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CASE REPORT & REVIEW

Switching from multiple-inhaler triple therapy to single, extrafine-inhaler triple therapy in severe refractory asthma with EGPA: beyond control. Case report and review of the literature

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Abstract

Eosinophilic granulomatosis with polyangiitis is a rare systemic vasculitis associated with asthma, eosinophilia and multi-organ involvement. This case report describes a 69-year-old male with severe, poorly controlled asthma who was diagnosed with eosinophilic granulomatosis with polyangiitis. Despite treatment with mepolizumab 300 mg and optimized inhaled therapies, comprising high-dose inhaled corticosteroids and long-acting β2-agonists and a long-acting muscarinic antagonist in two separate inhalers, the patient exhibited poor asthma control, accompanied by exacerbations of symptoms, increased reliance on oral corticosteroids, and a decline in lung function. Consequently, a comprehensive, multidisciplinary approach targeting comorbidities was deemed necessary, including the management of chronic rhinosinusitis with nasal polyps. Following a switch to a single-inhaler triple therapy, the patient demonstrated significant improvements in terms of asthma control, respiratory function, oscillometric measurements and fractional exhaled nitric oxide reduction. This report underscores the significance of personalized treatment strategies and a treatable-traits approach targeting small airway dysfunction, persistent airflow limitation and type 2 inflammation for effective disease management. A literature review on therapeutic advancements and clinical implications is also presented to provide clinicians with useful insights into managing severe asthma and single-inhaler triple therapy placement.

Keywords: asthma, chronic rhinosinusitis with nasal polyps, EGPA, eosinophilic granulomatosis with polyangiitis, FeNO, inhaled therapy, mepolizumab, small airway dysfunction, type 2 inflammation.

Citation

Menzella F, Cottini M, Tonin S, Corsi L, Bosi A, Ballarin A, Floriani A, Dartora C, Tacconi M, Lombardi C. Switching from multiple-inhaler triple therapy to single, extrafine-inhaler triple therapy in severe refractory asthma with EGPA: beyond control. Case report and review of the literature. *Drugs Context*. 2025;14:2025-2-3. https://doi.org/10.7573/dic.2025-2-3

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg–Strauss syndrome, is a rare systemic vasculitis associated with asthma, eosinophilia and multi-organ involvement. First described by Churg and Strauss in 1951, EGPA has since been reclassified, with the name change reflecting a broader understanding of its pathophysiology. The disease is characterized by three distinct phases: a prodromal phase with atopic symptoms such as asthma and allergic rhinitis; an eosinophilic phase with peripheral and tissue eosinophilia; and a vasculitic phase with necrotizing inflammation of small to medium-sized blood vessels.[1]

The incidence of EGPA is estimated to be 2.7 cases per million per year but prevalence rates vary geographically, with higher frequencies reported in populations with greater exposure to environmental allergens.[2]

EGPA predominantly affects the respiratory tract but often involves other systems, including the cardiovascular, neurological, gastrointestinal and renal systems. Advances in our understanding of the pathophysiology of the disease, including of T helper 2 (T_H2)-mediated immune response, have led to the development of novel therapeutic options. Epidemiological studies suggest that environmental factors, genetic predisposition and immune dysregulation may be important contributors to disease development.

The course of EGPA is divided into three successive stages: (1) the onset of asthma and sinusitis with marked eosinophilia; (2) hypereosinophilia, eosinophilic pneumonia and the onset of asthma; and (3) the onset of vasculitis. Often, however, the diagnosis of EGPA is challenging and may be made up to 10 years after the onset of asthma, which tends to worsen progressively.[3] Despite advancements in knowledge of the disease, the management of EGPA, especially in cases of severe, difficult-to-control asthma, remains complex and requires an individualized, multidisciplinary approach with progressive intensification of systemic treatment as well as inhaled drugs.

This case report describes a patient with EGPA and severe refractory asthma who was unresponsive to treatment with high-dose inhaled corticosteroids, long-acting β2-agonists (ICS/LABA) and a long-acting muscarinic antagonist (LAMA) in two separate inhalers. The patient significantly improved in terms of symptom control, respiratory function, oscillometric measurements and fractional exhaled nitric oxide (FeNO) reduction after switching to single-inhaler ICS/LABA/LAMA triple therapy. This article highlights the interplay between systemic inflammation, airway disease and type 2 inflammation. Additionally, we review the literature on EGPA and asthma management, focusing on therapeutic strategies and their implications for asthma control.

