involved in T-cell differentiation (Fig 3). In the low-sensitivity group, the expression levels of *IL7R* (CD127), the receptor for IL-7 and thymic stromal lymphopoietin (TSLP), were significantly increased. In addition, this group exhibited low expression of *TBX21,* a transcription factor for T_H1 cells, and high expression of *RORC,* a transcription factor for T_H17 cells. Similarly, in a comparative analysis of patients with severe and nonsevere asthma, the expression levels of *IL7R* and *RORC* were greater in the severe asthma group (see Fig E1 in the Online Repository).

Steroid sensitivity and inflammatory pathways

We evaluated the recovery of steroid sensitivity via the use of 3 inflammatory pathway inhibitors: PI3Kδ/γ, PI3Kδ, and p38 MAPK. Comparisons were made between patients with severe asthma and those with nonsevere asthma at visit 1 (Fig 4, *A*). The PI3Kδ/γ inhibitor greatly restored steroid sensitivity in patients with severe asthma. This finding was confirmed at visit 2, when steroid sensitivity recovered to a significantly greater extent in patients with severe asthma treated with the PI3Kδ/γ inhibitor (Fig 4, *B*).

Associations of clinical and molecular features with PI3K activation

We divided the subjects into 4 groups according to the median values of steroid sensitivity and recovery with the PI3Kδ/γ inhibitor at visit 1 (Fig 5, *A*) and compared their clinical characteristics (Table II). Group 4 (G4) had lower steroid sensitivity and greater recovery with the PI3Kδ/γ inhibitor, suggesting possibly reduced steroid sensitivity due to PI3Kδ/γ pathway activation. A comparison of G1 (high steroid sensitivity, low recovery) and

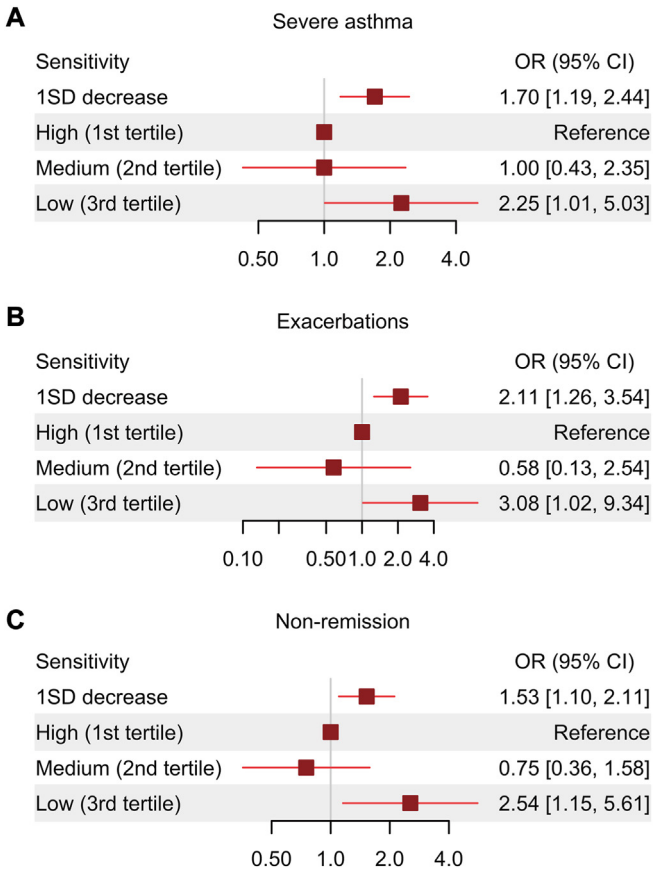

FIG 2. Forest plot of ORs of steroid sensitivity (based on *FKBP5* mRNA levels) for severe asthma **(A)**, exacerbation **(B)**, and clinical remission **(C)** at beginning of study (visit 1). Steroid sensitivity data were treated as continuous variable, and OR for 1 standard deviation (SD) decrease was calculated. Furthermore, OR for categorization of steroid sensitivity into tertiles was also calculated. *CI,* Confidence interval; *OR,* odds ratio.

