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ORIGINAL RESEARCH

# Costs of Oral Corticosteroid Use in Patients with Severe Asthma With/Without Chronic Rhinosinusitis with Nasal Polyps: Data from the Italian SANI Registry

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## ABSTRACT

***Introduction***: The burden of severe asthma on patients, especially on those with concomitant chronic rhinosinusitis with nasal polyps (CRSwNP), is substantial. Treatment intensification with oral corticosteroids is a common strategy for managing severe asthma exacerbations; however, prolonged exposure to systemic corticosteroids is associated with multisystem toxicity. This study aimed to quantify the association between oral corticosteroid use and annual asthma-related costs in patients with severe asthma with or without CRSwNP.

***Methods***: This pharmacoeconomic analysis was based on data from the Severe Asthma Network in Italy (SANI) registry. Asthma-related costs were estimated in the context of the Italian healthcare system and included exacerbations requiring treatment intensification, unplanned visits, admissions to hospital and emergency/intensive care units, and lost workdays. For each item, the mean annual cost per patient was estimated based on national tariffs and the frequency of the event. To quantify the association between oral corticosteroid treatment and costs, the study cohort was stratified according to oral corticosteroid use in the 1-year preceding inclusion in the SANI registry.

***Results***: A total of 669 patients from the SANI registry were included in the present analysis, 255 of whom had concomitant CRSwNP. Corticosteroid use was associated with significantly higher annual disease-related costs per patient compared with no corticosteroid use. Compared with the overall study cohort and patients without CRSwNP, patients with CRSwNP had higher disease-related costs (higher by €1307 and €1869, respectively).

***Conclusion***: Use of corticosteroids, in particular systemic corticosteroids, is associated with an

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increase in asthma-related costs. The concomitant presence of CRSwNP impacts negatively on costs. This study suggests that a thorough analysis of costs, expected benefits, and occurrence of adverse events is required when selecting treatment intensification strategies for managing uncontrolled severe asthma.

**Keywords:** Asthma; Chronic rhinosinusitis with nasal polyps; Corticosteroid-sparing; Oral corticosteroids; Severe asthma

**Key Summary Points**

*Why carry out this study?*

The economic burden of severe asthma on patients, especially in the presence of chronic rhinosinusitis with nasal polyps (CRSwNP), is substantial; asthma-related costs increase as symptom control decreases.

Systemic corticosteroids are commonly used for the management of severe asthma exacerbations; however, prolonged use is associated with multisystem toxicity.

This study aimed to quantify the association between oral corticosteroid use and annual asthma-related costs in a real-world cohort of patients with severe asthma with/without CRSwNP.

*What was learned from this study?*

The use of oral corticosteroids was associated with a significant increase in annual asthma-related costs per patient; a higher increase was observed in patients with severe asthma with CRSwNP.

The safety profile and economic impact of adverse event management should be taken into account when selecting treatments for uncontrolled severe asthma.

## INTRODUCTION

Severe asthma is defined by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) as "asthma that requires treatment with a high-dose inhaled corticosteroid plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy" [1]. According to the Global Initiative for Asthma (GINA), when classifying asthma as severe it is important to consider and exclude modifiable factors that can contribute to symptom exacerbation, including poor adherence to prescribed treatment and incorrect inhaler technique [1]. The disease burden of severe asthma on patients is substantial [2, 3]. Additionally, although severe asthma affects less than 10.0% of the asthma population [4, 5], it accounts for a large proportion of asthma-related costs [6, 7].

It is now generally recognized that severe asthma is clinically heterogeneous and that it is characterized by different phenotypes [8]. Comorbidities, including chronic rhinosinusitis (CRS), obstructive sleep apnea, obesity, gastroesophageal reflux disease, anxiety, and depression are common in severe asthma [3, 8]. The prevalence of CRS can reach 80.0% in patients with severe asthma [8]; in this setting, CRS is often accompanied by nasal polyps (CRS with nasal polyps; CRSwNP) [9] leading to the hypothesis that the two conditions may share common pathogenic mechanisms [3, 10]. The coexistence of severe asthma and CRSwNP complicates the treatment of both conditions [10, 11].