Case presentation

A 69-year-old man, a former scientific informant and current mountain bike coach, presented with severe, poorly controlled asthma. He had no history of smoking and had undergone a transverse colectomy for colon cancer in 2012. His medical history included eosinophilic asthma diagnosed in 2017 and chronic rhinosinusitis with nasal polyps (CRSwNP). At the time of diagnosis, laboratory tests showed a blood eosinophil count (BEC) of 800 cells/μL and a total serum immunoglobulin E (IgE) of 84 u/L. *Aspergillus*-specific immunoglobulin G (IgG) antibody (Asp IgG) was negative, and no intestinal parasites were detected. Prior to the diagnosis in 2017, the patient had experienced years of recurrent respiratory symptoms, including episodic wheezing and sinus infections, which were often misattributed to allergic rhinitis. In June 2020, the patient underwent respiratory evaluation at the Pulmonology Unit, S. Valentino Hospital Montebelluna, Marca Trevigiana, Italy. Despite treatment with two inhalations of formoterol/budesonide dry-powder inhaler 160/4.5 mcg every 12 hours and as-needed along with 100 mcg of nasal mometasone daily, his asthma remained sub-optimally controlled, characterized by worsening exertional dyspnoea, mucus plugging and frequent exacerbations requiring three or four annual courses of prednisone (25 mg for 15 days). Pulmonary function tests (PFTs) showed severe obstruction with a forced expiratory volume in 1 second (FEV_1) of 49% and significant post-bronchodilator reversibility. Laboratory investigations revealed blood hypereosinophilia (1,570 cells/μL) and normal IgE levels. FeNO was markedly elevated at 78 parts per billion (ppb), consistent with significant type 2 inflammation. A detailed diagnostic work-up included high-resolution computed tomography scan of the chest, which showed bilateral patchy ground-glass opacities consistent with eosinophilic infiltration. Electromyography studies showed peripheral mononeuropathy involving the lower extremities, a common neurological manifestation of EGPA. Bronchoalveolar lavage revealed an elevated eosinophil percentage, further supporting the diagnosis of EGPA. Imaging and serological findings confirmed the suspected diagnosis of EGPA with perinuclear antineutrophil cytoplasmic antibody (pANCA) positivity, peripheral mononeuropathy and respiratory involvement.[4]

In February 2021, the patient underwent functional endoscopic sinus surgery. Histological findings showed necrotizing vasculitis and extravascular eosinophil-rich granulomatous inflammation. Given this finding and the remaining criteria, the diagnosis of EGPA was confirmed according to the American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria.[5]

In agreement with rheumatologists, the patient was subsequently treated with mepolizumab (300 mg subcutaneously monthly), which resulted in partial improvement in his asthma symptoms. Despite biologic therapy, intermittent oral corticosteroids were still required for asthma symptom control. At a pulmonology visit in June 2021, an objective chest examination revealed diffuse wheezing; therefore, inhalation therapy was optimized by adding two consecutive inhalations of tiotropium bromide 2.5 mcg soft mist inhaler once per day and increasing the ICS/LABA dose to two inhalations of budesonide/formoterol 320/9 mcg twice per day. Spirometry performed in October 2021 showed a FEV_1 of 2,170 ml (73% of predicted), representing an increase of 49% compared to 2020. The patient's asthma control test (ACT) score was

17. Due to a relatively stable clinical picture, the patient received only spirometry in 2022 and 2023 (Table 1) and no pulmonological examinations. Inhalation and biologic therapy remained unchanged until 2024 when he returned to our centre due to worsening symptoms and, in particular, a progressive worsening in exertional dyspnoea and exacerbations.

In July 2024, the patient returned to our centre because of worsening dyspnoea even with mild-to-moderate exertion (grade 2 Modified British Medical Research Council [mMRC] scale and modified Borg category-ratio (CR)-10 Rated Perceived Exertion scale of 7). He was no longer able to participate in sports, and his symptoms were affecting his quality of life, requiring continued use of oral corticosteroids (OCS). The patient's ACT score was 15, FEV_1 65% of predicted, FEV_1/FVC 55% and FeNO 263 ppb; inhaled therapy was subsequently optimized to a pressurized metered-dose, single-inhaler extrafine triple therapy (SITT) of beclomethasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide (GB) 172/5/9 mcg. By August 2024, the patient reported significant respiratory improvement, with PFTs showing mild obstruction (FEV_1 82%, FEV_1/FVC 57%), FeNO reduced to 62 ppb, and an ACT score of 20; at this time, the use of OCS was discontinued. Over the following months, the patient had no asthma exacerbations, his respiratory symptoms further continued to improve and he finally returned for a pulmonological re-evaluation in December 2024. At this visit, ACT score was 22, Borg CR-10 score was 1 and mMRC grade was 0 with normalization of airflow limitation (FEV_1 91%, 2.67 lt; FEV_1/FVC 71.37; FEV_1 +85.7%, +25% and +8% compared to previous spirometry tests performed in 2019, 2020 and August 2024, respectively) (Table 1). The FeNO level detected was 21.5 ppb (−92% compared to July 2024) and BEC was 50 cells/μL. In addition to improvements in lung function, forced oscillometry (FOT) measurements, biomarkers (Figure 1) and

Table 1. Longitudinal variation in outcomes.