G4 (low steroid sensitivity, high recovery) revealed that G4 patients had a greater incidence of severe asthma (Fig 5, *B*) and a higher NLR. In addition, the comparison of G3 (low steroid sensitivity, low recovery) and G4 revealed that G4 patients were older and had a trend toward an increased NLR. We also quantified the gene expression levels of molecules related to the PI3K pathway involved in the steroid response in PBMCs at the time of isolation. G4 patients presented decreased expression of *NR3C1,* which encodes the glucocorticoid receptor, and *HDAC2, PTEN, GLCCI1,* and *NFE2L2,* which are molecules downstream of PI3K (Fig 5, *C*). Conversely, G3 patients presented significantly increased expression of *IL7R* and *RORC* in T cells (see Fig E2 in the Online Repository at www.jaci-global.org).

DISCUSSION

The results of our study revealed that patients with severe asthma exhibited a reduction in steroid sensitivity. This diminished responsiveness was identified as a risk factor for unfavorable clinical outcomes, including exacerbations and an inability to obtain clinical remission. These associations were consistently observed across both the initial visit and the 1-year follow-up in this study. These findings suggest that steroid sensitivity may serve as a useful indicator of asthma severity and a predictor of prognosis. Furthermore, we investigated the role of inflammatory pathways in reducing steroid sensitivity. In patients with severe asthma, activation of the PI3Kδ/γ pathway contributes to reduced steroid sensitivity.

To our knowledge, this is the first study to show that poor asthma treatment control is correlated with reduced steroid sensitivity. The disease of patients with severe asthma exhibited diminished sensitivity to steroids. Obtaining treatment control in patients with severe asthma remains challenging despite high-dose ICSs,[17] potentially as a result of the presence of drug resistance.[11,19] Given the substantial patient sample size and 1-year follow-up, our findings provide valuable real-world evidence. Previous studies have examined the relationship between asthma severity and steroid responsiveness, using the suppression rate of PBMC-secreted inflammatory cytokines as indicators.[20,21] Although these studies had modest sample sizes, they consistently demonstrated reduced steroid responsiveness in patients with severe asthma, which was consistent with our findings. The precise causality remains uncertain; however, a clear link exists between asthma severity and reduced steroid responsiveness. Patients with severe asthma show increased inflammation, which may contribute to reduced steroid responsiveness. Conversely, reduced steroid responsiveness may lead to inadequate therapeutic effects, potentially exacerbating inflammation and worsening asthma. Further research is needed to elucidate whether enhancing steroid sensitivity can improve asthma prognosis and treatment efficacy.

We focused on clinical remission, which has recently been proposed as a treatment goal for patients with asthma.[22-26] Our results showed that disease of patients with reduced steroid sensitivity was more likely to not result in clinical remission. Patients who did not experience clinical remission had inadequate asthma control, necessitating treatment adjustments. In patients with steroid-insensitive disease, obtaining remission may not be feasible by simply increasing the steroid dose. Clinical assessment of steroid sensitivity is expected to allow early introduction of biological agents and obtain remission. In addition, our results suggest that reduced steroid sensitivity is an independent risk factor for asthma exacerbation. A recent study in children with asthma used *FKBP5* mRNA levels to indicate steroid sensitivity and reported an association between reduced sensitivity and low asthma control scores.[27] We believe that steroid sensitivity is a valuable marker for assessing asthma prognosis. However, the data of this study suggest that steroid sensitivity does not distinctly differ between patients with favorable outcomes and those with unfavorable outcomes. This is due to additional risk factors for severe asthma and poor prognosis, such as airflow limitation, obesity, and comorbidities, which are also associated with poor drug response.[28-30]

