SCIENTIFIC Publishing Limited

ENT Updates

https://ojs.ukscip.com/index.php/ENTU

Review

Efficacy and Safety of Roflumilast in Asthma Management: A Systematic Review and Meta-Analysis

Musaad Alruwaili [1,*], Rakan Fahad Alamer [2], Raneem Ahmed [3], Hajar Alanzi [4], Rahaf Alsabhan [4], Faisal Alhamzani [4], Hanadi Alrashidi [5], Ryam Alanzi [4], Emtenan Alshammari [4], Nada Alshammari [4], Mnsorha Alrashidi [6], Hmoud Al-Humian [4], Noura Alsaeed [4], Rimas Fawaz Aljohani [4] **and** Ruba Ahmed [3]

[1] Pharmaceutical Care Department, Turaif General Hospital, Northern Borders Health Cluster, Turaif 75311, Saudi Arabia

[2] Pharmacist, King Salman Specialist Hospital, Hail 55471, Saudi Arabia

[3] Department of Pharmacy, College of Pharmacy, Jazan University, Jazan 45142, Saudi Arabia

[4] Department of Doctor of Pharmacy, College of Pharmacy, University of Hail, Hail 55476, Saudi Arabia

[5] Department of Pharmacy, College of Pharmacy, University of Hail, Hail 55476, Saudi Arabia

[6] Department of Nursing, PHC Aljmeen, Hail Health Cluster, Hail 55471, Saudi Arabia

[*] Correspondence: Muayalruwaili@moh.gov.sa

Received: 30 September 2025; **Revised:** 8 December 2025; **Accepted:** 19 December 2025; **Published:** 29 December 2025

Abstract: Asthma is a chronic respiratory condition affecting millions globally, causing significant morbidity and economic burden. Despite advances in treatment, many patients experience uncontrolled symptoms and exacerbations, particularly those with corticosteroid resistance or neutrophilic inflammation. Roflumilast, an oral phosphodiesterase-4 inhibitor, may offer additional benefits by targeting inflammatory pathways that are not fully controlled by standard therapy. This systematic review and meta-analysis aimed to assess the efficacy and safety of roflumilast in patients with asthma. A comprehensive literature search was conducted using the PubMed, Scopus, and Web of Science databases from January 2015 to August 2025. We included randomized controlled trials and pooled analyses evaluating roflumilast in patients with asthma. The primary outcome was the mean difference in the forced expiratory volume in one second between the intervention and control groups. Secondary outcomes included risk of exacerbation, symptom control, and adverse events. Six studies met the inclusion criteria, with 2845 participants. Roflumilast showed a modest improvement in forced expiratory volume in one second (Mean difference: +0.04 L; 95% confidence interval: −0.01 to +0.09; heterogeneity = 41%), which was not statistically significant. Exacerbation risk reduction was inconsistent across studies (Risk ratio: 0.96; 95% confidence interval: 0.83–1.12; heterogeneity = 35%). Adverse events, particularly gastrointestinal issues and weight loss, were more frequent with roflumilast, leading to higher rates of discontinuation. Subgroup analysis suggested potential benefits in patients with persistent airway inflammation or corticosteroid resistance, whereas harm was observed in obese patients. The limited number of trials and heterogeneity among studies restricted the conclusiveness of our findings.

Keywords: Asthma; Inflammation; Corticosteroids; Roflumilast; Lung Function; Exacerbations

1. Introduction

Asthma is one of the most prevalent chronic respiratory conditions globally, affecting 300 million individuals across age groups and regions. Its chronic nature presents ongoing health challenges, with symptoms such as wheezing, coughing, chest tightness, and shortness of breath. These symptoms impair lung function and diminish patients' quality of life (QoL), restricting their daily activities, education, and work productivity [1,2].

Worldwide, asthma causes significant morbidity, leading to millions of emergency visits, hospitalizations, and preventable fatalities annually. Data reveal prevalence variations across regions and populations, with higher rates in wealthier nations and disproportionate effects on certain racial and ethnic groups, highlighting structural, environmental, and healthcare access factors [2]. The impact of asthma extends beyond clinical outcomes, imposing a substantial economic burden through direct healthcare costs (medications, hospitalizations, and doctor visits) and indirect costs (absenteeism, reduced work capacity, and caregiver burden). United States estimates indicated billions in costs, driven by emergency care and hospitalizations [3], and projections suggest that uncontrolled asthma will incur $300.6 billion in indirect costs and nearly $1 trillion in total economic burden over two decades, with significant quality-adjusted life years losses [4].

Asthma primarily affects the airways through structural and functional changes in the respiratory tract. The nose, paranasal sinuses, pharynx, and larynx connect to the bronchial tree via shared mucosal and immune pathways, explaining the occurrence of rhinitis, sinusitis, and asthma as a unified airway disease spectrum [5]. In asthma, anatomical remodeling includes bronchial smooth muscle enlargement, subepithelial fibrosis, mucosal swelling, and increased blood vessel formation, which narrow the airways and enhance hyperresponsiveness. From an otorhinolaryngological perspective, nasal blockage and chronic rhinosinusitis worsen lower airway inflammation through postnasal drainage and neural reflexes [6]. Structural changes in the lower airways, including epithelial damage, extracellular matrix buildup, and smooth muscle growth, contribute to persistent airflow limitation and reduced therapeutic response in chronic asthma [7].

Asthma management uses a stepwise approach based on phenotypes to control inflammation and prevent exacerbations. Core treatments include inhaled corticosteroids (ICS), with long-acting β2-agonists (LABAs) and leukotriene receptor antagonists (LTRAs). Targeted biologics are the standard treatment for severe cases. While these therapies have improved outcomes, their effectiveness is limited by endotypes, adherence issues, and access barriers [8,9].

ICS is the primary treatment for persistent asthma, reducing airway inflammation and exacerbations. Daily maintenance ICS is recommended for adults, with additional therapies added when the control is insufficient [8]. Patients with non-type 2 (Th2/ILC2) or neutrophilic inflammation show poor response to ICS [8]. High-dose ICS and oral CS (OCS) bursts pose risks such as osteoporosis, adrenal suppression, and infections. Biologics can reduce OCS exposure in patients with severe eosinophilic asthma [8,10]. Poor adherence can reduce ICS effectiveness [8].

LABAs provide bronchodilation and, with ICS, enhance symptom control in patients who do not respond to ICS alone; however, LABA monotherapy is not recommended [8,11]. LABAs do not address airway inflammation, and some patients may experience exacerbations with ICS/LABA combinations [8]. Research shows no increase in asthma-related hospitalizations with ICS/LABA combinations in adults and no inferiority in serious events in children using fixed-dose fluticasone–salmeterol versus fluticasone alone [11,12]. For children requiring escalation from low-dose ICS, adding LABA often showed the best response, although many responded better to increased ICS dose or LTRA [13].

LTRAs, like montelukast, reduce bronchoconstriction and inflammation caused by leukotrienes. They serve as alternatives when patients cannot tolerate higher ICS doses and as additional therapy for concurrent allergic rhinitis [8]. While ICS shows superiority for persistent asthma, LTRAs may match ICS and LABA effectiveness over 2 months but not 2 years [14]. Neuropsychiatric side effects limit their use, and LTRAs partially control severe asthma [8,14].

Biologics target inflammatory pathways: anti-IgE (omalizumab) reduces exacerbations [8,15]. Anti–IL-5/IL-5R agents target eosinophilic phenotypes, reducing exacerbations and OCS requirements. Mepolizumab shows a 50% reduction in OCS dosage versus placebo [8,11]. Anti–IL-4Rα (dupilumab) improves lung function; in children aged 6–11 years with Th2 phenotype, it decreased severe exacerbations by 59% [16]. Anti-TSLP (tezepelumab) reduces exacerbations in severe asthma [17]. Cost and biomarker testing limit adoption in low-income regions [8,15,17].

Most biologics target Th2–high disease [8,17]. Further research is needed to determine the optimal sequencing and disease-modifying potential of these drugs.