	2020	2021	2022	2023	July 2024 (switch from MITT to SITT)	August 2024	December 2024
FEV_1 (%)	49	73	NA	NA	65	82	91
FEV_1 (mL)	1430	2170	NA	NA	1820	2210	2670
FeNO (ppb)	78	105	NA	NA	263	62	21.5
Rrs 5 Hz [$cmH_2O/(L/s)$]	NA	NA	NA	NA	4.9	NA	2.8
R 5-19 Hz [$cmH_2O/(L/s)$]	NA	NA	NA	NA	0.41	NA	0.06
Xrs 5 Hz [$cmH_2O/(L/s)$]	NA	NA	NA	NA	-2.22	NA	-1.10
AX [$cmH_2O/(L/s)$]	NA	NA	NA	NA	6.32	NA	3.81
Exacerbations	3	2	1	2	1	0	0
OCS (mg)	25 mg daily for 6 months	25 mg daily for 6 months	25 mg daily for 6 months	25 mg daily for 6 months	0	0	0
ACT	18	17	NA	NA	15	20	22
mMRC dyspnoea scale	NA	NA	NA	NA	2	0	0
Borg CR-10 score	NA	NA	NA	NA	7	3	1

ACT, asthma control test; AX, reactance area; Borg CR-10, Borg category-ratio 10; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; MITT, multiple-inhaler triple therapy; mMRC, modified Medical Research Council; NA, not available; OCS, oral corticosteroids; Rrs, respiratory system resistance; SITT, single-inhaler triple therapy; Xrs, respiratory system reactance.

patient-reported outcomes (Figure 2), the patient was able to return to exercise (cycling) without experiencing dyspnoea or signs of fatigue. During the treatment period with SITT between July and December 2024, the patient no longer required OCS given the improvement in asthma control and the absence of asthma exacerbations.

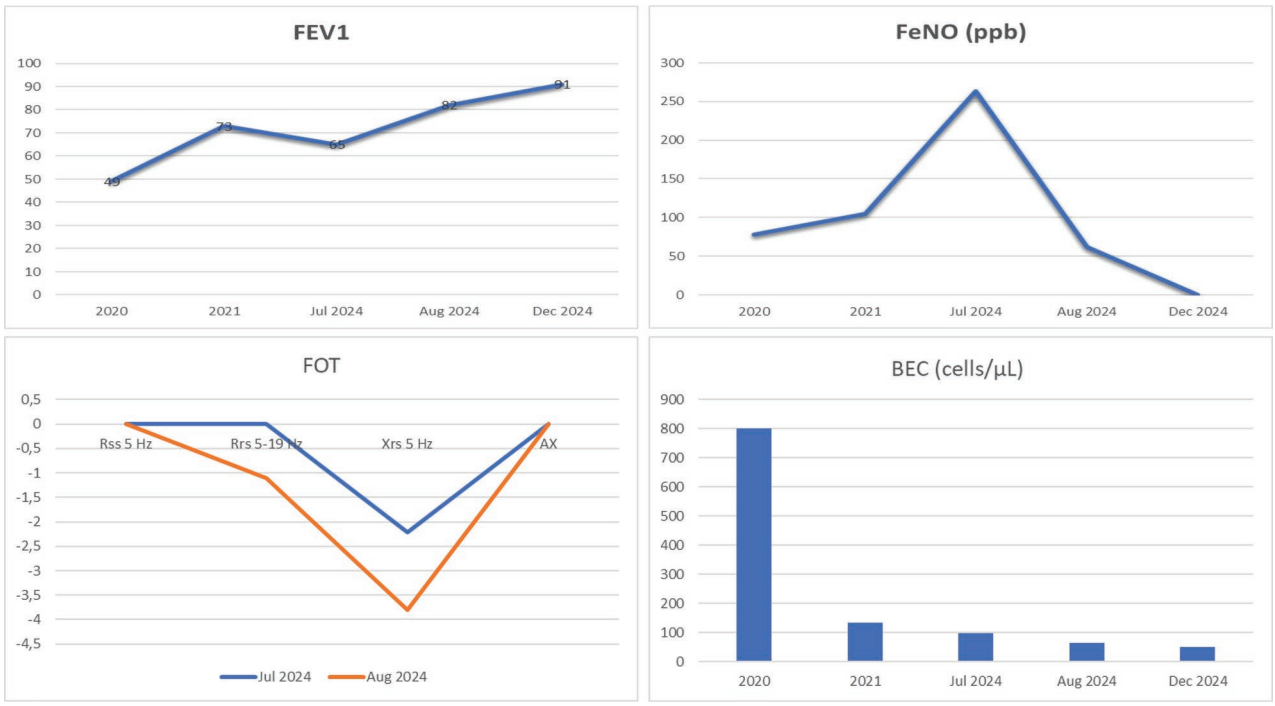
FOT was also performed on the patient to assess the impact of asthma on small airway dysfunction (SAD). The FOT, performed at baseline in July 2024 before starting SITT, showed total airway resistance (Rrs) at 5 Hz ($cmH_2O/(L/s)$) of 4.9, at 5/19 Hz inspiratory (insp) ($cmH_2O/(L/s)$) of 0.41, total respiratory system reactance (Xrs) at 5 Hz ($cmH_2O/(L/s)$) of −2.22, reactance area (AX) insp (cmH_2O/L) of 6.32. These parameters showed a clinically significant increase in total and peripheral resistance as well as reactance (Figure 1). Considering the spirometric and FOT parameters, the patient presented a central and peripheral obstruction pattern and a reduction in reactance, confirming the presence of SAD. After 6 months of treatment with SITT, these parameters improved significantly both in terms of resistance and reactance as well as based on Z-scores (Table 1), supporting improvements shown by spirometry from the point of view of a positive impact on the peripheral airways and the mechanical properties of the respiratory system.