This study investigated the mechanisms underlying reduced steroid sensitivity in patients with severe asthma by specifically examining the PI3K and MAPK pathways. Our findings suggest that reduced steroid sensitivity in severe asthma is associated with the activation of the PI3K pathway, particularly the PI3Kδ/γ pathway, as demonstrated by the dual PI3Kδ/γ inhibitor duvelisib (IPI-145).[31,32] Our previous research also suggested that steroid sensitivity in patients with severe asthma treated with benralizumab may be impaired by activation of the PI3K pathway.[33] Bi et al analyzed PBMCs from 10 patients with severe asthma and evaluated TNF-α–induced IL-8 production via a MAPK inhibitor (BIRB796) and a PI3Kα/β/δ/γ inhibitor (BEZ235).[21] These results highlight the role of the PI3K pathway, rather than the

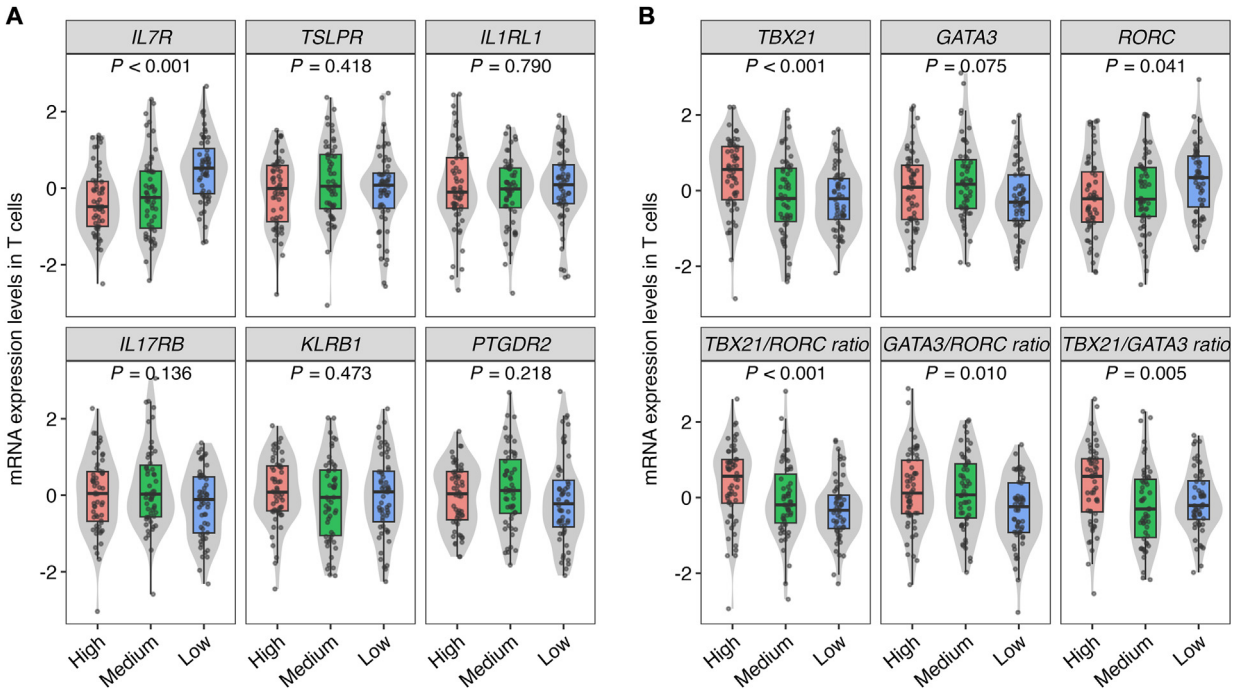

FIG 3. Comparison of gene expression levels in T cells when subjects were divided into 3 groups according to sensitivity tertile (based on *FKBP5* mRNA levels). **(A)** Association of steroid sensitivity with gene expression levels of epithelial cell–derived cytokine receptors and type 2 innate lymphoid cell (ILC2)-related cell surface markers. **(B)** Association between steroid sensitivity and gene expression levels of transcription factors involved in cell differentiation. Expression levels of each mRNA were expressed as $\log_2$-transformed values and normalized to mean value of zero.

