ORIGINAL ARTICLE

Analysis of trends in single inhaler triple therapy (SITT) use and clinical characteristics of patients with severe asthma: data from the IRSA registry

SITT in severe asthma: an IRSA registry analysis

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Summary

Background. Triple therapy with inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA), and long-acting muscarinic antagonists (LAMA) is recommended for severe asthma patients with uncontrolled symptoms. Single-inhaler triple therapy (SITT) may offer additional clinical and practical benefits. This study analyzes the clinical profiles of patients receiving LAMA-containing regimens using real-world data from the Italian Registry on Severe Asthma (IRSA). **Methods.** We conducted a cross-sectional analysis of 2,155 patients with severe asthma enrolled in IRSA between 2018 and May 2025. Patients were stratified based on LAMA use ("LAMA Yes" vs. "LAMA No") and assessed across demographics, lung function, biomarkers, asthma control, healthcare utilization, and comorbidities. **Results.** Patients on triple therapy were older, had a greater smoking history, and worse lung function (FEV_1 and FVC, $p<0.001$). They also reported poorer asthma control (mean ACT 16 vs. 17.5, $p<0.001$), more exacerbations (3.6 vs. 2.8/year, $p<0.001$), higher systemic corticosteroid use, and more comorbidities, including obesity and bronchiectasis. Interestingly, no significant differences were observed in type 2 inflammation markers (eosinophils, FeNO). The odds of receiving a LAMA prescription increased with age and a higher number of exacerbations. **Conclusions.** Triple therapy, especially through SITT, identifies a clinically complex asthma phenotype with a high disease burden. Despite growing evidence supporting efficacy and adherence benefits, triple therapy remains relatively underutilized in clinical

practice, albeit with a significant increase from 2023 to the present. These findings highlight the need for more careful prescribing and further real-world evidence to optimize SITT positioning before escalation to biologic treatments.

Key Words

Triple therapy; asthma; biomarkers; exacerbations; lung function.

Introduction

Severe asthma is a heterogeneous condition that affects a minority of asthma patients but consumes a disproportionate share of healthcare resources due to poor symptom control and frequent exacerbations. International guidelines recommend a stepwise approach to therapeutic management, which includes treatment intensification for uncontrolled patients. The addition of a long-acting muscarinic antagonist (LAMA) to baseline inhaled corticosteroid (ICS) and long-acting β2-agonists (LABA) therapy (triple therapy) has been shown to be effective in improving lung function and reducing exacerbations.

Managing severe asthma requires a personalized approach that incorporates the identification of treatable traits. Among these, small airways dysfunction (SAD) and persistent airflow limitation (PAL) have emerged as important phenotypes. However, these are still under-recognized in current GINA guidelines (1–3).

As highlighted by the ATLANTIS study cohort, SAD is present in over 90% of asthma patients, regardless of disease severity, and is associated with poorer asthma control (4). PAL, defined as post-bronchodilator FEV_1 (Forced Expiratory Volume in 1 second)/FVC (Forced Vital Capacity) ratio < lower limit of normal (LLN), is also observed in patients with mild asthma and represents a strong predictor of exacerbations (5–6). This suggests the need for more intensive treatment even in milder cases (3,5,6). A critical point of asthma management concerns the method of administration of inhalation therapy, which is even more important for triple therapy. Multiple-inhaler triple therapy (MITT) involves the use of two separate inhalers, ICS/LABA and a LAMA. In contrast, extrafine single-inhaler triple therapy (SITT) consolidates all three components into a single inhaler (7).

In this regard, the pivotal phase 3 TRIMARAN and TRIGGER studies evaluated the efficacy of BDP/FF/GB extrafine (beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide) compared with BDP/FF in patients with uncontrolled moderate-severe asthma (3). The results showed significant improvement in quality of life, longer time to first exacerbation, particularly in the PAL subgroup, and safety profiles overlapping with those of the ICS/LABA formulation. Currently, SITT BDP/FF/GB is the only option available in Italy approved by the Italian Medicines Agency AIFA.

Although both approaches provide the same pharmacological agents, SITT confers significant clinical but also practical advantages, combining ICS, LABA, and LAMA in a single device, aims to control type 2 inflammation, improve bronchial obstruction and reduce polypharmacy and enhance adherence (7,8). This strategy enables simultaneous targeting of multiple pathophysiological mechanisms (8).

This study aims to characterize and compare patients treated with triple therapy (LAMA Yes) versus those on dual therapy (LAMA No) in the real-world setting of the Italian Registry on Severe Asthma (IRSA).

Materials and methods

A cross-sectional analysis was performed on data extracted in July 2025 from the IRSA registry, an observational, multicenter registry including 98 Allergy and Pulmonology centers distributed across Italy. Details on the set-up of the registry and methods of data collection have been previously reported (9). For

the definition of T2 status, two cut-off values for eosinophils have been used, reflecting the criteria for prescription of biologics in Italy:

• T2_300 phenotype (T2high): total IgE > 150 and/or eosinophils > 300 and/or Fractional Exhaled Nitric Oxide (FeNO) > 25;

• T2_150 phenotype (T2high + T2low): total IgE > 150 and/or eosinophils > 150 and/or FeNO > 25.