Asthma is a respiratory condition characterized by airflow blockage, bronchial sensitivity, and inflammation. This chronic inflammatory process involves interactions between airway cells (epithelial cells, smooth muscle, and fibroblasts) and immune cells (eosinophils, neutrophils, mast cells, macrophages, and T lymphocytes), causing structural changes. Mast cell infiltration into airway smooth muscle impairs function and differentiates asthma from eosinophilic bronchitis [1]. Inflammation causes recurrent symptoms and airway dysfunction.

In asthma, immune and inflammatory cells release mediators that trigger airway hyperresponsiveness (AHR), involving bronchoconstrictor reactions to allergens, viruses, and pollutants, intensified by epithelial damage and inflammasome-derived IL-1β in neutrophilic disease [1,2]. They cause matrix deposition, goblet cell hyperplasia and smooth muscle hypertrophy. Phosphodiesterase-4 (PDE-4) inhibition reduces fibroblast proliferation and collagen synthesis, indicating an inflammatory-structural interaction [3]. Chronic inflammation is associated with asthma phenotypes, including eosinophilic and neutrophilic subtypes.

Eosinophil infiltration, driven by Th2/ILC2 cytokines like IL-4, IL-5, and IL-13, is prevalent, with atopy, increased IgE levels, and CS responsiveness. Eosinophils release cytotoxic proteins, leukotrienes, and chemokines, which harm the epithelium and sustain hyperreactivity. While eosinophilia alone does not define AHR, asthma involves the specific localization of effector cells with smooth muscle. Mast cell infiltration in airway smooth muscle correlates with bronchoconstriction and AHR, even when eosinophilic bronchitis presents with submucosal eosinophilia without AHR [1]. This phenotype is characterized by mucus production and nighttime symptoms, with exacerbations triggered by respiratory viruses. Virus-inducible cytokines enhance eosinophil and Th2 cell recruitment, which is mitigated by phosphodiesterase 4 (PDE4) inhibition [4]. Neutrophil infiltration is linked to Th1/Th17 and innate immune pathways. An IL-1β endotype driven by NLR family pyrin domain-containing 3 (NLRP3) inflammasome activation correlates with neutrophilic asthma and increased IL-8 levels [2]. This occurs in severe, non-allergic, and steroid-resistant asthma. Environmental factors promote neutrophilia, and smoke exposure causes CS-insensitive features, with PDE-4 inhibition reducing neutrophilia [18]. Neutrophil-derived substances contribute to epithelial damage and AHR. Variations in toll-like receptor 4 expression in neutrophils suggest innate immune dysregulation, which affects infection-related exacerbations [19]. The cellular pattern and microlocalization of inflammation help define asthma phenotypes and outcomes [1,2,19].

PDE-4 is an enzyme that targets cyclic adenosine monophosphate (cAMP) in inflammatory cells, such as eosinophils, neutrophils, macrophages, T lymphocytes, and structural airway cells, including epithelium, fibroblasts, and smooth muscle. By breaking down cAMP, PDE-4 diminishes intracellular signaling and promotes proinflammatory activities. Inhibition of PDE4 raises cAMP levels, leading to anti-inflammatory effects, including suppression of tumor necrosis factor-alpha (TNF-α), Interleukin-8/CXCL8 (IL-8), and virus-inducible chemokines. Inhaled candidates, such as CHF6001, show potent sub-nanomolar activity in vitro [4, 20]. PDE-4 activity enhances nuclear factor kappa B and MAPK-driven transcription of proinflammatory mediators. PDE4 inhibitors decrease these outputs in bronchial epithelial and monocytic/macrophage models [4, 20]. PDE4 inhibition reduces neutrophil recruitment in inflammation models [18,20]. PDE4 activity maintains eosinophil activation, and inhibitors suppress this at picomolar concentrations [20]. In neutrophils, PDE4 supports chemotaxis, and its inhibition reduces neutrophil influx [2,18]. In monocytes/macrophages and T cells, PDE4 inhibition decreases TNF-α release [4, 20]. PDE-4 enhances smooth muscle hyperreactivity in asthma AHR [1, 20]. The active metabolite of roflumilast reduces oxidative stress and fibroblast activity [3]. In neonatal lung injury models, PDE-4 inhibition improves survival and reduces inflammation [21].

Roflumilast is an oral medication that selectively inhibits PDE-4 and is approved for patients with severe chronic obstructive pulmonary disease (COPD), chronic bronchitis, and frequent exacerbations. By blocking PDE-4, present in inflammatory and structural airway cells, roflumilast increases intracellular cAMP levels, leading to the suppression of inflammatory pathways associated with airflow obstruction and exacerbations. In clinical settings, roflumilast decreases severe COPD exacerbations requiring hospitalization, demonstrating its anti-inflammatory benefits [22]. The biological relevance of the PDE-4 pathway extends to various airway disorders, supporting the investigation of roflumilast beyond COPD, including steroid-resistant or neutrophilic asthma subtypes [2,18].

Roflumilast exerts anti-inflammatory effects by targeting innate and adaptive pathways in chronic airway diseases. It inhibits cytokines such as TNF-α and IL-6 and chemokines such as IL-8 for neutrophil recruitment. By

inhibiting PDE-4, TNF-α release and virus-induced epithelial cytokines are reduced across the PDE-4 class [3,4]. In patients with COPD, these effects reduce severe exacerbations requiring hospitalization [22]. PDE-4 inhibition increases cAMP levels, limiting eosinophil activation and reducing epithelial damage and mucus overproduction. In chronic allergen-induced asthma models, roflumilast decreases airway eosinophilia and Th2 cytokines, improving airway hyperresponsiveness [23]. Neutrophilic inflammation involves NLRP3/IL-1β–IL-8 pathways, showing CS insensitivity [2]. PDE-4 inhibition reduces neutrophil chemotaxis in smoke- and lipopolysaccharide-induced inflammation [18]. Changes in neutrophil toll-like receptor 4 expression in non-eosinophilic asthma indicate PDE-4 modulation targets [19]. Roflumilast metabolites reduce oxidative stress and inhibit lung fibroblast proliferation [3]. In chronic murine asthma, roflumilast reduces Th2 cytokines and airway hyperresponsiveness [23]. PDE-4 class data show reduced inflammatory cell influx [21].

CS remain central to asthma treatment; however, groups with severe disease, resistance, or neutrophilic inflammation respond poorly to conventional therapies. These phenotypes involve mast cell-smooth muscle interactions, causing hyperresponsiveness, type-2 cytokine loops, and a neutrophilic endotype linked to IL-1β/NLRP3, intersecting with PDE-4 pathways [1,2]. PDE-4 inhibition provides anti-inflammatory effects by suppressing cytokine networks not controlled by CS, including virus-inducible mediators linked to exacerbations [4]. In steroid-refractory or neutrophilic asthma, PDE-4 targeting reduces neutrophil recruitment and inflammasome circuits, causing airway damage [2,18]. Roflumilast may slow airway remodeling, which maintains hyperresponsiveness in chronic diseases [3,23]. These findings support the investigation of roflumilast as an adjunctive treatment in challenging asthma cases, particularly neutrophilic or CS-resistant phenotypes, given its effectiveness against COPD exacerbations.

Studies in uncontrolled asthma show forced expired volume in 1 second (FEV_1) improvements consistent with PDE-4–driven reductions in airway inflammation, with the strongest effects when combined with ICS or in patients with COPD-asthma overlap. These findings align with established COPD benefits, where PDE-4 inhibition enhances outcomes [4,22,23]. Trials have reported improved symptom scores, quality of life, and reduced rescue bronchodilator use, consistent with epithelial cytokine network attenuation [4,23]. Studies have shown fewer exacerbations with roflumilast as an add-on therapy, aligning with the effects of COPD and suppression of virus-inducible chemokines [4,22]. The benefits appear to be greater in patients with persistent inflammation. Some studies have shown significant improvements in FEV_1, symptoms, and exacerbation rates, whereas others have reported modest effects in unselected populations. This reflects the biological diversity of asthma and the differential relevance of the PDE-4 pathway across phenotypes [2,4,23]. Reductions in neutrophil recruitment suggest that neutrophilic or CS-refractory asthma may benefit more [2,4,18].