MAPK pathway, in reducing steroid responsiveness. PI3Kδ and PI3Kγ are associated with the activities of eosinophils, dendritic cells, and T cells,[34,35] which contribute to asthmatic inflammation. A study on a dual PI3Kδ/γ inhibitor (AZD8154) in patients with asthma demonstrated that it effectively inhibited IL-5 and IL-17 release in PBMCs stimulated with anti-CD2/3/28, outperforming the effects of PI3Kδ or PI3Kγ inhibitors alone.[36] These findings suggest that both the PI3Kδ and -γ isoforms are critical in the pathophysiology of asthma. This may explain why idelalisib (CAL-101),[37] a PI3Kδ-selective inhibitor, did not restore steroid sensitivity in this study. In contrast, an evaluation using a PI3Kδ inhibitor demonstrated that IC87114 restored steroid responsiveness in a chronic obstructive pulmonary disease–like model. This finding was determined by measuring the inhibition of TNF-α–induced IL-8 production in monocyte-derived cultured cells exposed to cigarette smoke extract.[38] Similarly, when the same cultured cells were subjected to oxidative stress stimulation with H_2O_2, the PI3Kα/β/δ inhibitor LY294002 restored steroid responsiveness.[39] Activation of the PI3K pathway reduces the expression and function of key steroid response molecules such as HDAC2.[40] Steroids exert anti-inflammatory effects via HDAC2 by binding to the glucocorticoid receptor encoded by *NR3C1*.[12] PTEN inhibits PI3K pathway activation,[40] whereas GLCCI1 is involved in the steroid response.[41,42] The expression levels of these molecules are lower in patients with reduced steroid sensitivity because of activation of the PI3K pathway (G4), suggesting that activation of the PI3K pathway decreases their expression, thereby reducing steroid sensitivity. Although this study did not reveal a relationship between reduced steroid sensitivity and the MAPK pathway, previous studies have suggested its involvement.[12,43] Given the different asthma pathophysiologies that activate the PI3K and MAPK pathways, further research is needed to explore the relationships between inflammation and reduced steroid responsiveness.

This study revealed no associations between steroid sensitivity and markers of type 2 inflammation. However, steroid treatment is generally more effective in asthma patients with type 2 inflammation than in those without type 2 inflammation. In asthmatic patients not receiving ICSs, increases in FEV_1 were more significant in those with type 2 inflammation, as indicated by gene expression levels in airway epithelial cells.[44] Similarly, steroid-based anti-inflammatory treatment increased FEV_1 more significantly in patients with eosinophilic asthma, as indicated by the sputum eosinophil count.[45] However, another study of patients receiving continuous ICS treatment revealed that approximately half had persistent type 2 inflammation, as indicated by *IL4, IL5,* and *IL13* gene expression in sputum samples, and that these patients were older and had more severe symptoms.[46] It is reasonable to assume that in patients with asthma, which predominantly involves type 2 inflammation, resistance to steroid treatment develops concurrently with disease progression and worsening of symptoms. In contrast, our study revealed an association between reduced steroid sensitivity and an increased NLR. Recently, the NLR has been identified as a marker of inflammatory disease, with a high NLR being associated with poor prognosis[47] and asthma exacerbation.[48] Because the NLR reflects abnormal immunity and systemic inflammation, it may also be related to steroid responsiveness.

To understand the role of type 2 innate lymphoid cells and epithelial cytokines, the expression levels of cell surface markers