Discussion and review

To our knowledge, this is the first reported case of a patient with EGPA and severe asthma treated with SITT after switching from multiple-inhaler triple therapy (MITT) add-on to a monoclonal antibody (mAb).

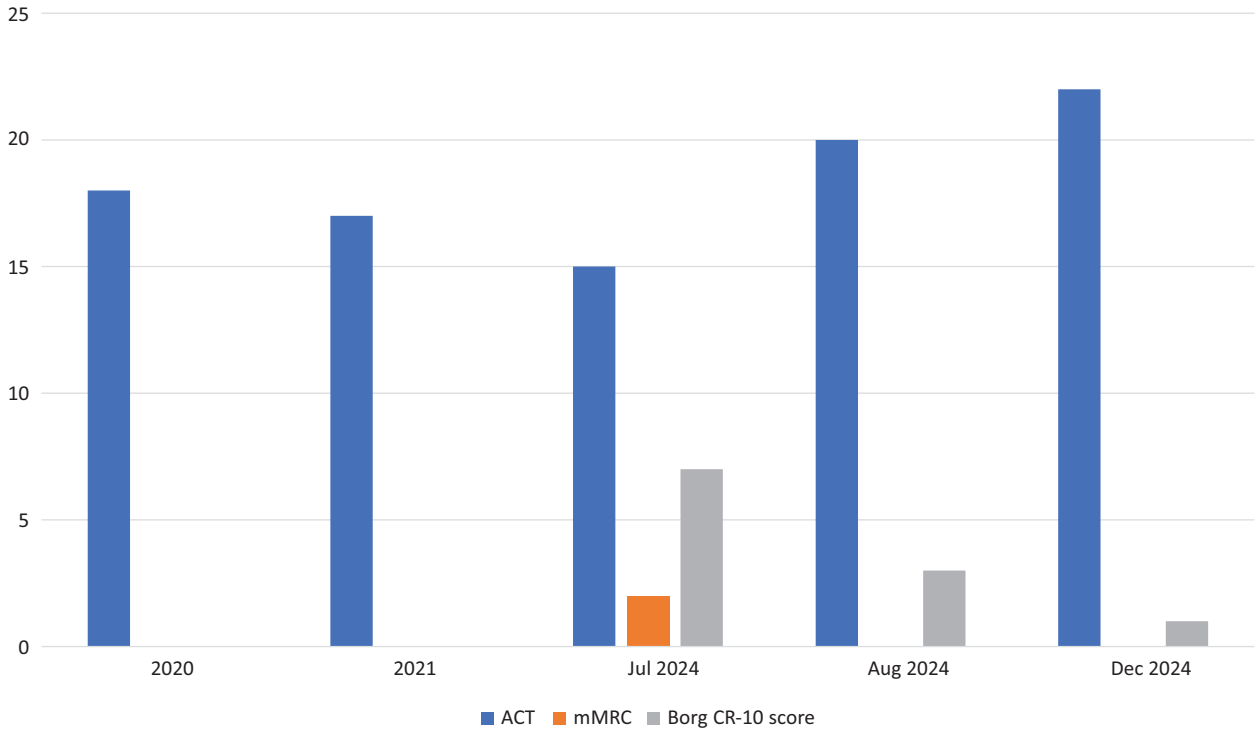
EGPA is a T_H2-mediated disease presenting with overlapping vasculitic and eosinophilic phenotypes. Diagnosis is made based on clinical criteria, eosinophil counts, ANCA status and biomarkers such as FeNO, with pANCA positivity observed in 30–40% of cases.[6,7] In this patient, a mixed phenotype required a tailored approach combining biologics, FeNO monitoring and optimized inhaled therapies. The pathogenesis of EGPA involves complex immune dysregulation, primarily driven by T_H2 cytokines such as IL-4, IL-5 and IL-13. IL-5 plays a central role in eosinophil proliferation and survival, making it a critical therapeutic target. Other factors, including IL-17 and the complement system, have also been implicated, suggesting a multifaceted inflammatory process. The role of ANCA antibodies in