Treatment of severe asthma continues to be based on inhaled corticosteroids to which other agents, such as long-acting beta-agonists (LABAs), tiotropium, theophylline, leukotriene receptor antagonists, biologics, or interventions such as bronchial thermoplasty, can be added [12, 13]. In the case of poor asthma control, intensification of corticosteroid treatment with high-dose inhaled corticosteroids or systemic (oral) corticosteroids is a common strategy. However, the need for corticosteroid-sparing strategies to limit the risk of toxicities related to prolonged systemic corticosteroid use is widely recognized [14, 15]. According to the GINA 2021

guidelines for the management of difficult-to-treat and severe asthma, the development of strategies to minimize the use of oral corticosteroids is a high priority [1]. Common side effects induced by long-term use of oral corticosteroids include diabetes, obesity, hypertension, dyspeptic disorders, adrenal suppression, osteoporosis, cataracts, and psychiatric disorders [16–20]. The overuse of corticosteroids indicates that severe asthma treatment is currently suboptimal; overuse has also been shown to contribute to the elevated costs associated with severe asthma management, with expenditures growing significantly as disease control decreases [17, 21, 22]. Optimizing treatment is therefore crucial, not only for improving patient outcomes but also for reducing costs [6, 7]. Strategies to reduce the use of systemic corticosteroids include the optimization of inhaled background therapies (inhaled corticosteroids, considering adding long-acting muscarinic agents, improving treatment adherence and inhalation technique), the use of biological agents (monoclonal antibodies directed against immunoglobulin E, interleukin 5 or its receptor, interleukin 4 receptor, or thymic stromal lymphopoietin) or other steroid-sparing agents (e.g., methotrexate, cyclosporine), bronchial thermoplasty, and/or long-term use of macrolides [23, 24]. All these strategies should be evaluated according to a personalized management strategy based on severe asthma phenotypes. An international Expert Consensus on reducing oral steroid use in asthma made the following recommendation: "Tapering (down to a minimal efficacious dose or complete weaning, if possible) should be attempted in all patients with asthma receiving maintenance oral corticosteroid therapy, regardless of comorbidities" [25]. The Expert Consensus also noted that the approach to, and rate of, oral corticosteroid tapering needs to be individualized for each patient [25].

A number of registries that collect real-life clinical data on patients with severe asthma have been developed in many countries, with the ultimate goal of addressing the unmet needs of patients with uncontrolled asthma [26–31]. The Severe Asthma Network in Italy (SANI) registry, promoted by GINA Italy, the Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC), and the Italian Respiratory Society (SIP-IRS), was conceived to collect homogeneous data on patients with severe asthma, in the real-life setting and over the long term [9, 11, 30].

This paper reports the results of a pharmacoeconomic analysis of the SANI registry that quantified the association between corticosteroid use and annual asthma-related costs, with a focus on patients with severe asthma with/without CRSwNP.

## METHODS

### Study Population

The study included all patients with severe asthma registered in the SANI registry up to March 2020 with complete data for therapies available; the SANI registry has been described in detail elsewhere [30]. Inclusion criteria for enrolment into this registry are: age > 12 years; diagnosis of severe asthma according to the ERS/ATS criteria [8]; and uncontrolled asthma despite treatment with high-dose inhaled corticosteroids plus LABA. To accurately describe the real-life population of Italian patients with severe asthma, no exclusion criteria have been applied. Following the enrolment visit, patients who meet the inclusion criteria are followed-up regularly over a period of 10 years. Information collected at the enrolment visit and during follow-up include: demographic data, medical history, asthma control in the previous month, adherence to treatment, presence of potential risk factors, concomitant treatments, treatments for comorbidities (e.g., corticosteroids for nasal polyposis), drug-related adverse events, level of inflammatory markers, reasons for discontinuation of biologics, and quality of life assessment via the Asthma Quality of Life Questionnaire (AQLQ).

### Study Design

This was a pharmacoeconomic analysis of data extracted from the SANI registry. The registry-based study was performed in accordance with the Helsinki Declaration of 1964, and its later

amendments. All patients signed an informed consent. The collected data were anonymized, meaning that all identifiers have been irreversibly removed.

The protocol was approved by the Central Ethics Committee (Comitato Etico Area Vasta Nord-Ovest Toscana; protocol number: study number 1245/2016, protocol number: 73714) and all other centers' local ethics committees.

The permission to access and use the data from the registry was granted by the registry owners, as the study itself was promoted by the registry steering committee.

For analysis purposes, the study cohort was divided into two groups based on the presence or absence of CRSwNP. The objective of the analysis was to quantify the association between corticosteroid use and disease-related costs in a real-world population of patients with severe asthma.

### Extracted Variables

The following variables were collected from the SANI registry: demographic data, medical history, smoking status, data related to the diagnosis and severity of asthma, relevant comorbidities, common adverse events associated with the use of oral corticosteroids, healthcare resources used (e.g., outpatient visits, diagnostic tests, admission to hospital, and duration of hospital stay), diagnosis related group (DRG) codes, procedure codes, treatment schedules (e.g., prescription of drugs for obstructive respiratory diseases and related comorbidities), and quality of life (AQLQ).