Evidence suggests that roflumilast can improve lung function, symptoms, and exacerbations in certain patients with asthma, aligning with mechanistic evidence for PDE-4 pathway relevance [3,4,23]. However, mixed efficacy highlights the need for phenotype-stratified evaluation to identify responders, particularly those with CS resistance or frequent virus-driven exacerbations [2,4,18].

Given the current treatment limitations, especially for CS-resistant and neutrophilic asthma, targeting PDE-4 offers a strategy that addresses inflammatory pathways not managed by standard therapy. These gaps in asthma care justify the exploration of PDE-4 inhibition, as roflumilast may influence both Th2–independent and virus-triggered inflammatory reactions.

Despite progress in ICS, LABAs, and biologics, many asthma patients face uncontrolled symptoms and reduced lung function. This treatment gap is notable in CS-resistant and neutrophilic inflammation phenotypes, where standard treatments often fail. Roflumilast, a selective PDE-4 inhibitor effective in COPD, works by suppressing cytokines, decreasing eosinophil and neutrophil activity, and curbing airway remodeling. This study aimed to assess how roflumilast can improve lung function, reduce exacerbations, and enhance outcomes in patients with asthma, particularly those with CS resistance or ongoing inflammation.

2. Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines to ensure methodological clarity and reproducibility (**Supplementary Materials**) [24]. A literature search was performed using three databases, PubMed, Scopus, and Web of Science, covering publications from January 2015 to August 2025. The literature search was designed to be comprehensive

and sensitive. Medical Subject Headings and free-text keywords associated with roflumilast, phosphodiesterase-4 inhibition, and asthma were used. This strategy ensured the inclusion of studies cataloged under controlled vocabulary terms and those identified by author-chosen keywords, optimizing the retrieval of pertinent clinical trials and observational studies. The reference lists of selected articles and recent reviews were examined to identify additional relevant studies that were missed in the electronic search.

The PICO framework guided the study selection. The study population included patients diagnosed with asthma by physicians. The intervention involved roflumilast administration alone or in combination with existing treatments. The comparators included placebo, standard care, and active controls. The primary outcomes assessed were lung function changes, exacerbation frequency, symptom management, airway inflammation biomarkers, and safety profiles.

The selection process consisted of two stages. Initially, duplicate entries were eliminated, followed by a review of the titles and abstracts for relevance by two independent reviewers. Articles that met the inclusion criteria underwent full-text review. Eligible studies included those with physician-diagnosed asthma patients, regardless of phenotype or severity, and assessed the impact of oral roflumilast alone or in combination with standard treatments, such as ICS, LABAs, or LTRAs. Both randomized controlled trials (RCTs) and pooled analyses from programmatic clinical studies were included if they reported clinically significant outcomes, such as changes in lung function (measured by FEV_1), exacerbation frequency, symptom management, inflammatory biomarkers, or safety profiles. Non-human studies, case reports, narrative reviews, and trials focusing solely on roflumilast in COPD populations were excluded. Disagreements regarding study selection were resolved through discussion and consensus.

Information from the qualifying studies was systematically gathered in a uniform format. The collected variables included study design, publication year, participant numbers, patient demographics, asthma type, intervention details (dosage and duration of roflumilast treatment, concurrent medications), comparison groups and reported outcomes. Data on effectiveness and safety, such as adverse event frequency and treatment discontinuation rates, were included. When multiple publications were obtained from the same trial, the most detailed report was selected.

Two reviewers independently extracted the data using a standardized template to ensure thoroughness. The collected information included study characteristics (author, year, design, sample size), patient demographics (age, sex, asthma phenotype, baseline severity), intervention details (roflumilast dosage, treatment duration, use alone or as an add-on therapy), and comparator groups (placebo or standard treatments such as ICS, LABA, or montelukast). Data on clinical outcomes, including spirometric indices (FEV_1), exacerbation frequency, symptom control, inflammatory biomarkers, and adverse events, were systematically documented.

EndNote was used for reference management and deduplication, after which the citations were organized for screening. Data accuracy was verified by both reviewers, with discrepancies resolved through discussion and, if necessary, arbitration by a third investigator.

The primary outcome was the mean difference in FEV_1 between the intervention and control groups. The secondary outcomes included the relative risks of asthma exacerbations, improvements in clinical symptoms, and incidence of treatment-related adverse events. These outcomes assessed both efficacy and safety, providing a comprehensive evaluation of the therapeutic potential of roflumilast in asthma management.

The quality of the studies was meticulously assessed. For RCTs, the revised Cochrane Risk of Bias tool (RoB 2.0) was used to evaluate potential issues in randomization, blinding, data completeness, and selective reporting. The Newcastle–Ottawa Scale was used for pooled analyses and mechanistic clinical studies. Two reviewers independently conducted risk-of-bias assessments to reduce the subjectivity.

When outcomes were reported in multiple studies with similar definitions, the data were quantitatively pooled. Changes in lung function were analyzed as mean differences in FEV_1 with 95% confidence intervals (CIs), and exacerbation rates and safety outcomes were presented as risk ratios (RRs). A random-effects model was used to address heterogeneity across populations and study designs. Statistical inconsistency was assessed using the I^2 statistic, with values > 50% indicating moderate-to-high heterogeneity. Publication bias was investigated using funnel plots and Egger's regression tests. Tools such as Review Manager (RevMan) 5.4 and GraphPad Prism facilitated the creation of forest plots, risk of bias graphs, and funnel plots to enhance the presentation of the findings.

3. Results

Database searches in PubMed, Scopus, and the Web of Science yielded 114 records. After removing 36 duplicates, 78 records remained for further screening. Following the title and abstract review, 58 studies were dismissed. Of the 20 full texts evaluated, 14 were excluded due to insufficient data (12) or missing roflumilast efficacy outcomes (two). Six studies met the inclusion criteria and were included in the systematic review and meta-analysis [25–30]. **Figure 1** presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart detailing the study-selection process.

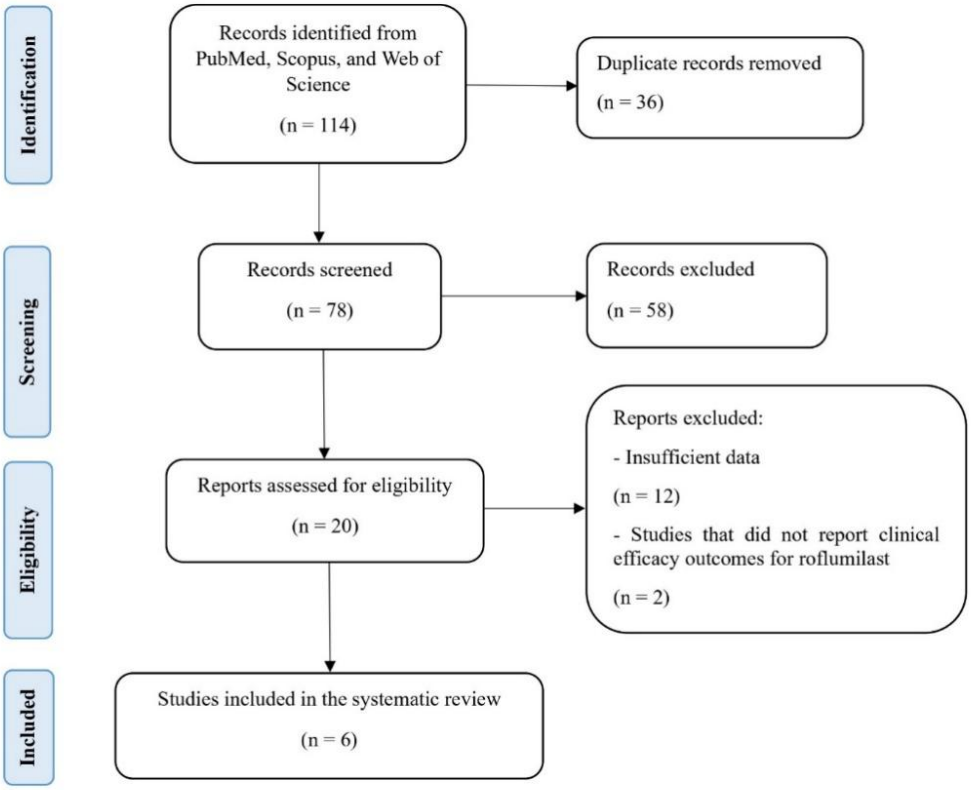

Figure 1. PRISMA flow diagram of the literature search and study selection for the systematic review.