Figure 1. Longitudinal variation of lung function, FOT measures and biomarkers.



AX, reactance area; BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FOT, forced oscillometry; Rrs, respiratory system resistance; Xrs, respiratory system reactance.

Figure 2. Patient reported outcomes.



ACT, asthma control test; Borg CR-10, Borg category-ratio 10; mMRC, modified medical research council.

EGPA is less well-defined compared to other vasculitides, such as granulomatosis with polyangiitis but their presence is associated with a vasculitic phenotype and poorer prognosis.[8]

Genetic studies have revealed polymorphisms in genes regulating the T_H2 response, including *IL5* and *IL13*, as potential contributors to the susceptibility of EGPA. Environmental triggers, such as allergens, infections and certain medications, have been identified as precipitating factors.[9] These insights have shaped the development of targeted therapies, including biologics that inhibit specific cytokine pathways.

A notable example is mepolizumab, a mAb that targets IL-5, which has been shown to have a transformative effect on the management of EGPA through its capacity to reduce exacerbation rates, enhance asthma control and decrease oral corticosteroid dependence, as evidenced by clinical trials.[10] Furthermore, significant reductions in FeNO levels have been observed in response to biologics, underscoring their capacity to effectively modulate type 2 inflammation.[11] In this context, FeNO monitoring has emerged as a valuable biomarker for assessing therapeutic response. The phase III MIRRA study by Wechsler et al. demonstrated that mepolizumab significantly reduced the frequency of EGPA flares and allowed for corticosteroid tapering.[12]

The phase III MANDARA study for benralizumab in patients with EGPA was the first head-to-head trial of a biologic in patients with EGPA.[13] The authors demonstrated that more than half of patients achieved remission with this unique antibody-dependent cellular cytotoxicity-based biologic. MANDARA compared benralizumab with mepolizumab in patients with EGPA receiving OCS with or without stable immunosuppressive therapy. The study was designed to randomize patients to receive either a single 30 mg subcutaneous injection of benralizumab or three separate 100 mg subcutaneous injections of mepolizumab, once every 4 weeks.[13] Benralizumab met the study's primary endpoint, which demonstrated non-inferior remission rates compared to mepolizumab.[14] The primary endpoint of adjusted remission rate was 59% for patients treated with benralizumab at weeks 36 and 48, compared to 56% for mepolizumab (difference in rates: 3%, 95% CI−13 to 18).[14] Remission in EGPA was defined as Birmingham Vasculitis Activity Score of 0 and OCS dose ≤4 mg/day.[14] Dupilumab, although not yet approved for EGPA, has shown promise in treating eosinophilic asthma and CRSwNP, making it a potential candidate for managing overlapping phenotypes.[15] This biological agent remains controversial in this area, although the open-label extension study Traverse has largely dispelled doubts about the risk of exacerbation of EGPA in patients treated with this mAb.[16]