Patients not included in the two above-mentioned categories were considered as “non-T2 phenotype” (i.e., total IgE ≤ 150 + eosinophils ≤ 150 + FeNO ≤ 25).

All the patients enrolled between 2018 and May 2025 were extracted for the analysis (study population).

Demographics, lung function, inflammatory biomarkers, asthma control, therapeutic options, and comorbidities were analyzed and compared between patients on LAMA therapy and those not on LAMA therapy. Based on this classification, patients were then categorized into two subgroups: "LAMA Yes" if on treatment with ICS/LABA/LAMA triple therapy (MITT or SITT), and "LAMA No" if on treatment with ICS/LABA dual therapy or other therapies not containing a LAMA.

The following baseline variables were analyzed:

- Demographics: sex, age, body mass index (BMI), education level, smoking status.
- Lung function: FEV_1 and FVC, pre- and post-bronchodilator (BD).
- Biomarkers: blood eosinophil count, total IgE, and Fraction of Exhaled Nitric Oxide (FeNO).
- Asthma control and healthcare utilization: Asthma Control Test (ACT), exacerbations (annual incidence rate, frequency of patients with exacerbations), emergency room (ER) visits, and hospitalizations in the previous 12 months.
- Concomitant therapies: use of oral corticosteroids (OCS), biologics, and bronchial thermoplasty.
- Comorbidities: sinusitis, nasal polyps, obesity (BMI > 30), osteoporosis, diabetes, bronchiectasis.

Statistical analysis

Differences between the two groups were assessed using t-test and chi-squared test for continuous and categorical variables, respectively, on both the total population and on a subgroup of patients enrolled between 2023 and May 2025, as a sensitivity analysis to increase the number of patient on LAMA. A multiple logistic regression was performed to identify variables associated with LAMA prescription. The covariates for the model were chosen based on the results of the correlations found between baseline characteristics and LAMA use, and on clinical judgement after checking for collinearity. Results were reported as means (with standard deviations), absolute and relative (%) frequencies, or odds ratios (with 95% Confidence intervals), as appropriate. A p-value < 0.05 was considered statistically significant. A complete case strategy was adopted to handle missing data for each variable, since they resulted as missing completely at random from previous sensitivity analyses on IRSA (9). All the analyses were performed with STATA v 18.5 (StataCorp LLC, Texas, USA).

Results

Demographic and Clinical Characteristics

A total of 2,155 patients with a diagnosis of severe asthma were included in the analysis. Patients in the "LAMA Yes" group (37.1%) were significantly older (mean age 57.6 vs. 54.4 years, <0.001) and had a more significant smoking history in terms of both frequency of active/ex smokers (32% vs. 26.8%, p=0.019) and pack/years (16.7 vs. 12.6, p=0.001), compared with patients not on LAMA (62.9%). There were no significant

differences in terms of educational level (Table 1). The sensitivity analysis strongly confirmed the relationship between LAMA and exposure to smoke (Table S1), but not with age, due to the lower sample size.

Lung Function and Inflammatory Biomarkers

The "LAMA Yes" group showed significantly greater impairment in respiratory function, with lower FEV_1 and FVC values, both in liters and as a percentage of predicted ($p<0.001$ for all parameters in the sensitivity analysis shown in Table S2). From the point of view of biomarkers, there were no significant differences in blood eosinophil count (BEC) (mean 481/mm³ vs. 502/mm³, p=0.513). While the mean blood eosinophil count (BEC) did not differ significantly, a stratified analysis showed a significant difference in eosinophil categories (p=0.020), suggesting a less pronounced T2 inflammatory profile in patients using LAMA (Table 2).

Asthma Control and Therapies

Consistent with the more severe clinical picture, patients on triple therapy had worse disease control, as indicated by lower mean ACT scores (16 vs. 17.5, $p<0.001$) and a higher percentage of patients with uncontrolled disease (ACT<20: 72.2% vs. 59%, $p<0.001$). This aspect was translated into a higher mean number of annual exacerbations (3.6 vs. 2.8, $p<0.001$) and greater use of specialist visits, ER visits, and hospitalizations ($p<0.001$) (Table 3). Chronic OCS use was significantly more frequent in the LAMA group (32.4% vs. 27.3%, p=0.017), as was the mean daily dose (23.8 mg vs. 11.8 mg, $p<0.001$) (Table 3).

Comorbidities

The comorbidity profile differed significantly. Patients in the "LAMA Yes" group had a higher prevalence of obesity (BMI>30: 23.9% vs. 17.9%, $p<0.001$), osteoporosis (21.3% vs. 15.6%, $p<0.001$), diabetes (9.7% vs. 7.1%, p=0.016), and bronchiectasis (24.7% vs. 18.4%, $p<0.001$). Surprisingly, the prevalence of sinusitis and nasal polyps was significantly lower in this group ($p<0.001$ for both).