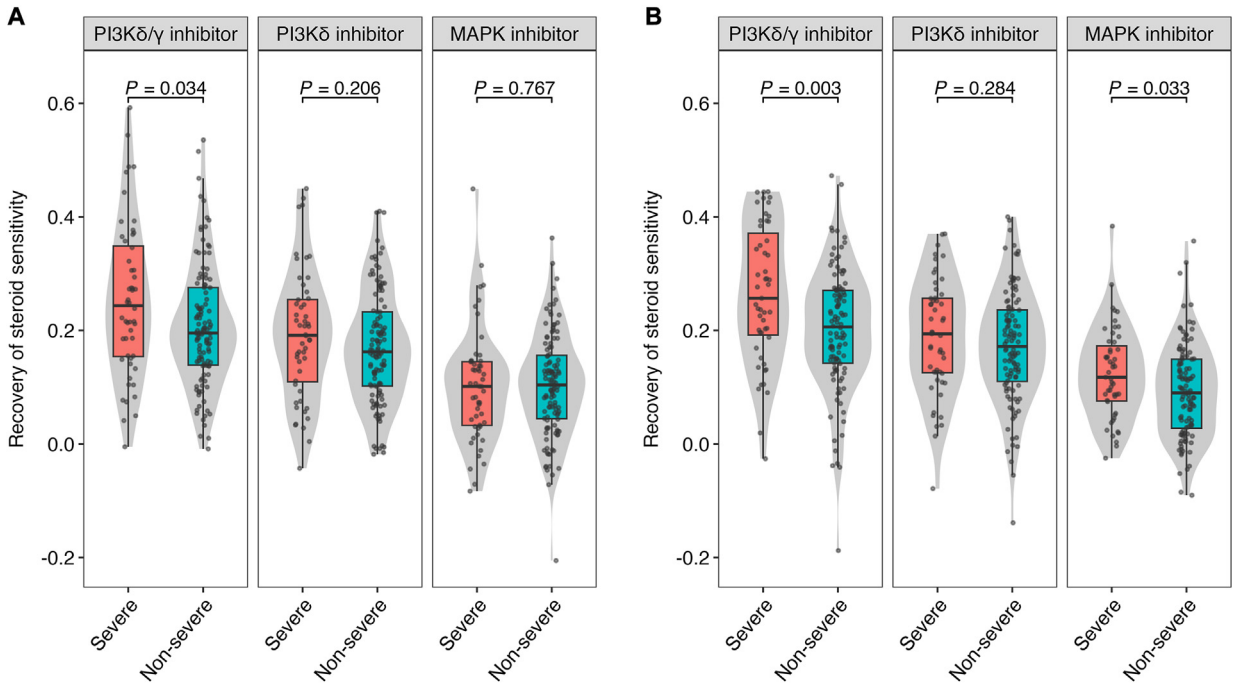

FIG 4. Associations between steroid sensitivity and inflammatory pathways in patients with severe asthma. Evaluation of recovery of steroid sensitivity when inflammatory pathway inhibitors were combined with dexamethasone, as assessed at beginning of study (visit 1) **(A)** and at 1-year follow-up (visit 2) **(B)**. Recovery of steroid sensitivity was determined by subtracting *FKBP5* induction level after treatment with dexamethasone alone from *FKBP5* induction level after cotreatment with inhibitor and dexamethasone. PI3Kδ/γ inhibitor (IPI-145, duvelisib), PI3Kδ inhibitor (CAL-101, idelalisib), and p38 MAPK inhibitor (BIRB796, doramapimod) were used. Recovery of steroid sensitivity was calculated as follows: $\log_2$(*FKBP5* mRNA level in inhibitor and dexamethasone cotreatment well) − $\log_2$(*FKBP5* mRNA level in dexamethasone-treated well).