The advent of novel therapeutic interventions targeting IL-17, IL-33 and thymic stromal lymphopoietin has emerged as a promising avenue for research, with preliminary findings suggesting their potential efficacy in cases of refractory disease.[17] These advancements hold great promise for further expanding the therapeutic repertoire for EGPA in forthcoming years. The interplay between EGPA and asthma underscores the necessity to address the issues of SAD, persistent airflow limitation (PAL) and elevated FeNO. SAD, defined by abnormalities in small airways (<2 mm in diameter), plays a pivotal role in asthma pathogenesis, contributing to disease progression and poor control. The ATLANTIS study provided valuable insights into SAD, reporting that 91% of patients with asthma exhibited SAD, regardless of disease severity.[18] However, in the SAD sub-group, poorer asthma control has been shown.[18] Furthermore, a post-hoc analysis of ATLANTIS revealed that PAL (defined as an FEV_1/FVC ratio below the lower limit of normal) was prevalent in 33% of patients with asthma and was strongly associated with exacerbations and severe asthma progression.[19] Additionally, in this study, PAL was associated with more severe SAD suggesting a potential link between these two conditions. Similar to patients with SAD, PAL was found not only in severe disease but also in a large percentage of patients with milder disease, highlighting the potential for comprehensive assessment of both conditions. In the latter, individuals with mild asthma exhibited a correlation between PAL and eosinophilic inflammation, along with an elevated risk of exacerbations. These findings are noteworthy as they imply that SAD and PAL serve as independent predictors of a future risk of exacerbations and poor asthma control. Consequently, increasing treatment intensity should be contemplated in these individuals, regardless of the Global Initiative for Asthma (GINA) step of severity. Furthermore, elevated FeNO, a hallmark of type 2 inflammation, underscores the role of airway inflammation in disease control.[19]

In patients with EGPA, SAD may be exacerbated by eosinophilic inflammation and airway remodelling. Advanced imaging techniques, such as CT-based airway analysis and hyperpolarized gas MRI, are advanced imaging techniques that have emerged as valuable tools for detecting SAD. Advanced imaging techniques can complement traditional PFTs and FeNO monitoring in identifying early airflow abnormalities, guiding therapeutic decisions.[20]

Inhaled therapies targeting SAD are critical for optimizing asthma control.[21] Extra-fine formulations, characterized by aerodynamic particle diameters ≤2 µm, ensure effective distribution throughout the bronchial tree, including the small airways. The combination of beclomethasone dipropionate and formoterol fumarate (BDP/FF) in an extra-fine formulation has demonstrated superior efficacy compared to traditional formulations.[22]

In the PRISMA study, patients treated with extra-fine BDP/FF exhibited a 39.1% higher probability of achieving asthma control in comparison to those administered other ICS/LABA combinations.[23] Of note, this enhancement was accomplished with reduced ICS doses, underscoring the clinical significance of particle size in the management of asthma. The synergistic action of BDP and FF in reducing bronchial hyperreactivity and FeNO further supports the use of this formulation in addressing SAD and improving patient outcomes.[24]

A systematic review and meta-analysis of observational real-life studies demonstrates that extrafine ICSs have significantly higher odds of achieving asthma control with lower exacerbation rates at significantly lower prescribed doses than fine-particle ICSs.[25]

A critical component of asthma management pertains to the delivery method of triple therapy. MITT involves the utilization of distinct inhalers for ICS/LABA and a LAMA. Conversely, SITT consolidates all three components into a single inhaler. Whilst both approaches deliver the same pharmacological agents, SITT confers substantial practical advantages. Studies have shown that SITT enhances adherence in comparison to open triple therapy.[26] Adherence rates tend to be higher in patients using a single inhaler due to the simplicity of the regimen, which reduces the probability of missed doses.[26] Additionally, SITT mitigates the potential for errors in dosing and inhaler technique, which are common with the use of multiple devices. Improved adherence and proper technique result in enhanced asthma control and a reduction in exacerbations.[27,28]

The pivotal TRIMARAN and TRIGGER studies evaluated the efficacy of BDP/FF/GB compared to BDP/FF in patients with uncontrolled moderate-to-severe asthma.[29] The results included a significant improvement in FEV_1 at week 26 (+57 mL in TRIMARAN and +73 mL in TRIGGER); a reduction in annualized exacerbation rates (a 12% overall reduction and a 33.5% reduction in patients with the PAL phenotype); longer time to first exacerbation, particularly in the PAL sub-group; and safety profiles comparable to those of the ICS/LABA formulation, with no significant increase in adverse events. Subsequent post-hoc analyses enhanced understanding of the heterogeneity amongst the various patient subpopulations enrolled in the phase III trials and the seasonal impact.[30–33] These analyses suggest that triple therapy may offer particular benefits to specific sub-groups, as follows:

- Patients with greater airway reversibility exhibited a more pronounced response to BDP/FF/GB.
- Seasonal exacerbation rates exhibited a peak during winter, a period that BDP/FF/GB was able to attenuate, particularly in patients with PAL.
- Notably, BEC did not exert a significant influence on treatment response, thereby supporting its wide applicability.