Factors associated with triple therapy prescription

To identify the factors independently associated with the prescription of LAMA at baseline, we performed a multiple logistic regression analysis. The final model included 1,273 patients and was statistically significant. The results of the regression are detailed in Table 4.

The analysis identified several significant predictors of LAMA use. The odds of being prescribed a LAMA increased with age (OR 1.02, 95% CI [1.01, 1.03], p=0.001). The frequency of severe exacerbations was also a strong predictor; compared to patients with no exacerbations in the previous year, the odds of receiving LAMA were significantly higher for those with 2 exacerbations (OR 1.76, 95% CI [1.21, 2.56], p=0.003) and for those with more than 2 exacerbations (OR 2.49, 95% CI [1.78, 3.47], $p<0.001$).

Conversely, two factors were associated with lower odds of LAMA prescription. Patients with a FEV_1/FVC preBD ratio ≥ 0.70 had lower odds of being on LAMA therapy (OR 0.70, 95% CI [0.55, 0.89], p=0.003). The presence of nasal polyps was also associated with lower odds of LAMA use (OR 0.65, 95% CI [0.51, 0.83], $p<0.001$).

Patient sex, smoking status, obesity (BMI ≥ 30 kg/m²), and age of symptom onset were not significantly associated with LAMA prescription in this model.

Stratification of triple therapy prescription

Out of 2,155 severe asthma patients, 37.1% were on triple therapy (MITT or SITT). In the overall population enrolled in the IRSA registry, the percentages of patients in SITT and MITT were 2% and 35.2%, respectively. In detail, patients in Medium Strength SITT were 0.6% while those in High Strength SITT were 1.6%. Regarding the MITT subgroup, patients on tiotropium 5 mcg were 26.3% and those on tiotropium 18 mcg 8.9%. When evaluating clinicians' prescribing habits, the prevalence of patients on triple therapy (MITT+SITT) rose from 43.75% in 2018 to 83.3% in May 2025 (+90.4%). Looking only at SITT prescriptions, in 2023 (the year it was introduced on the Italian market), 8.76% had received this therapy, in 2024 36.76%, and finally in the first 5 months of 2025, 41.67% (+375.7%) (Figure 1).

Regarding patients undergoing biological therapy, 54.9% of these were in MITT or SITT. A notable trend was observed in the use SITT among patients with severe asthma treated with biologics versus those not receiving biologic therapy (Figure 2). Overall, SITT was prescribed nearly twice as frequently in patients not receiving biologics compared to those on biologics (2.79% vs 1.39%). However, the temporal trend indicates that this difference gradually diminished over the years and became non-significant in 2025. This narrowing gap may reflect improved precision in therapy selection or evolving clinical prescribing practices. Nevertheless, these findings should be interpreted cautiously due to the limited sample size for 2025, which includes only the first few months of the year.

Discussion

In the Italian real-life setting, patients with severe asthma treated with triple therapy represent a population with a greater disease burden, characterized by worse control, more compromised lung function, and a less pronounced T2 inflammatory profile. The addition of a LAMA identifies a more complex and difficult-to-manage patient phenotype.

International guidelines recommend a stepwise approach to therapeutic management, which includes treatment intensification for uncontrolled patients. The addition of a LAMA to baseline ICS/LABA therapy (triple therapy) has been shown to be effective in improving asthma control.

Real-world data from registries are essential to understand how this option is used in clinical practice and the characteristics of the patients who receive it. The Italian Registry on Severe Asthma (IRSA), a result of the collaboration between AAIITO (Associazione Allergologi Immunologi Italiani Territoriali e Ospedalieri) and Associazione Italiana Pneumologi Ospedalieri - Italian Thoracic Society (AIPO-ITS), prospectively collects data from a large cohort of patients throughout the country. The purpose of this analysis was to describe and compare the baseline characteristics of patients with severe asthma enrolled in the IRSA registry, stratifying them by the use or non-use of a LAMA-containing therapy.

This analysis from the IRSA registry provides a detailed snapshot of the severe asthma patient treated with triple therapy in Italy. The data clearly show that the addition of a LAMA is not a random choice but identifies a subgroup of patients with an intrinsically more severe and complex disease.

The profile of the patient on triple therapy (older, with a greater smoking history, higher BMI, and worse bronchial obstruction) suggests the presence of features that may overlap (at least in part) with those of Chronic Obstructive Pulmonary Disease (COPD). The lower evidence of T2 inflammation in this group reinforces the hypothesis that LAMA is preferentially used in patients with disease mechanisms that are not purely allergic or T2-mediated, where cholinergic bronchospasm plays a more relevant role.

However, it should be reiterated that the addition of LAMA can also be effective in patients with T2 asthma endotype, as demonstrated by a post-hoc analysis of the TRIMARAN and TRIGGER studies, where SITT demonstrated efficacy regardless of BEC (10).