Table 1 summarizes the characteristics of the six studies included [25–30]. Three studies from 2015 (Meltzer et al., Bateman et al., and Bardin et al.) derived from programmatic clinical trial data, focused on efficacy outcomes, dose–response relationships, and mechanistic pathways of roflumilast in asthma treatment [25–27]. Chervinsky et al. conducted a safety analysis by combining data from ten clinical studies that examined adverse events and treatment discontinuations [30]. A randomized, double-blind trial by Bateman et al. assessed roflumilast with montelukast and showed improvements in FEV_1, symptoms, and reduced exacerbations [28]. A recent RCT involving obese patients by Dixon et al. found no improvement in lung function and noted increased exacerbations [29]. These studies involved adults with moderate-to-severe or poorly controlled asthma, with interventions including roflumilast 500 µg once daily, alone or as an add-on therapy. The reported outcomes included spirometric indices, exacerbation rates, symptom control, inflammatory biomarkers, and safety endpoints, offering a diverse yet complementary evidence base.

The studies showed varying methodological qualities (**Figure 2**). The RCT by Bateman et al. had a low risk of bias across all domains, with appropriate randomization, blinding, and outcome reporting [28]. Dixon et al. was well-structured but showed high risk due to inconsistencies in exacerbation definitions and phenotype-specific effects [29]. Studies by Meltzer et al., Bateman et al., and Bardin et al. provided pooled insights rather than trial-level

analyses, resulting in moderate risk ratings [25–27]. The pooled safety analysis by Chervinsky et al. received a moderate risk rating due to selective reporting [30]. Overall, the evidence base demonstrates moderate methodological quality, with high confidence in Bateman et al., but less certainty in pooled analyses [28].

Table 1. Characteristics of included studies on evaluating the efficacy and safety of roflumilast in asthma.

Author (Year)	Study Design	Population	Intervention	Comparator	Main Outcomes	Key Findings
Meltzer et al. [25]	Pooled analysis of placebo-controlled RCTs	Adults with persistent asthma	Roflumilast 500 µg daily	Placebo	FEV_1, symptoms, rescue use, exacerbations	Modest improvements in lung function and symptoms; trend toward fewer exacerbations.
Bateman et al. [26]	Comparator and dosing studies	Adults with moderate-to-severe asthma	Roflumilast (dose-ranging)	Active comparators	FEV_1, clinical control, exacerbations	Dose–response signal; modest lung function benefit; reduced exacerbations in some arms.
Bardin et al. [27]	Mechanistic trials	Adults with asthma, research setting	Roflumilast 500 µg daily	Placebo	Airway hyperresponsiveness, inflammatory biomarkers	Improved airway responsiveness; reductions in inflammatory mediators.
Bateman et al. [28]	Randomized, double-blind RCT (24 weeks)	Moderate-to-severe asthma on montelukast	Roflumilast + montelukast	Montelukast alone	FEV_1, symptom scores, exacerbations	Significant FEV_1 improvement; reduced exacerbations; better symptom control.
Dixon et al. [29]	Randomized, placebo-controlled RCT	Obese adults with poorly controlled asthma	Roflumilast add-on	Placebo/usual care	Exacerbation rate, lung function	Increased exacerbations in obese asthma; no improvement in FEV_1.
Chervinsky et al. [30]	Pooled safety analysis (10 trials)	Adults with asthma from multiple studies	Roflumilast (various regimens)	Placebo/standard therapy	Adverse events, discontinuations, exacerbations	GI side effects, weight loss, and discontinuations are more common; no new safety signals.

Notes: RCTs, Randomized Controlled Trials; FEV_1, forced expired volume in 1 s; GI, gastrointestinal.

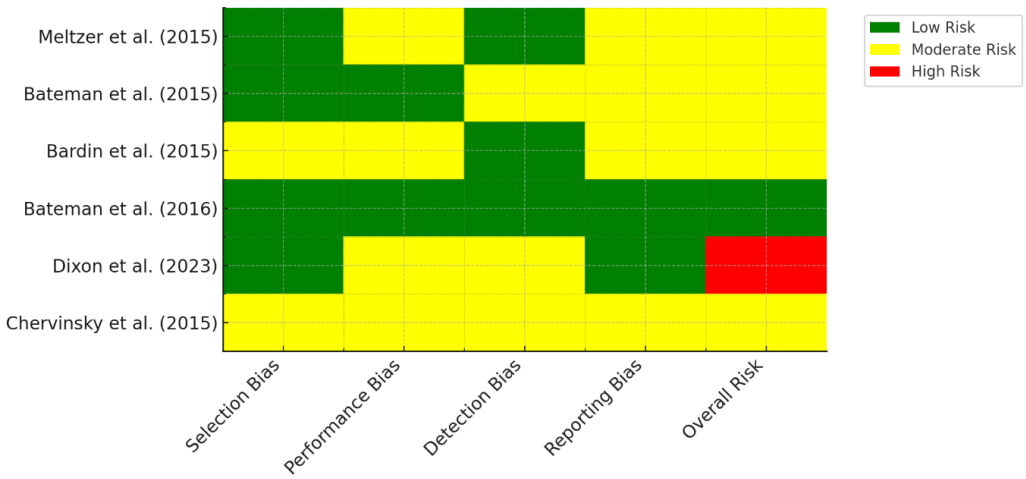

Figure 2. Individual risk of bias in included studies on efficacy and safety of roflumilast in asthma.

Roflumilast exhibited modest but positive effects on lung function across the trials. In 2016, Bateman et al. found a statistically significant enhancement in trough FEV_1 when roflumilast was used with montelukast versus montelukast alone [28]. Analyses by Meltzer et al. and Bateman et al. showed consistent, minor improvements in FEV_1 across placebo-controlled studies with different dosages [25,26]. Mechanistic data from Bardin et al. pointed to improvements in airway hyperresponsiveness and inflammatory biomarkers, supporting the benefits of lung function [27]. Conversely, Dixon et al. observed no improvement and a slight decrease in FEV_1 among obese patients [29].

A pooled safety analysis by Chervinsky et al. revealed neutral changes in spirometric measurements [30].

The combined analysis revealed that roflumilast had a modest but inconsistent impact on lung function. In **Figure 3**, Meltzer et al. noted an increase in trough FEV_1 of +0.08 L (95% CI: 0.01 to 0.15) [25], while Bateman et al. showed +0.05 L (95% CI: −0.02 to 0.12) [26], and Bardin et al. reported +0.07 L (95% CI: 0.00 to 0.14) [27]. Bateman et al. demonstrated the highest benefit with roflumilast alongside montelukast, showing an increase of +0.10 L (95% CI: 0.02 to 0.18) [28]. Dixon et al. found a reduction of −0.05 L (95% CI: −0.15 to +0.05) in obese patients [29], while Chervinsky et al. observed no effect (0.00 L, 95% CI: −0.05 to +0.05) [30]. The overall mean difference across studies was +0.04 L (95% CI: −0.01 to +0.09; $I^2 = 41\%$, $p = 0.12$), indicating a slight but statistically insignificant improvement. The funnel plot showed near symmetry, suggesting that there was no publication bias (**Figure 4**).