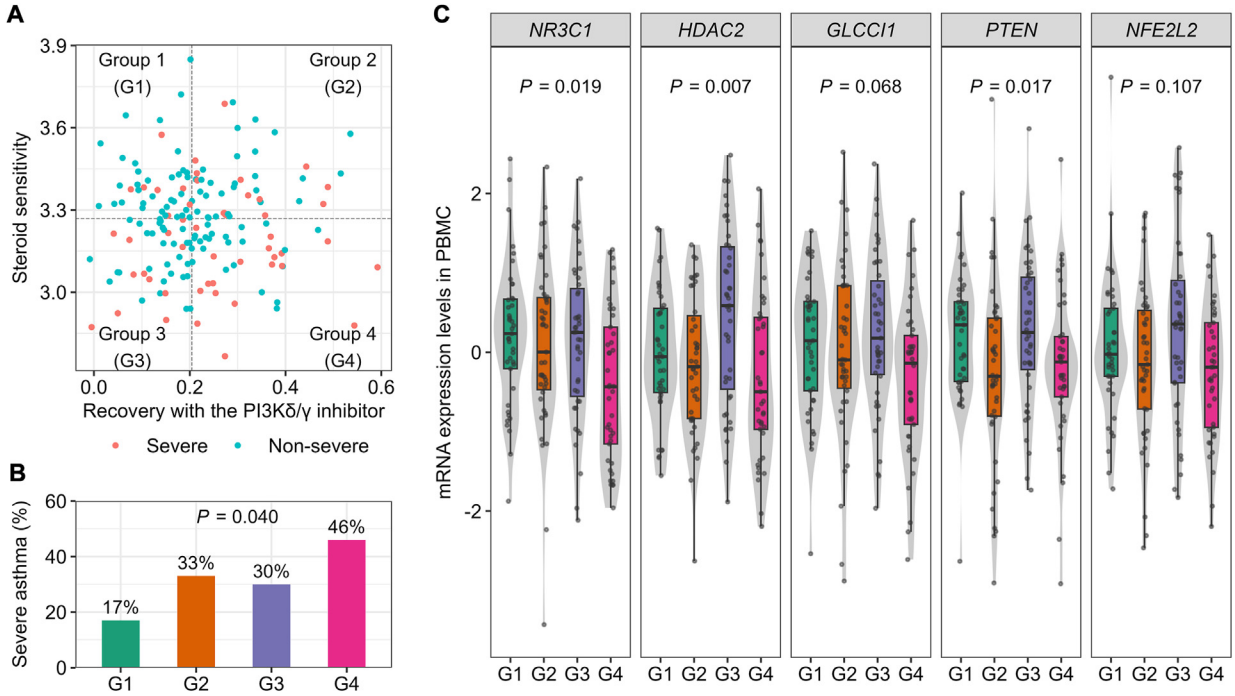

FIG 5. Molecular pathologic characteristics of reduced steroid sensitivity due to activation of PI3Kδ/γ pathway (based on *FKBP5* mRNA levels). **(A)** Subjects were divided into 4 groups (G1-G4) according to their median steroid sensitivity and median amount of recovery of steroid sensitivity with PI3Kδ/γ inhibitor (IPI-145, duvelisib). **(B)** Percentages of patients with severe asthma in 4 groups. **(C)** Comparison of gene expression levels of PI3K pathway–related molecules associated with steroid responsiveness in PBMCs among 4 groups.

TABLE II. Patient characteristics stratified into 4 groups according to median values of steroid sensitivity and recovery with PI3Kδ/γ inhibitor at visit 1