The poorer clinical control, higher number of exacerbations, and greater consumption of healthcare resources and OCS confirm that triple therapy is correctly used as a step-up treatment in patients who do not respond adequately to standard therapies. The association with systemic comorbidities like diabetes and osteoporosis is likely an indirect marker of the greater disease burden and the more frequent and prolonged use of systemic steroids. The finding of a lower prevalence of nasal polyps in the LAMA group is difficult to interpret and warrants further investigation; it could reflect the existence of distinct severe asthma endotypes, in which upper and lower airway pathology are not always correlated. Furthermore, althoughThis insights are essential polyps comorbidity is a well-known worsening factor in severe asthma, it has been demonstrated that this kind of patients are better responders to treatments, and probably they do not need step-up of treatment (11).

Confirming these claims, our study identified several significant predictors of LAMA use. The odds of receiving a LAMA prescription increased with age. The frequency of severe exacerbations was also a strong predictor, particularly for patients with more than two exacerbations per year.

However, the cross-sectional design of the study requires highlighting that the data represent an *association*, not a causality. For example, the results show that patients with more severe disease are *prescribed* LAMA therapy; the therapy is not the *cause* of their severe disease. It should be reiterated that this distinction is critical for the correct interpretation of the findings.

At present, little real-life evidence has yet been published. In an interesting Italian observational study, 32 patients with severe asthma and small airway dysfunction (SAD) were switched from separate ICS/LABA and LAMA inhalers to SITT (extrafine beclomethasone/formoterol/glycopyrronium) (12). None had previously received biologic treatments. After three months, patients showed significant clinical improvements, including ACT scores, enhanced large and small airway function (spirometry and oscillometry), and reduced airway inflammation (FeNO at 350 ml/s, $p < 0.001$). These findings support the effectiveness of SITT as an optimized treatment strategy for patients with uncontrolled asthma and SAD.

The available clinical evidence suggests:

- SAD and PAL are relevant and independent risk factors (2,4,6,13)
- SITT is effective in patients inadequately controlled with ICS/LABA, particularly in those with PAL and SAD (11,12)
- Medium-dose SITT may serve as a safer alternative for patients at risk of ICS-related side effects (14)
- A therapeutic trial of SITT should be considered before escalating to biologic therapy (14)

According to the Cochrane review, SITT particularly the high-dose formulations, reduces asthma flare-ups and is probably better tolerated due to fewer side effects than dual therapy. In addition, triple inhaled therapy may or may not improve symptoms or quality of life compared with dual therapy. Increasing the potency of inhaled steroids from medium to high doses is probably beneficial in triple inhaled therapy, but probably not in dual therapy (15).

In our study, the comparative analysis highlighted that the group on LAMA therapy had a significantly higher use of oral corticosteroids (OCS). The prevalence of patients treated with OCS was 32.4% in the LAMA group versus 27.3% in the non-LAMA group ($p=0.017$), with the daily dose also being significantly higher. Regarding biologic therapies, a trend of slightly lower use was observed in the LAMA group (63.0% vs 66.7%), with borderline statistical significance ($p=0.051$).

No marked differences emerged for the use of high-dose ICS (according to GINA or ERS criteria, as shown by the sensitivity analysis in Table S3), nor for the prescription of individual biologic drugs (omalizumab,

mepolizumab, benralizumab, dupilumab). The data from this analysis suggest that, in the real-world context of the IRSA registry, patients with severe asthma on LAMA therapy present a profile of greater clinical severity. This is robustly evidenced by the greater dependence on oral corticosteroids, both in terms of prevalence of use and overall therapeutic burden (duration and dosage).

The addition of a LAMA to maximal inhaled therapy is therefore configured as a strategy adopted in particularly complex and inadequately controlled patients. The signal of a lower use of biologic drugs in this subgroup, although not fully significant, could indicate that for some patients, the optimization of bronchodilation with LAMA could be a key factor. However, after the marketing authorization of beclometasone/formoterol/glycopyrronium formulated as SITT in Italy, the use of LAMA has progressively increased from 2023 also in patients on biologic therapy, suggesting an important role of triple therapy not only before, but also after initiation of biologics, especially in the absence of a clear T2-guided phenotype.

Phase 3 TRIMARAN and TRIGGER studies evaluated the efficacy of BDP/FF/GB compared to ICS/LABA therapy. Primary endpoints included improvement in pre-dose FEV_1 and reduction in exacerbation rates (3). Key results were a significant increase in FEV_1 and PEF at 26 weeks (11), 15–20% reduction in exacerbation rates, prolonged time to first moderate or severe exacerbation with a comparable safety profile (3). In patients with PAL, triple therapy demonstrated superior efficacy with a 33.5% reduction in severe exacerbations (12). Benefits were particularly evident during seasonal peaks (16) and were independent of eosinophil levels or reversibility (9). In another post-hoc analysis of the TRIMARAN and TRIGGER studies, BDP/FF/G SITT has shown the ability to normalize airflow in a subset of asthma patients who initially present with persistent airflow limitation (PAL), suggesting that PAL is not always a fixed trait. Data from the TRIMARAN and TRIGGER trials showed significant improvements in lung function, with PAL reductions of 23% and 31%, respectively. These findings support the role of triple therapy in reversing airflow obstruction and challenge the stability of PAL as a defining asthma phenotype (17).