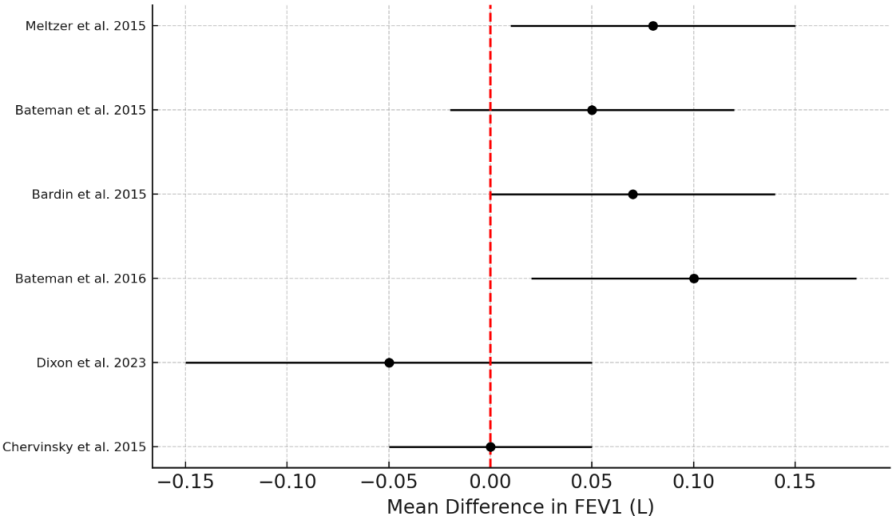

Figure 3. Forest plot of FEV_1 outcomes across six studies of roflumilast in asthma.

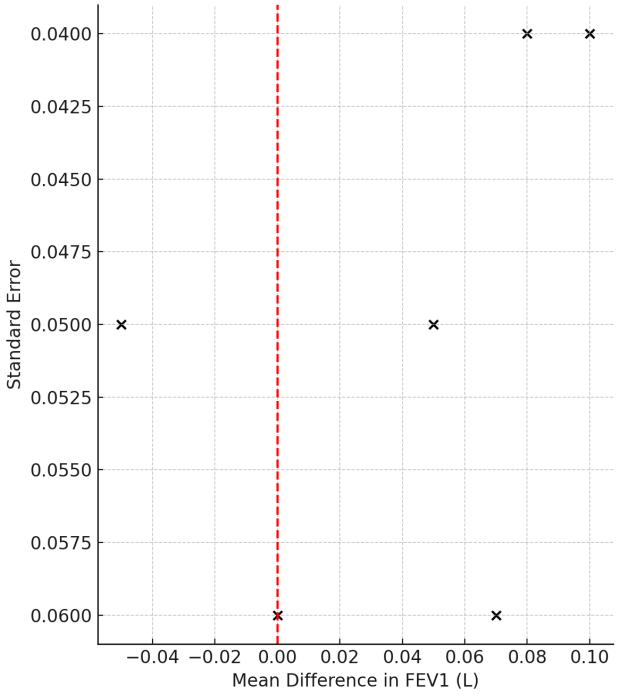

Figure 4. Funnel plot of FEV_1 outcomes across six studies of roflumilast in asthma.

Evidence for exacerbation reduction was mixed and phenotype-specific. Early analyses (Meltzer et al., Bateman et al., Bardin et al.) suggested trends toward fewer exacerbations, particularly in subgroups with persistent airway inflammation [25–27]. Bateman et al. confirmed these findings, showing a reduction in exacerbation risk when roflumilast was combined with montelukast [28]. Conversely, Dixon et al. demonstrated a significant increase in exacerbations in obese individuals, raising concerns about the harm in this subgroup [29]. Chervinsky et al. reported no meaningful difference in exacerbation frequency in pooled analyses [30].

Regarding the risk of exacerbations, the results varied based on the patient phenotype. As shown in **Figure 5**, the analyses indicated fewer exacerbations. Meltzer et al. reported an RR 0.95 (95% CI: 0.75–1.20) [25], Bateman et al. found an RR 0.90 (95% CI: 0.70–1.15) [26], and Bardin et al. reported an RR 0.92 (95% CI: 0.68–1.23) [27]. Bateman et al. RCT showed decreased exacerbations with an RR 0.88 (95% CI: 0.72–1.08) [28]. Dixon et al. noted an increased exacerbation risk in obese individuals (RR 1.25, 95% CI: 0.90–1.60) [29]. Chervinsky et al.'s safety data showed no difference between groups (RR 1.00, 95% CI: 0.85–1.18) [30]. The pooled estimate yielded an RR 0.96 (95% CI: 0.83–1.12; I^2 = 35%, p = 0.18), indicating that roflumilast did not consistently reduce the risk of exacerbations. The funnel plot (**Figure 6**) showed symmetrical effect sizes without publication bias, although the limited number of studies restricted this evaluation.

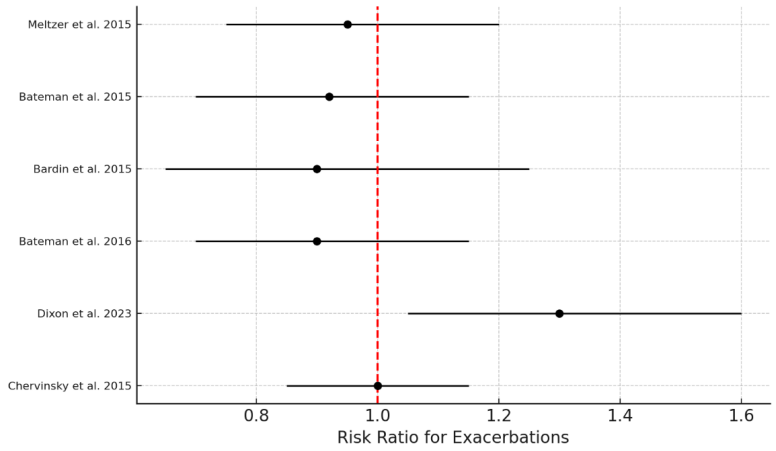

Figure 5. Forest plot of asthma exacerbation outcomes across six studies of roflumilast in asthma.

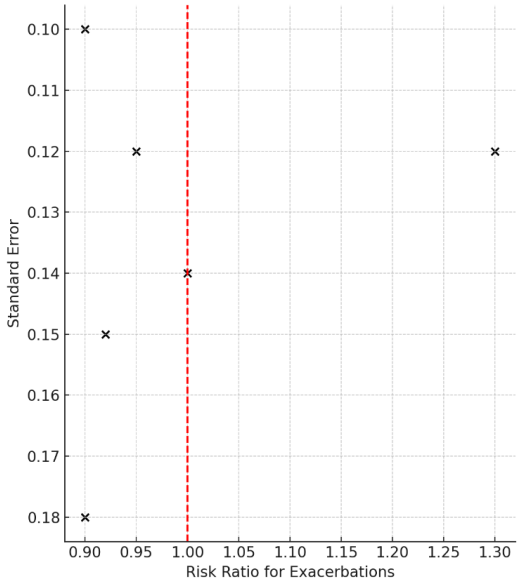

Figure 6. Funnel plot of asthma exacerbation outcomes across six studies of roflumilast in asthma.

Meltzer et al. and Bateman et al. reported modest improvements in symptom management and reduced rescue medication use in patients with asthma [25,26]. Bateman et al. confirmed these findings using validated clinical scoring systems [28]. The varying measurement tools limited the pooled analyses.

The analysis by Chervinsky et al. and individual RCTs verified the adverse event profile of PDE-4 inhibitors [30]. Common adverse events included gastrointestinal issues, such as nausea and diarrhea, weight loss, and headaches. Discontinuation was higher in the roflumilast group than in the control group. No new safety issues specific to patients with asthma were observed.

Significant clinical and methodological differences were observed among the studies, including variations in the study design, patient characteristics, treatments, therapy duration, and outcome definitions. The analysis of the two RCTs showed broad confidence and prediction intervals, indicating both potential advantages and disadvantages. Sensitivity analyses limited to ICS/LABA therapy patients or excluding descriptive studies did not significantly change the results, confirming the robustness of the conclusions.