Characteristic	Group				*P* value
	G1	G2	G3	G4	
No. of patients	41	43	44	41	
Severe asthma, no. (%)	7 (17.1)	14 (32.6)	13 (29.5)	19 (46.3)	.040
Age (years), median (IQR)	71 (64, 76)	72 (62, 77)	58 (50, 72)	73 (59, 78)	.004
Sex, M/F (no.)	22/19	26/17	21/23	23/18	.694
BMI (kg/m^2), median (IQR)	23.6 (21.2, 26.3)	24.3 (21.1, 26.4)	23.6 (21.0, 25.9)	24.2 (20.9, 27.2)	.934
Current/ex-smoker (no.)	1/18	1/18	4/25	1/22	.305
Smoking pack years, median (IQR)	0.0 (0.0, 26.0)	0.0 (0.0, 23.0)	7.2 (0.0, 30.2)	5.5 (0.0, 41.0)	.378
GINA step 1/2/3/4/5 (no.)	4/0/5/28/4	1/3/2/29/8	1/3/1/31/8	2/1/1/21/16	.034
FENO (ppb), median (IQR)	33 (19, 54)	41 (25, 66)	29 (18, 45)	25 (18, 44)	.160
Total serum IgE (IU/mL), median (IQR)	160 (67, 367)	308 (146, 698)	220 (80, 609)	268 (57, 664)	.383
Peripheral blood cells (/μL), median (IQR)					
Neutrophil	3894 (3210, 5018)	3796 (3023, 4368)	4047 (3153, 5322)	3775 (2993, 4402)	.617
Lymphocyte	1836 (1319, 2345)	1627 (1265, 2104)	1638 (1463, 2175)	1326 (996, 1673)	.005
Monocyte	391 (300, 468)	360 (280, 414)	364 (276, 438)	339 (292, 446)	.911
Eosinophil	278 (139, 481)	240 (137, 420)	320 (160, 480)	189 (70, 324)	.076
Basophil	48 (31, 61)	50 (30, 62)	49 (33, 65)	38 (22, 50)	.038
NLR, median (IQR)	2.17 (1.68, 2.85)	2.48 (1.43, 3.10)	2.35 (1.86, 2.92)	3.00 (2.02, 3.63)	.061
FVC (L), median (IQR)	3.03 (2.38, 3.66)	2.99 (2.52, 3.51)	2.99 (2.68, 3.67)	2.82 (2.27, 3.39)	.549
FVC (% predicted), median (IQR)	99.5 (91.1, 111.4)	102.1 (93.7, 106.6)	99.9 (88.6, 114.4)	96.9 (83.7, 102.8)	.180
FVC (L) <LLN, no. (%)	4 (9.8)	6 (14.0)	7 (15.9)	9 (22.0)	.505
FEV_1 (L), median (IQR)	1.80 (1.52, 2.44)	2.09 (1.56, 2.62)	2.22 (1.77, 2.67)	1.72 (1.39, 2.45)	.111
FEV_1 (% predicted), median (IQR)	81.7 (67.0, 92.5)	94.5 (70.4, 101.6)	84.7 (71.2, 107.9)	77.9 (62.4, 93.3)	.258
FEV_1 (L) <LLN, no. (%)	21 (51.2)	13 (30.2)	15 (34.1)	20 (48.8)	.127
FEV_1/FVC, median (IQR)	65.0 (58.6, 71.2)	70.4 (56.3, 76.6)	72.3 (64.2, 79.4)	69.4 (59.3, 81.0)	.070
FEV_1/FVC <LLN, no. (%)	28 (68.3)	18 (41.9)	16 (36.4)	17 (41.5)	.015
ACT, mean (SD)	22.5 (2.9)	22.3 (4.1)	22.6 (3.8)	21.9 (3.4)	.774
ACQ, mean (SD)	0.7 (0.8)	0.7 (0.9)	0.5 (0.9)	0.7 (0.8)	.795
Exacerbation, no. (%)	4 (9.8)	3 (7.0)	7 (15.9)	7 (17.1)	.439
Clinical remission, no. (%)	19 (46.3)	26 (60.5)	18 (40.9)	11 (26.8)	.019
ICS dose (μg/d), median (IQR)	500 (500, 500)	500 (500, 500)	500 (500, 500)	500 (500, 1000)	.054
Medication, no. (%)					
ICS	37 (90.2)	42 (97.7)	42 (95.5)	38 (92.7)	.448
LABA	40 (97.6)	39 (90.7)	40 (90.9)	38 (92.7)	.596
LAMA	16 (39.0)	18 (41.9)	19 (43.2)	19 (46.3)	.928
LTRA	15 (36.6)	10 (23.3)	17 (38.6)	15 (36.6)	.397
Theophylline	2 (4.9)	2 (4.7)	4 (9.1)	4 (9.8)	.746
OCS	0	0	4 (9.1)	7 (17.1)	.001
Biologics	3 (7.3)	8 (18.6)	6 (13.6)	13 (31.7)	.033

ACQ, Asthma Control Questionnaire; *ACT,* Asthma Control Test; *BMI,* body mass index; *GINA,* Global Initiative for Asthma; *IQR,* interquartile range; *LABA,* long-acting β_2-agonist; *LAMA,* long-acting muscarinic antagonist; *LLN,* lower limit of normal; *LTRA,* leukotriene receptor antagonist; *OCS,* oral corticosteroid; *SD,* standard deviation.