Data from the IRSA registry show an increasing prescription trend of triple therapy, especially in patients with low T2 biomarkers, SAD, PAL, or seasonal exacerbation patterns.

For comparison, a previous IRSA registry analysis published in 2023 showed that 36.8% of patients enrolled were on triple therapy while a Severe Asthma Network Italy (SANI) registry analysis showed that 35.9% had been treated with LAMA in addition to ICS/LABA (in both studies no distinction was made between MITT and SITT because they predated the introduction in Europe and Italy) (9,18).

The analysis conducted on the large real-world cohort from the IRSA registry provides a detailed picture of the clinical profile of severe asthma patients prescribed a triple therapy including a LAMA. Our results show that, in routine clinical practice, patients receiving triple therapy represent a subgroup with a significantly higher disease burden compared to those on dual therapy. This phenotype is characterized by older age, higher BMI, a greater smoking history, more impaired lung function, and most notably, poorer asthma control, as evidenced by lower ACT scores and a higher frequency of exacerbations and healthcare resource utilization. These real-world data help fill an important knowledge gap left by randomized controlled trials (RCTs). While RCTs demonstrate the efficacy of triple therapy in highly selected patient populations, the present analysis provides insight into the actual patient profiles receiving this treatment in clinical practice. Our findings help clarify the appropriate positioning of triple therapy across different asthma pheno/endotypes. Specifically, we observed that patients on LAMA-containing regimens often exhibit a less pronounced type 2 inflammatory profile, with significantly lower blood eosinophil counts and FeNO levels. This suggests a clinical tendency to employ LAMAs in patients with less eosinophilic airway obstruction, where cholinergic mechanisms may play a predominant role.

Our observations are consistent with the literature identifying extrafine triple therapy as an effective option for patients with difficult-to-control asthma. The “LAMA Yes” cohort, showing the poorest clinical control, represents the ideal target for therapeutic intensification.

Based on the data, LAMA add-on therapy appears to be underutilized, as many patients on dual therapy still experience poor control and frequent exacerbations, suggesting a need for treatment escalation. This real-world evidence points to a critical need to improve prescribing appropriateness. Future challenges include defining a “LAMA user” phenotype to better guide therapeutic decisions and generating more real-world evidence to identify ideal candidates for SITT.

The results strongly support using SITT as a “pre-biologic trial,” especially for patients with poor control and a non-prominent T2 inflammatory profile. This approach could significantly improve clinical outcomes and potentially delay or avoid the need for biologic therapy, offering both clinical and healthcare sustainability benefits. To achieve this, it is essential to integrate various diagnostic techniques to precisely define each patient's phenotype and ensure the highest therapeutic appropriateness.Although its use is growing since the 2023 introduction of SITT, triple therapy prescription in Italy remains limited, a finding supported by previous analyses. The prescription of triple therapy in Italy is still limited—a fact consistent with prior research—though it has been increasing since SITT became available in 2023.. In any case, increasing the prescribing trend may have important implications in terms of improving clinical outcomes, as highlighted by clinical trials (16). In this regard, a recent real-life Italian study showed that 34.6% of a small cohort of patients treated with SITT after switch from MITT at 1-year follow-up did not require add-on biologic therapy due to improved control (19).

A very important aspect in the daily management of asthma at any level of severity is treatment adherence. In this regard, a retrospective cohort study compared the adherence of asthma patients who had started different forms of MITT (n = 5,115) and one of the SITT options available in the United States (i.e., fluticasone furoate-umeclidinium-vilanterol) (n = 1,396) by observing them for 12 months (20). Adjusting for baseline differences in the MITT and SITT cohort, the authors found that patients starting SITT were 31% more likely to be adherent (proportion of days covered ≥ 0.8: 40.6% vs. 31.3%) and 49% more likely to be persistent (25.9% vs. 15.1%).

Another very important point is the direct and indirect costs of asthma. A pharmacoeconomic study used a Markov cohort state transition model (focused on exacerbations) to study the cost-effectiveness of SITT BDP/FF/G medium- or high-dose versus BDP/FF medium- or high-dose and BDP/FF/G high-dose versus BDP/FF high-dose + tiotropium (21). This model examined cost, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER) based on the English National Health Service perspective (2020 costs). The results showed that both mid- and high-dose SITT were cost-effective compared with mid- and high-dose BDP/FF in adults with asthma not controlled by ICS/LABA. In addition, high-dose SITT was superior to MITT with high-dose BDP/FF + tiotropium. It will then be crucial to confirm this evidence in terms of lower cost uptake with real data as well, possibly multicenter prospective data. For all these reasons, a step change and greater attention to the benefits of this treatment option in frail and complex patients is needed.