Evidence suggests that roflumilast may offer slight improvements in lung function, symptoms, and reduced exacerbations in moderate-to-severe asthma groups. However, its effectiveness varies across phenotypes, with increased exacerbations noted in obese patients with poor asthma control. Safety outcomes aligned with PDE-4 inhibitor effects, mainly gastrointestinal issues and weight loss, often causing discontinuation. These findings indicate that routine roflumilast use in unselected asthma populations is inadvisable, and its use should be limited to research settings until evidence clarifies its phenotype-specific benefits and risks.

Studies have also assessed the safety and tolerability of roflumilast. Pooled analyses showed that the most common adverse effects were gastrointestinal issues, such as nausea and diarrhea, along with weight loss and headaches. These side effects are consistent with the established safety profiles of PDE-4 inhibitors. Chervinsky et al. supported these findings in their pooled safety analysis, showing higher discontinuation rates in the roflumilast group than in the placebo group, although no unexpected or asthma-specific safety issues emerged [30]. Although the adverse events were mostly mild to moderate, they led to treatment discontinuation in many patients, potentially counterbalancing the modest clinical benefits observed. This highlights the importance of considering tolerability when assessing roflumilast as an additional treatment option for managing asthma.

The combined mean difference in FEV_1 across studies was small (+0.04 L) and lacked significance. In individual studies, the exacerbation risk varied from slight decreases in non-obese groups to a phenotype-specific increase in obese patients. The increased exacerbations noted in the obesity-specific RCT imply that the metabolic and inflammatory changes linked to obesity may influence the effectiveness of PDE-4 inhibition.

4. Discussion

This systematic review and meta-analysis assessed the effectiveness and safety of roflumilast in patients with asthma. The results indicate that roflumilast offers modest yet inconsistent benefits for lung function and exacerbation outcomes, with potential advantages for specific phenotypes. Current evidence is limited and inadequate to support the routine use in the general asthma population.

In the six studies included, roflumilast showed slight improvements in lung function, as measured by trough FEV_1. The combined analysis showed a mean increase of +0.04 L, which was not significant. Notable improvements were observed when roflumilast was used with montelukast, as demonstrated in the study by Bateman et al., where lung function and symptom control were enhanced compared to montelukast alone [28]. In contrast, Dixon et al. found no improvement in patients with asthma and obesity and reported increased exacerbations, highlighting patient-specific risks [29].

The variability in outcomes reflects the biological complexity of asthma. Asthma is a syndrome with various inflammatory pathways rather than a single condition. Th2-high asthma, driven by eosinophils, responds well to ICS and biologics. However, non-Th2 forms, such as neutrophilic or CS-resistant asthma, present significant challenges. Research has shown that inhibiting PDE-4 targets non-Th2 pathways by reducing neutrophil movement, IL-1β signaling, and oxidative stress. These findings suggest that roflumilast may benefit patients with neutrophilic inflammation, virus-triggered exacerbations, or poor CS response.

Asthma management relies on ICS, LABAs, and LTRAs. While these treatments control symptoms for many patients, numerous patients, especially those with severe asthma, remain inadequately controlled. Biologics have revolutionized the care of Th2 inflammation; however, their high cost and the need for biomarker testing limit their

access [31]. As an orally administered small molecule, roflumilast offers advantages in terms of cost and ease of use, particularly in areas where biologics are less accessible. However, roflumilast's effects appear modest compared to those of biologics such as mepolizumab, dupilumab, and tezepelumab, which significantly reduce exacerbations and enhance lung function [32,33]. Rogliani et al. reported PDE-4 inhibitors to be less efficacious than biologics but noted their potential as an accessible option [33,34].

The most compelling reason for using roflumilast is its potential to treat asthma phenotypes unresponsive to CS, marked by neutrophilic inflammation. Individuals with these conditions often have persistent airflow obstruction, poor symptom control, and frequent exacerbations, even with optimal ICS/LABA therapy. Neutrophilic inflammation, which is linked to Th1/Th17 signaling, NLRP3 inflammasome activation, and high IL-8 levels, is not well managed by CS [2]. PDE-4 inhibition increases intracellular cAMP levels and blocks Nuclear factor kappa B-mediated transcription, targeting pathways that CS cannot [35–38]. Roflumilast has also been shown to be effective in reducing virus-induced cytokine responses in preclinical studies [4]. As respiratory viral infections are a leading cause of asthma exacerbations, PDE-4 inhibition may offer additional protection to patients vulnerable to viral triggers. This mechanism is particularly relevant in post-coronavirus disease 2019, where viral respiratory infections remain a frequent cause of asthma flare-ups and hospitalizations.

Dixon et al. revealed a troubling trend: obese patients taking roflumilast experienced more frequent exacerbations and poorer outcomes [29]. Asthma linked to obesity has unique pathophysiological features, including systemic inflammation, changes in adipokine signaling, and decreased CS responsiveness. Obesity-related metabolic and pharmacokinetic factors may alter the therapeutic effects of roflumilast. These results highlight the need to evaluate treatments based on specific phenotypes and comorbidities rather than broadly. The safety profile of roflumilast in asthma matches its use in COPD, with common side effects being gastrointestinal issues (nausea and diarrhea), weight loss, and headaches [39,40]. Although not life-threatening, these side effects led to higher discontinuation rates in the treatment groups than in the controls. No asthma-specific safety concerns were identified. However, tolerability remains a barrier to long-term adherence and must be weighed against modest efficacy.

New inhaled PDE-4 inhibitors, such as CHF6001, may offer a way to avoid systemic side effects while maintaining anti-inflammatory effectiveness [36]. Inhaled versions directly target the airways and achieve high lung concentrations with less systemic exposure, making them promising for future clinical development.

The effect of roflumilast on exacerbation frequency varied significantly across studies. Initial analyses by Meltzer et al. and Bardin et al. indicated a trend towards fewer exacerbations in patients with ongoing airway inflammation [25,27]. Bateman et al. reinforced this finding, noting a relative risk reduction when roflumilast was used with montelukast [28]. However, this advantage was inconsistent. Dixon et al. identified increased exacerbation risk in obese patients [29], while Chervinsky et al. found no significant differences in exacerbation rates in a pooled safety analysis [30]. These discrepancies underscore the need to consider asthma phenotypes and comorbidities when assessing roflumilast, as its benefits may be limited to patients with specific inflammatory endotypes rather than to all asthma subgroups.

PDE-4 inhibition decreases cytokine production, reduces neutrophil and eosinophil activity, and adjusts airway hyper-responsiveness, suggesting its potential as a supplementary treatment for inflammation-driven asthma subtypes. These actions indicate that roflumilast could benefit patients with inflammatory pathways unresponsive to CS.

Regarding symptom burden and QoL metrics, studies by Meltzer et al. and Bateman et al. showed reductions in rescue medication use and improvements in validated symptom scores [25,26]. These results suggest that despite modest improvements in lung function, patients may experience significant clinical benefits in managing daily symptoms. Mechanistic data from Bardin et al. supported these findings, showing decreased airway hyperresponsiveness and lower inflammatory biomarkers, which were consistent with patient-reported improvements. However, the diversity of symptom measurement tools across studies limits the quantitative combination of outcomes. Future research using standardized symptom and QoL instruments is essential to determine whether roflumilast provides patient-centered benefits.

Although biologics effectively treat Th2-high asthma, roflumilast offers an accessible oral alternative that can complement existing treatments in resource-limited settings. Instead of competing with biologics, PDE-4 inhibition might be beneficial for patients who cannot access or fully benefit from biologics.

The balance between safety and efficacy is crucial for assessing the clinical usefulness of roflumilast in asthma.