and cytokine receptors in T cells were examined, with a focus on *TSLPR* and *IL7R* (the receptor for TSLP), *IL1RL1* (IL-33), and *IL17RB* (IL-25).[49] Our results indicate that increased *IL7R* expression is correlated with a reduced steroid response. IL7R is critical for T-cell differentiation and proliferation.[50] Genetic polymorphisms in the *IL7R* gene are associated with an increased risk of asthma,[51] suggesting an important role in asthma-related inflammation.[52] Transcription factors associated with T-cell differentiation were also measured. *RORC,* which is associated with T_H17 differentiation, was elevated in patients with low steroid responsiveness, particularly those with disease that did not respond to a PI3Kδ/γ inhibitor (G3). Previous studies have shown that T_H17 inflammation contributes to steroid resistance in non–type 2 inflammatory conditions.[8] These findings suggest that T_H17 inflammation may cause steroid resistance through a mechanism independent of PI3K pathway activation.

To determine steroid sensitivity, we examined the mRNA levels of *FKBP5* and *TSC22D3,* which are known to be induced by steroids.[53,54] After 24 hours of incubation, the expression of both genes increased in response to dexamethasone. *FKBP5* upregulation was associated with clinical outcomes, whereas a trend toward an association with *TSC22D3* upregulation was observed, although this difference was not statistically significant. *FKBP5* and *TSC22D3* are upregulated by steroids in immune and airway epithelial cells, with *FKBP5* being more consistently upregulated across cell types.[54] Because *FKBP5* expression is completely suppressed by glucocorticoid receptor–specific antagonists,[55] it may serve as a more sensitive indicator of steroid responses via the glucocorticoid receptor. Conversely, glucocorticoid-induced leucine zipper (GILZ), encoded by *TSC22D3,* exerts anti-inflammatory effects by influencing several signaling pathways, including NF-κB, AP-1, Ras, and Raf.[56] Additionally, GILZ plays a regulatory role in cell survival and death. In the absence of IL-2, a cytokine crucial for T-cell activation, GILZ expression was induced, resulting in delayed T-cell apoptosis. Conversely, T-cell activation suppressed GILZ expression via IL-2

production.[56] Consequently, GILZ expression is regulated not only by corticosteroids but also by inflammatory conditions and various circulating factors, including cytokines, which complicates the assessment of steroid responsiveness.

This study has several limitations. First, as a single-center observational study, its results, validated by 2 visits including a 1-year follow-up, require replication in different patient cohorts. Second, although steroid sensitivity was assessed *ex vivo* in patient PBMCs, further investigation is needed to confirm consistency with steroid treatment efficacy. Finally, the study period coincided with the coronavirus disease 2019 pandemic, and its impact on the results remains unclear.

In conclusion, our results revealed a correlation between decreased steroid sensitivity and severe asthma as well as poor clinical outcomes. Furthermore, we discovered that the reduced steroid sensitivity observed in severe asthma is due to the activation of the PI3K pathway, specifically the PI3Kδ/γ pathway, which affects the expression of steroid-responsive molecules downstream of PI3K, such as HDAC2, and consequently reduces steroid sensitivity. Measurement of steroid sensitivity appears to be useful for assessing the severity of asthma and determining appropriate pharmacologic interventions. In addition, inhibiting the activation of the PI3K pathway may represent a novel therapeutic strategy to preserve steroid sensitivity in patients with asthma.

DISCLOSURE STATEMENT

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Key messages

- **Patients with severe asthma demonstrated a decline in steroid sensitivity, as evidenced by a reduction in dexamethasone-induced *FKBP5* expression in their PBMCs.**
- **Reduced steroid sensitivity was identified as a risk factor for failure to obtain clinical remission and exacerbation.**
- **In patients with severe asthma, inhibition of the PI3Kδ/γ pathway significantly improved steroid sensitivity.**

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