Our study has some limitations that should be highlighted. It is a cross-sectional analysis of registry data, without the possibility of defining clinical outcomes due to the study design. Furthermore, the 2025 data are limited to the first 5 months of the year, so the data for this year should be interpreted with caution and will need to be confirmed in future analyses on IRSA, when the number of patients enrolled in 2025 becomes large enough to make the data more reliable.

Concluding remarks

This real-world analysis from the IRSA registry shows that severe asthma patients receiving triple therapy in Italy present with the highest disease burden and clinical complexity. Although prescribing trends are improving, there remains substantial room for optimization. These findings reinforce the need for further real-world evidence to support more appropriate prescribing practices and validate the strategic positioning of triple therapy—particularly SITT—as a key therapeutic step to consider prior to initiating biologic treatments, especially in patients with non-T2-dominant inflammatory profiles. These insights are essential to guide future research and further personalize the therapeutic approach in this complex disease.

Our cross-sectional study from registry data provides an interesting and useful snapshot of Italian clinicians' approach to the management of severe asthma with a focus on triple therapy; it will then be important to reevaluate this information longitudinally and prospectively in order to understand how prescriptive attitudes and management evolve in the Italian national context. Simplification of the inhalation regimen, such as the application of SITT, can be useful for the majority of patients given the positive clinical, adherence, and pharmacoeconomic outcomes, without ever forgetting the sharing of decisions, and the educational aspects. Consequently, a personalized approach is of utmost importance.

Supplementary material

Available at: https://zenodo.org/records/16785798

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Contributions

FM: conceptualization, coordination, writing - original draft. MM, MMB, LA, LC, FDM, AV, AM, CM: writing - original draft. MM: statistical analysis. All authors: writing - review & editing, patients enrollment.

Conflict of interests

FM reports research grants and fees for talks and consulting from GlaxoSmithKline, AstraZeneca, Sanofi-Regeneron, Chiesi, Merck, Insmed. MM reports personal fees from Chiesi Farmaceutici (consulting), GlaxoSmithKline (consulting, talks), Sanofi (talks), and AstraZeneca (consulting). The other authors declare that they have no conflict of interests related to this work.

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Table 1. *Demographic and clinical characteristics*

	Long acting muscarinic antagonist (LAMA)		
	No	**Yes**	**Test**
N	1,356 (62.9%)	799 (37.1%)	
Gender			
Males	538 (39.7%)	312 (39.0%)	0.774
Females	818 (60.3%)	487 (61.0%)	
Age	54.462 (14.508)	57.632 (12.934)	<0.001
BMI	27.139 (16.351)	27.389 (10.297)	0.705
Education level			
High school diploma	664 (49.0%)	362 (45.3%)	0.066
Bachelor's degree	235 (17.3%)	128 (16.0%)	
Elementary/middle school diploma	457 (33.7%)	309 (38.7%)	
Countryside residence			
No	711 (81.5%)	468 (79.6%)	0.355
Yes	161 (18.5%)	120 (20.4%)	
Smoking			
Never	831 (73.3%)	543 (68.0%)	0.019
Ex	249 (22.0%)	220 (27.5%)	
Yes	54 (4.8%)	36 (4.5%)	
Pack/years	12.593 (13.327)	16.730 (15.951)	0.001
Active exposure to smoke			
No	831 (73.3%)	543 (68.0%)	0.011
Yes	303 (26.7%)	256 (32.0%)	
Age at onset of symptoms	32.289 (85.950)	33.150 (73.927)	0.822
Age at diagnosis	37.301 (81.409)	43.722 (126.778)	0.305

Data are means (standard deviation) or frequencies (%)
BMI, Body Mass Index.

Table 2. Lung function and biomarkers.

	Long acting muscarinic antagonist (LAMA)		
	No	**Yes**	**Test**
N	1,356 (62.9%)	799 (37.1%)	
FEV_1 (L)	2.462 (8.647)	2.320 (9.532)	0.770
FEV_1 (%)	75.178 (20.292)	67.670 (21.084)	<0.001
FEV_1 postBD (L)	3.860 (49.031)	5.159 (84.903)	0.683
FEV_1 postBD (%)	81.846 (21.091)	75.105 (21.540)	<0.001
FVC (L)	3.695 (10.641)	12.685 (167.275)	0.123
FVC (%)	90.165 (18.672)	83.876 (19.376)	<0.001
FVC postBD (L)	8.494 (116.408)	9.918 (136.034)	0.813
FVC postBD (%)	94.570 (18.535)	88.840 (18.846)	<0.001
FEV_1/FVC (%)	71.238 (14.584)	69.747 (30.071)	0.220
FEV_1/FVC postBD (%)	73.882 (15.171)	72.198 (29.049)	0.111
FEV_1/FVC ≥ 70%			
No	371 (45.1%)	320 (56.8%)	<0.001
Yes	451 (54.9%)	243 (43.2%)	
IgE value	537.315 (1,409.548)	487.337 (1,322.122)	0.559
Eosinophils (%)	6.387 (6.436)	6.340 (6.062)	0.872
Eosinophils (cells/mm3)	502.179 (756.922)	481.066 (565.207)	0.513
Eosinophil (categories)			
<150 cells/mm3	321 (30.0%)	197 (25.5%)	0.020
150-300 cells/mm3	168 (15.7%)	154 (19.9%)	
>300 cells/mm3	580 (54.3%)	422 (54.6%)	
FENO value ppb	45.873 (41.317)	40.524 (40.286)	0.083
Allergic asthma			
No	322 (29.5%)	252 (32.5%)	0.176
Yes	768 (70.5%)	524 (67.5%)	
T2_300*			
No	290 (26.5%)	216 (27.4%)	0.658
Yes	806 (73.5%)	573 (72.6%)	
T2_150°			
No	189 (17.2%)	120 (15.2%)	0.239
Yes	907 (82.8%)	669 (84.8%)	