SITT has also shown benefits in improving respiratory function and reducing FeNO. Studies have supported these findings, with reports of faster symptom relief, sustained improvement in lung function measures and reduced type 2 inflammation.[34] These benefits are attributed to the uniform delivery of all therapeutic components, which optimize bronchodilation whilst simultaneously reducing airway inflammation. In addition, patients with SAD or persistent airflow limitation appear to derive greater benefit from SITT due to its enhanced deposition in the distal airways.

In this context, a further *post hoc* analysis of the TRIGGER and TRIMARAN trials examined whether airflow limitation (particularly post-salbutamol PAL) is a stable phenotype. The data showed a reduction in the prevalence of PAL of 23% (p=0.063) and 31% (p=0.017) for patients receiving BDP/FF/GB in TRIMARAN and TRIGGER, respectively.[31]

From a pharmacokinetic perspective, SITT formulations are designed to optimize the delivery of all components simultaneously, ensuring consistent therapeutic coverage throughout the bronchial tree, including the small airways. Studies comparing SITT with MITT have shown that patients on SITT reported a better quality of life and experienced fewer hospitalizations due to exacerbations.[35] However, MITT may still be preferred in cases where specific dose titration or flexibility is required such as in patients with varying severity of asthma or comorbidities.[36]

The results from the literature described above are confirmed in the present clinical case, in which a patient with severe asthma in EGPA was being treated with high-dose mepolizumab and was experiencing declining lung function, frequent use of OCS, severe dyspnoea that severely impaired quality of life and high FeNO levels. By simply switching from MITT to SITT, the patient showed considerable improvement in clinical status, respiratory function, patient-reported outcomes and biomarkers. To date, few cases have been published in the literature on the efficacy of SITT in improving the complex clinical picture of patients with severe asthma. A retrospective cohort study of SITT with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) showed that patients with asthma had significantly fewer flare-ups and reduced use of OCS and short-acting β-agonists after starting treatment with fluticasone furoate/umeclidinium/vilanterol compared to the pre-treatment period.[34]

To date, only one study has investigated treatment with extra-fine SITT in severe asthma, in which the authors treated 32 patients for only 3 months and demonstrated that the transition from MITT to extra-fine SITT resulted in significant improvements in ACT and SAD parameters, including an increase in FEV and an improvement in airway resistance and responsiveness parameters measured by impulse oscillometry. In addition, a significant reduction in airway inflammation was demonstrated by a reduction in FeNO (p<0.001).[37]

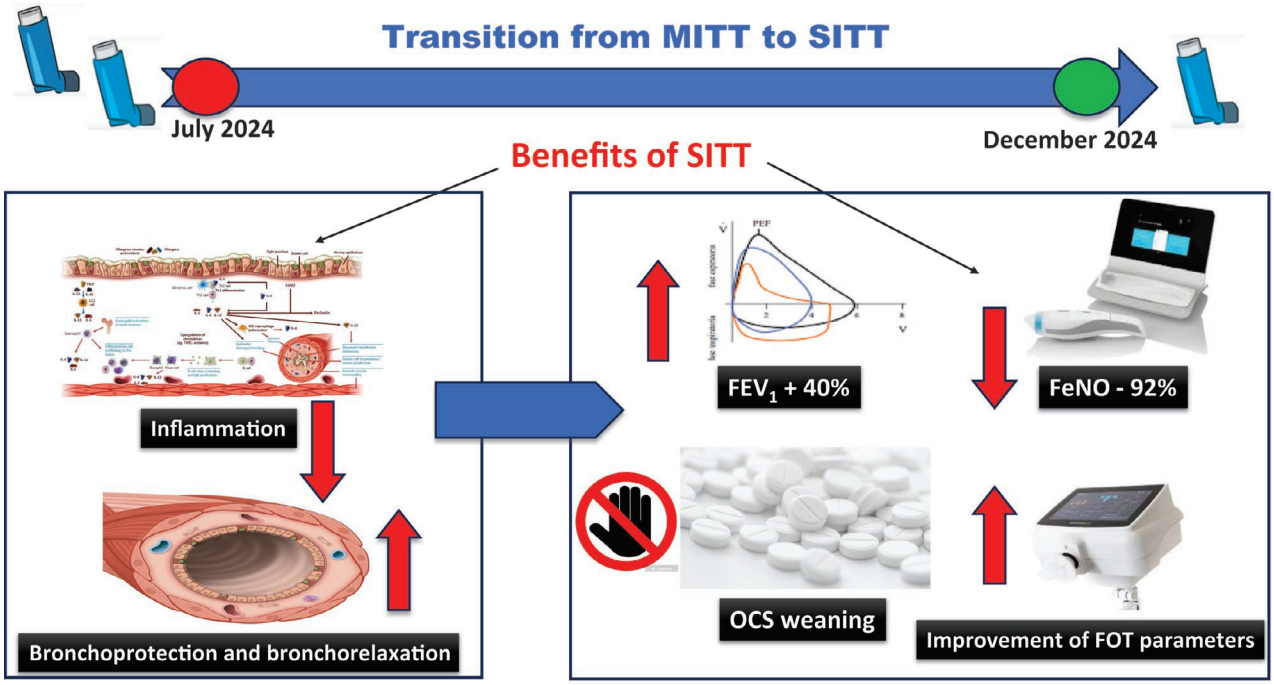
Within the limitations of a case report, the complexity of our patient's clinical picture and the large and rapid improvement in asthma control, respiratory function and biomarkers after the initiation of SITT support the use of this therapeutic option in patients with EGPA and asthma (Figure 3). Therefore, more attention should be paid to this option for eligible patients, sometimes even early in the clinical course of a patient to achieve the best possible results. It is important to reevaluate the patient over a longer period of observation and treatment to define the sustainability of the excellent results achieved in the short term and any further changes in the parameters studied.