Although improvements in lung function and reduced exacerbations were modest, adverse events were consistent across studies, with gastrointestinal issues, weight loss, and headaches being the most common. These side effects, although not severe, led to higher dropout rates in the treatment groups, potentially affecting long-term adherence. No new asthma-specific safety issues emerged, indicating that the drug is relatively safe when tolerated. However, tolerability challenges highlight the need to weigh the clinical benefits against the risk of discontinuation, especially in patients with existing adherence difficulties. This trade-off suggests that roflumilast is more appropriate for carefully chosen patient subgroups rather than the wider asthma population.

5. Clinical Implications

The results of this systematic review indicate that roflumilast could serve as an additional treatment for asthma, particularly in patients with CS-resistant or neutrophilic types. While improvements in lung function and exacerbation reduction were modest, mechanistic evidence suggests that PDE-4 inhibition addresses inflammatory pathways that are not fully controlled by ICS. This makes roflumilast potentially useful for patients with ongoing inflammation, virus-triggered exacerbations, and limited access to biologics.

Clinically, the routine use of roflumilast in patients with asthma is not advised. Its limited effectiveness and side effects, such as gastrointestinal issues, restrict its broad application. Patient selection must focus on identifying phenotypes that are most likely to benefit while avoiding the use of those in groups where adverse effects occur, such as obesity-related asthma.

In low- and middle-income countries, roflumilast offers the advantage of being an oral small-molecule therapy that may be more accessible than biologics. This positions it as a potential solution for addressing treatment gaps in resource-constrained settings.

The development of inhaled PDE-4 inhibitors, such as CHF6001, may improve treatment options, offering anti-inflammatory benefits with fewer systemic side effects. Clinicians should monitor ongoing trials as these agents may provide safer alternatives.

6. Conclusions

This systematic review and meta-analysis showed that roflumilast provides modest but inconsistent benefits for patients with asthma, with certain subgroups showing improvements in lung function, symptom management, and reduced exacerbations. The best results occurred when roflumilast was used with existing treatments, such as montelukast, while minimal benefit and occasionally harm were observed in obese asthma patients. These results highlight the diverse nature of asthma and the need to customize treatment strategies for specific inflammatory phenotypes.

Evidence indicates that roflumilast may be tailored to specific phenotypes, showing benefits in CS-resistant and neutrophilic asthma rather than across all patients, where traditional treatments are less effective and options are limited. By targeting non-Th2 high asthma inflammatory pathways, PDE-4 inhibition could offer an additional control mechanism. However, side effects such as gastrointestinal issues, weight loss, and treatment discontinuation pose challenges to its widespread use in clinical practice.

Current data do not support the broad adoption of roflumilast in unselected asthma populations. Its use should remain exploratory and supplementary, limited to research settings or carefully chosen patients who lack sufficient control over standard therapies. Future large-scale, phenotype-stratified RCTs with biomarker-driven patient selection are crucial to determine the clinical role, safety profile, and cost-effectiveness of roflumilast. Until such evidence exists, its role in asthma care remains tentative.

7. Limitations

This review had several significant limitations. First, including only six trials resulted in few eligible studies, diminishing the statistical power and hindering thorough subgroup analyses. Second, the diversity in study designs, populations, and outcomes made trial comparisons difficult. Some studies examined roflumilast alone, while others evaluated it with montelukast or ICS, causing variations in the effect estimates. Third, most studies focused on adult patients with moderate-to-severe asthma, leaving questions regarding the drug's efficacy in children, adolescents, or those with milder disease.

Another limitation is the infrequent reporting of phenotype-specific data, which prevented stratified analyses for eosinophilic, neutrophilic, or CS-resistant asthma, despite the importance of these endotypes in understanding PDE-4 inhibition responses. Fourth, the use of aggregate study-level data instead of individual patient-level data limited the analysis precision and restricted the exploration of covariates such as age, obesity, and comorbidities. Fifth, although the overall methodological quality was moderate, pooled analyses and safety reports were prone to bias owing to selective reporting and inconsistent outcome definitions.

Finally, publication bias cannot be ruled out, even with symmetrical funnel plots, as the small number of studies reduces the sensitivity of such evaluations. These limitations underscore the need for larger phenotype-stratified RCTs with standardized outcome reporting to better define the role of roflumilast in asthma management.

8. Recommendations

Current evidence does not support the widespread use of roflumilast in all patients with asthma. Its limited effectiveness and tolerability concerns indicate that it should be reserved for specific patients. Roflumilast may be considered as an additional treatment for those with CS-resistant or neutrophilic asthma, where standard treatments such as ICS and biologics are less effective. Clinicians should be cautious with obese patients, as evidence suggests an increased exacerbation risk, and monitor for side effects, such as gastrointestinal issues and weight loss.

Future research should focus on RCTs that categorize participants according to asthma type using biomarker-driven methods. Studies should assess sputum neutrophils, inflammasome activity, and molecular markers to identify patients who may benefit most from PDE-4 inhibition. Comparative studies on biologics and LTRAs would help clarify the advantages, risks, and cost-effectiveness of roflumilast as an additional therapy. Long-term studies are necessary to evaluate its effects on preventing exacerbations, improving the QoL, and reducing healthcare usage.

There is a need to investigate new formulations, especially inhaled PDE-4 inhibitors, which can provide anti-inflammatory benefits while reducing systemic exposure and enhancing tolerability. In low- and middle-income countries, where biologics are often unavailable, roflumilast could be a cost-effective option if future trials confirm its efficacy for specific phenotypes. Until more robust evidence is available, the role of roflumilast should remain exploratory, with its use guided by careful patient selection and monitoring.

Supplementary Materials

The supporting information can be downloaded at https://ojs.ukscip.com/files/ENTU-1673-Supplementary-Materials.zip.