Data are means (standard deviation) or frequencies (%)

BD, Bronchodilator; FeNO: Fractional Exhaled Nitric Oxide; FEV1 : Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; ppb, parts per billion.

*T2_300 phenotype: IgE > 150 and/or Eos > 300 and/or FeNO > 25

°T2_150 phenotype: IgE > 150 and/or Eos > 150 and/or FeNO > 25

Table 3. Asthma control and treatments.

Variable	No LAMA (N=1,356)	Yes LAMA (N=799)	Test (p-value)
Asthma Control			
ACT Score	17.5 (5.3)	16.0 (5.0)	<0.001
ACT < 20 (Not Controlled)	619 (59.0%)	539 (72.2%)	<0.001
Exacerbations (last 12 months)			
Annual incidence rate	2.8 (3.4)	3.6 (4.3)	<0.001
Exacerbation Category			<0.001
0 Exacerbations	252 (23.2%)	109 (14.1%)	
1 Exacerbation	182 (16.8%)	99 (12.8%)	
2 Exacerbations	242 (22.3%)	178 (23.1%)	
>2 Exacerbations	408 (37.6%)	385 (49.9%)	
Emergency Room Visits	224 (20.6%)	211 (27.4%)	<0.001
Hospitalizations	0.18 (0.64)	0.33 (0.90)	<0.001
Therapies			
High ICS Dose (GINA)	601 (44.3%)	460 (57.6%)	<0.001
Biologic Therapy	711 (52.4%)	439 (54.9%)	0.259
OCS Maintenance Use	300 (27.3%)	256 (32.4%)	0.017

Data are means (standard deviation) or frequencies (%)

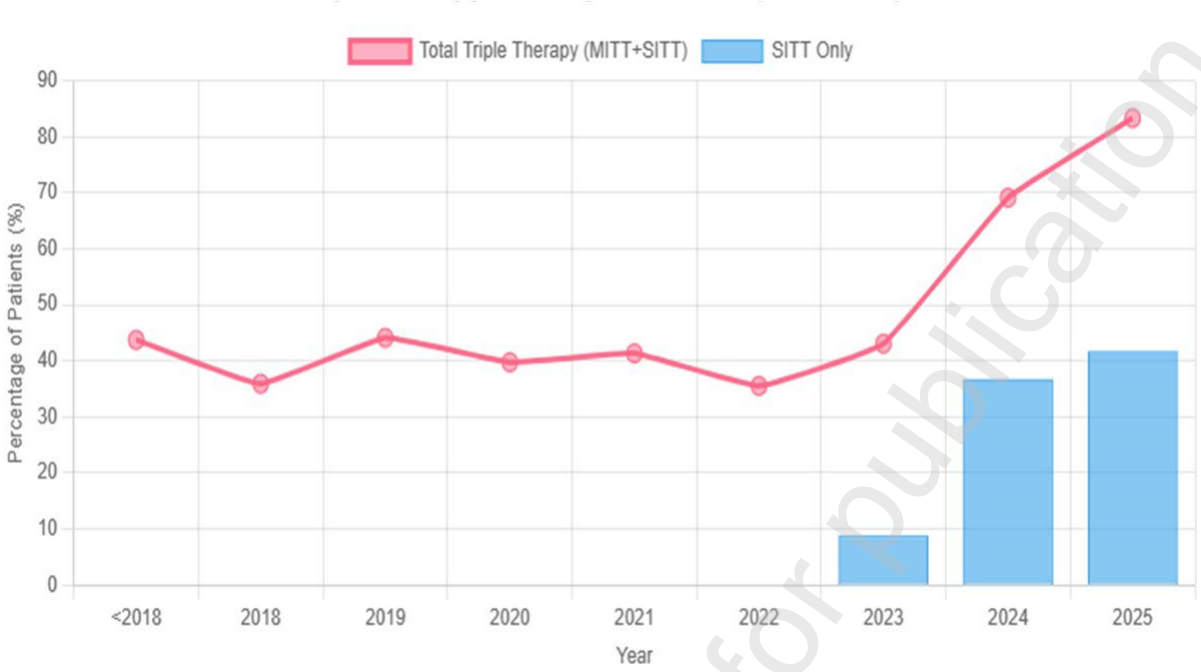
ACT, Asthma Control Test; ICS, Inhaled Corticosteroids; LAMA, Long acting muscarinic antagonist; OCS, Oral Corticosteroids

Table 4. Multiple logistic regression analysis of predictors for LAMA prescription.