The findings from this case highlight several key points for the management of asthma and EGPA:

- Targeting SAD and FeNO: inhaled therapies with extra-fine formulations are essential to effectively treat SAD, reduce FeNO and improve asthma control.
- Early detection of SAD, PAL and type 2 inflammation: incorporating advanced PFTs, FeNO monitoring and imaging into routine assessment can help stratify patients and guide therapeutic decisions.
- Personalized treatment approaches: combining biologics with optimized inhaled therapies tailored to disease phenotype is critical for the management of severe asthma and EGPA.
- Inhaler simplification: the use of SITT can improve adherence and respiratory function, lower FeNO and reduce inhaler technique errors, contributing to better outcomes.
- Multidisciplinary care: addressing comorbidities, such as CRSwNP, and tailoring interventions through a team-based approach are critical to achieving comprehensive disease control.

The latest GINA guidelines have not yet defined the precise position of SITT in relation to MITT and biologics or

Figure 3. Pathophysiological mechanisms and effects of MITT to SITT transition.



FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FOT, forced oscillometry; MITT, multiple-inhaler triple therapy; OCS, oral corticosteroids; SITT, single-inhaler triple therapy.

the importance of SAD and PAL in asthma management; this omission has been described by some authors as the 'silent zone' of the GINA report.[38,39] However, based on the results of the current literature the following recommendations can be made:

- SITT should be considered before biologics in patients with moderate-to-severe asthma who remain uncontrolled on ICS/LABA.
- High-dose ICS as part of SITT is preferable to high-dose escalation of ICS/LABA alone.
- Triple therapy offers an alternative to OCS in selected patients.

Based on the current evidence, the following treatment strategies are proposed: (1) in uncontrolled moderate asthma, medium-dose SITT could be considered in patients with PAL and/or SAD before switching to high-dose ICS/LABA; (2) in severe asthma with PAL or frequent exacerbations, high-dose SITT is recommended before switching to systemic corticosteroids or biologics. Assessment of adherence and inhaler techniques are critical to optimizing outcomes.

Conclusion

This case highlights the challenges of managing EGPA in the context of severe asthma. Whilst biologics, such as mepolizumab, have revolutionized the treatment of EGPA, adjunctive therapies targeting SAD, PAL and type 2 inflammation, such as extrafine SITT, are essential to optimizing outcomes. A multidisciplinary approach incorporating personalized treatment strategies, FeNO monitoring and a simplified inhaler regimen can significantly improve disease control and quality of life for patients with EGPA. Further research is needed to refine therapeutic algorithms, explore new biological agents and investigate the role of advanced imaging and biomarkers in guiding therapy in this complex disease. Extrafine SITT represents an important advance in the treatment of asthma, improving control and reducing exacerbations in patients with persistent airflow limitation or frequent exacerbations. Further research is needed to refine patient selection and long-term treatment strategies.

Contributions: FM designed, wrote and approved the manuscript. The other authors contributed equally to the preparation of this manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2025/04/dic.2025-2-3-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/switching-from-multiple-inhaler-triple-therapy-to-single-extra-fine-inhaler-triple-therapy-in-severe-refractory-asthma-with-egpa-beyond-control-case-report-and-review-of-the-literature

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Provenance: Invited; externally peer reviewed.

Submitted: 18 February 2025; **Accepted:** 31 March 2025; **Published:** 29 April 2025.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

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