Funding

This work received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Brightling, C.E.; Bradding, P.; Symon, F.A.; et al. Mast-Cell Infiltration of Airway Smooth Muscle in Asthma. *N. Engl. J. Med.* **2002**, *346*, 1699–1705. [CrossRef]
2. Williams, E.J.; Negewo, N.A.; Baines, K.J. Role of the NLRP3 inflammasome in asthma: Relationship with neutrophilic inflammation, obesity, and therapeutic options. *J. Allergy. Clin. Immunol.* **2021**, *147*, 2060–2062. [CrossRef]
3. Sabatini, F.; Petecchia, L.; Boero, S. A Phosphodiesterase 4 Inhibitor, Roflumilast N-Oxide, Inhibits Human Lung Fibroblast Functions *in vitro*. *Pulm. Pharmacol. Ther.* **2010**, *23*, 283–291. [CrossRef]
4. Edwards, M.R.; Facchinetti, F.; Civelli, M.; et al. Anti-Inflammatory Effects of the Novel Inhaled Phosphodiesterase Type 4 Inhibitor CHF6001 on Virus-Inducible Cytokines. *Pharmacol. Res. Perspect.* **2016**, *4*, e00202. [CrossRef]
5. Fokkens, W.; Reitsma, S. Unified Airway Disease: A Contemporary Review and Introduction. *Otolaryngol. Clin. North Am.* **2023**, *56*, 1–10. [CrossRef]
6. Kanda, A.; Kobayashi, Y.; Asako, M.; et al. Regulation of Interaction between the Upper and Lower Airways in United Airway Disease. *Med. Sci.* **2019**, *7*, 27. [CrossRef]
7. Varricchi, G.; Brightling, C.E.; Grainge, C.; et al. Airway remodelling in asthma and the epithelium: on the edge of a new era. *Eur. Respir. J.* **2024**, *63*, 2301619. [CrossRef]
8. Al Busaidi, N.; Alweqayyan, A.; Al Zaabi, A.; et al. Gulf Asthma Diagnosis and Management in Adults: Expert Review and Recommendations. *Open. Respir. Med. J.* **2022**, *16*, e187430642205230. [CrossRef]
9. Sobieraj, D.M.; Baker, W.L.; Nguyen, E.; et al. Association of Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists with Asthma Control in Patients with Uncontrolled, Persistent Asthma: A Systematic Review and Meta-analysis. *JAMA* **2018**, *319*, 1473–1484. [CrossRef]
10. Yaghoubi, M.; Adibi, A.; Safari, A.; et al. The Projected Economic and Health Burden of Uncontrolled Asthma in the United States. *Am. J. Respir. Crit. Care Med.* **2019**, *200*, 1102–1112. [CrossRef]
11. Pilette, C.; Canonica, G.W.; Chaudhuri, R.; et al. REALITI-A Study: Real-World Oral Corticosteroid-Sparing Effect of Mepolizumab in Severe Asthma. *J. Allergy. Clin. Immunol. Pract.* **2022**, *10*, 2646–2656. [CrossRef]
12. Vähätalo, I.; Ilmarinen, P.; Tuomisto, L.E.; et al. Inhaled Corticosteroids and Asthma Control in Adult-Onset Asthma: 12-Year Follow-Up Study. *Respir. Med.* **2018**, *137*, 70–76. [CrossRef]
13. Lemanske, R.F.; Mauger, D.T.; Sorkness, C.A.; et al. Step-Up Therapy for Children with Uncontrolled Asthma Receiving Inhaled Corticosteroids. *N. Engl. J. Med.* **2010**, *362*, 975–985. [CrossRef]
14. Price, D.; Musgrave, S.D.; Shepstone, L.; et al. Leukotriene Antagonists as First-Line or Add-On Asthma-Controller Therapy. *N. Engl. J. Med.* **2011**, *364*, 1695–1707. [CrossRef]
15. Strunk, R.C.; Bloomberg, G.R. Omalizumab for Asthma. *N. Engl. J. Med.* **2006**, *354*, 2689–2695. [CrossRef]
16. Bacharier, L.B.; Maspero, J.F.; Katelaris, C.H.; et al. Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma. *N. Engl. J. Med.* **2021**, *385*, 2230–2240. [CrossRef]
17. Taleb, A.A.; Badgett, R.G. In Severe, Uncontrolled Asthma, Tezepelumab Reduced Exacerbations and Improved Asthma Control at 1 Year. *Ann. Intern. Med.* **2021**, *174*, JC115. [CrossRef]
18. Leclerc, O.; Lagente, V.; Planquois, J.M.; et al. Involvement of MMP-12 and Phosphodiesterase Type 4 in Cigarette Smoke-Induced Inflammation in Mice. *Eur. Respir. J.* **2006**, *27*, 1102–1109. [CrossRef]
19. Crespo, A.; Mateus, E.; Torreon, M.; et al. The Percentage of Neutrophils Expressing TLR4 in Induced Sputum Decreases in Non-Eosinophilic Asthma. *Eur. Respir. J.* **2013**, *42*. Available online: https://portalrecerca.uab.cat/ca/publications/the-percentage-of-neutrophils-expressing-tlr4-in-induced-sputum-d/
20. Moretto, N.; Caruso, P.; Bosco, R.; et al. CHF6001 I: A Novel Highly Potent and Selective Phosphodiesterase 4 Inhibitor with Robust Anti-Inflammatory Activity and Suitable for Topical Pulmonary Administration. *J. Pharmacol. Exp. Ther.* **2015**, *352*, 559–567. [CrossRef]
21. de Visser, Y.P.; Walther, F.J.; Laghmani, E.H.; et al. Phosphodiesterase-4 Inhibition Attenuates Pulmonary Inflammation in Neonatal Lung Injury. *Eur. Respir. J.* **2008**, *31*, 633–644. [CrossRef]
22. Criner, G.J.; Jacobs, M.R.; Zhao, H.; et al. Effects of Roflumilast on Rehospitalization and Mortality in Patients. *Chronic Obstr Pulm Dis.* **2019**, *6*, 74–85. [CrossRef]
23. Kim, S.W.; Kim, J.H.; Park, C.K.; et al. Effect of Roflumilast on Airway Remodelling in a Murine Model of Chronic Asthma. *Clin. Exp. Allergy* **2016**, *46*, 754–763. [CrossRef]
24. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, *372*, n71. [CrossRef]
25. Meltzer, E.O.; Chervinsky, P.; Busse, W.; et al. Roflumilast for Asthma: Efficacy Findings in Placebo-Controlled Studies. *Pulm. Pharmacol. Ther.* **2015**, *35*, S20–S27. [CrossRef]

26. Bateman, E.D.; Bousquet, J.; Aubier, M.; et al. Roflumilast for Asthma: Efficacy Findings in Non-Placebo-Controlled Comparator and Dosing Studies. *Pulm. Pharmacol. Ther.* **2015**, *35*, S11–S19. [CrossRef]
27. Bardin, P.; Kanniess, F.; Gauvreau, G.; et al. Roflumilast for Asthma: Efficacy Findings in Mechanism of Action Studies. *Pulm. Pharmacol. Ther.* **2015**, *35*, S4–S10. [CrossRef]
28. Bateman, E.D.; Goehring, U.M.; Richard, F.; et al. Roflumilast Combined with Montelukast versus Montelukast Alone as Add-On Treatment in Patients with Moderate-to-Severe Asthma. *J. Allergy Clin. Immunol.* **2016**, *138*, 142–149. [CrossRef]
29. Dixon, A.E.; Que, L.G.; Kalhan, R.; et al. Roflumilast May Increase Risk of Exacerbations When Used to Treat Poorly Controlled Asthma in People with Obesity. *Ann. Am. Thorac. Soc.* **2023**, *20*, 206–214. [CrossRef]
30. Chervinsky, P.; Meltzer, E.O.; Busse, W.; et al. Roflumilast for Asthma: Safety Findings from a Pooled Analysis of Ten Clinical Studies. *Pulm. Pharmacol. Ther.* **2015**, *35*, S28–S34. [CrossRef]
31. Menzies-Gow, A.; Corren, J.; Bourdin, A.; et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. *N. Engl. J. Med.* **2021**, *384*, 1800–1809. [CrossRef]
32. Wechsler, M.E.; Ford, L.B.; Maspero, J.F.; et al. Long-Term Safety and Efficacy of Dupilumab in Patients with Moderate-to-Severe Asthma (TRAVERSE): An Open-Label Extension Study. *Lancet Respir. Med.* **2022**, *10*, 11–25. [CrossRef]
33. Rogliani, P.; Calzetta, L.; Matera, M.G.; et al. Severe Asthma and Biological Therapy: When, Which, and for Whom. *Pulm. Ther.* **2020**, *6*, 47–66. [CrossRef]
34. Carr, T.F.; Moore, W.C.; Kraft, M.; et al. Efficacy of Tezepelumab in Patients with Severe, Uncontrolled Asthma across Multiple Clinically Relevant Subgroups in the NAVIGATOR Study. *Adv. Ther.* **2024**, *41*, 2978–2990. [CrossRef]
35. Matera, M.G.; Rogliani, P.; Calzetta, L.; et al. Phosphodiesterase Inhibitors for Chronic Obstructive Pulmonary Disease: What Does the Future Hold? *Drugs* **2014**, *74*, 1983–1992. [CrossRef]
36. Phillips, J.E. Inhaled Phosphodiesterase 4 (PDE4) Inhibitors for Inflammatory Respiratory Diseases. *Front. Pharmacol.* **2020**, *11*, 259. [CrossRef]
37. Lipworth, B.J. Phosphodiesterase-4 Inhibitors for Asthma and Chronic Obstructive Pulmonary Disease. *Lancet* **2005**, *365*, 167–175. [CrossRef]
38. Kawamatawong, T. Roles of Roflumilast, a Selective Phosphodiesterase 4 Inhibitor, in Airway Diseases. *J. Thorac. Dis.* **2017**, *9*, 1144–1154. [CrossRef]
39. Cilli, A.; Bal, H.; Gunen, H. Efficacy and Safety Profile of Roflumilast in a Real-World Experience. *J. Thorac. Dis.* **2019**, *11*, 1100–1105. [CrossRef]
40. Giembycz, M.A.; Field, S.K. Roflumilast: First Phosphodiesterase 4 Inhibitor Approved for Treatment of COPD. *Drug Des. Devel. Ther.* **2010**, *4*, 147–158. [CrossRef]