Variable	OR	Std. Err.	z-value	p-value	95% Conf. Interval
Age (per year)	1.02	0.005	3.40	0.001	1.01 - 1.03
Sex (Female vs. Male)	0.96	0.119	-0.34	0.733	0.75 - 1.22
Smoking (Former/Current vs. Never)	1.27	0.166	1.80	0.072	0.98 - 1.64
Obesity (BMI ≥ 30)	1.26	0.183	1.62	0.105	0.95 - 1.68
Age of Symptom Onset	1.00	0.004	0.21	0.834	0.99 - 1.01
$FEV_1/FVC \geq 0.70$	0.70	0.084	-2.96	0.003	0.55 - 0.89
Nasal Polyps	0.65	0.079	-3.52	<0.001	0.51 - 0.83
Exacerbation History (vs. None)					
1 Exacerbation	1.36	0.284	1.46	0.143	0.90 - 2.05
2 Exacerbations	1.76	0.335	2.98	0.003	1.21 - 2.56
>2 Exacerbations	2.49	0.423	5.37	<0.001	1.78 - 3.47

BMI, Body Mass Index; FEV1 : Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; OR, Odds ratio.

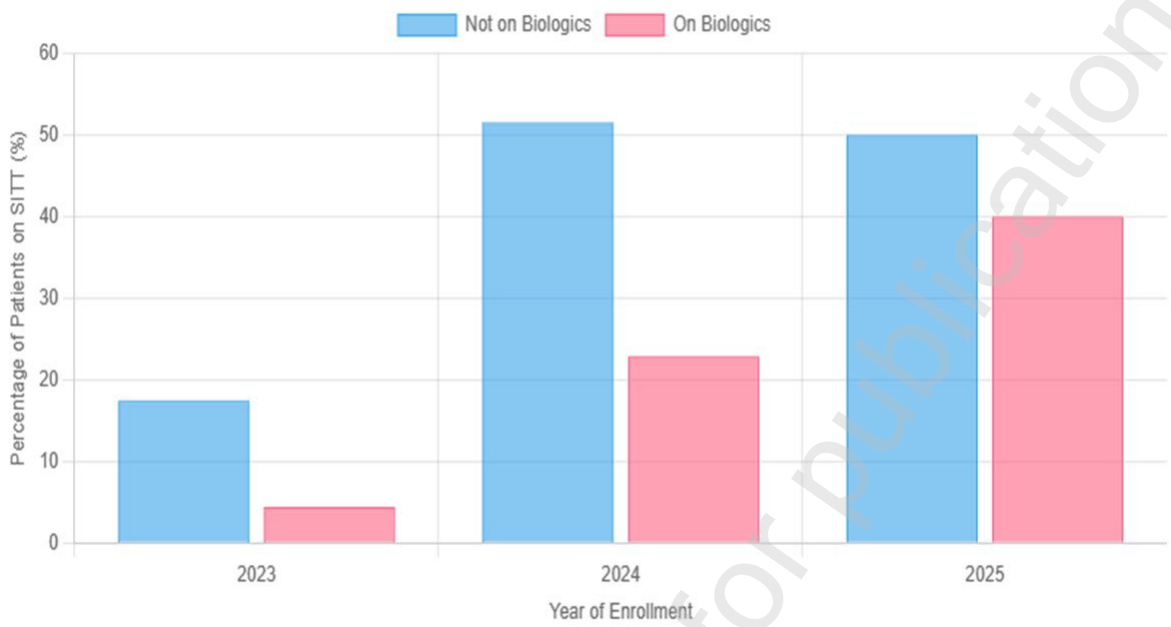
Figure 1. Triple therapy prescription trends (2018-2025).



MITT, Multiple-Inhaler Triple Therapy; SITT, Single-Inhaler Triple Therapy.

The chart illustrates the rising prevalence of triple therapy (MITT or SITT) and the rapid adoption of Single-Inhaler Triple Therapy (SITT) since its introduction to the Italian market in 2023. The overall use of triple therapy increased from 43.75% in 2018 to 83.3% in the first five months of 2025. This growth was largely driven by SITT, which was used by 41.67% of patients by early 2025.

Figure 2: SITT prescription trends among patients with and without biologics (2023–2025).



The chart displays the percentage of severe asthma patients prescribed SITT, stratified by whether they were receiving biologic therapy. SITT was initially prescribed more frequently in patients not receiving biologics. However, the temporal trend indicates that this difference gradually diminished over the years, becoming non-significant by 2025. These findings should be interpreted with caution due to the limited sample size for 2025.