### Analysis of Costs

This analysis accounted for costs related to common adverse event management associated with the use of oral corticosteroids, days of work lost, admissions to the intensive care unit or use of assisted ventilation, visits to the emergency care unit, hospital admissions due to asthma, unplanned visits, and exacerbations requiring the use of corticosteroids. Costs were estimated in the context of the Italian healthcare system and were based on the national DRG system. For each item considered, the mean annual cost per patient was estimated based on national tariffs and the frequency of the event, in the entire study cohort as well as in patients with or without CRSwNP. To quantify the association between corticosteroid treatment and annual costs, the study cohort was stratified according to the use of corticosteroids for ≥ 1 day in the 1-year prior to registry enrolment. In patients treated with corticosteroids, estimated costs were differentiated by the various routes of corticosteroid administration, namely oral, inhaled, or intranasal.

### Statistical Analysis

Statistical analysis was performed using SPSS 20.0 software (SPSS, Chicago, IL, USA). Continuous variables were reported using descriptive statistics, e.g., mean values ± standard deviation (SD), standard error, minimal and maximal values, and range; categorical variables were reported using absolute numbers and frequencies (%). The statistical significance of differences between reported variables in the various subgroups was analyzed using Student's $t$ test or analysis of variance (ANOVA), depending on the result of Kolmogorov–Smirnov normality of distribution test. In order to interpret ANOVA results about the statistical significance of the difference between means of variables with different sample sizes, the Tukey–Kramer test was performed. A $p$ value of $< 0.05$ was considered statistically significant.

## RESULTS

### Characteristics of the Study Population

Complete data were available for 669 patients from 46 centers specialized in the treatment of severe asthma across 13 Italian regions, (Liguria, Piemonte, Lombardia, Veneto, Emilia Romagna, Toscana, Lazio, Marche, Campania, Calabria, Puglia, Sardegna, and Sicilia) covering the entire national territory (Fig. 1).

A total of 255 patients (38.1%) had concomitant CRSwNP. Among these patients, the mean

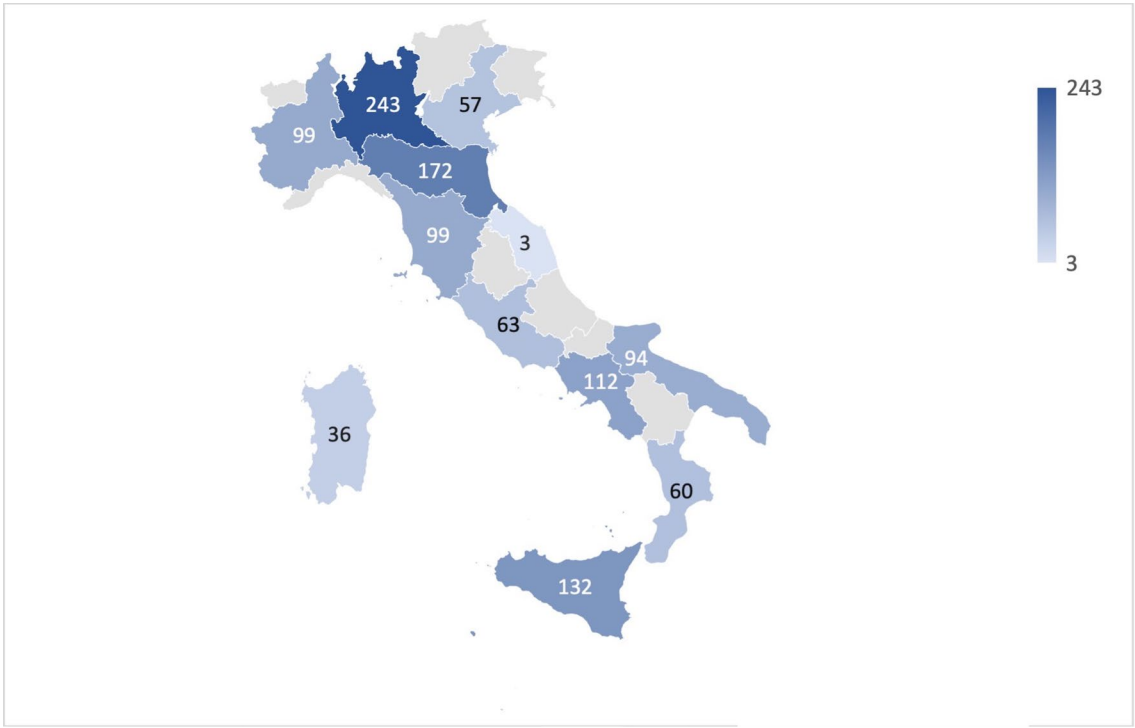


**Fig. 1** Geographical distribution of the study population ($n$ = 1194)

duration of a nasal polyposis diagnosis was > 15 years. Over the 1-year period prior to inclusion in the SANI registry, oral corticosteroids were taken by 106 patients (41.6%) with CRSwNP and by 88 patients (21.3%) without CRSwNP (Fig. 2).

## Analysis of Costs

In the overall population of patients with severe asthma, the mean annual cost per

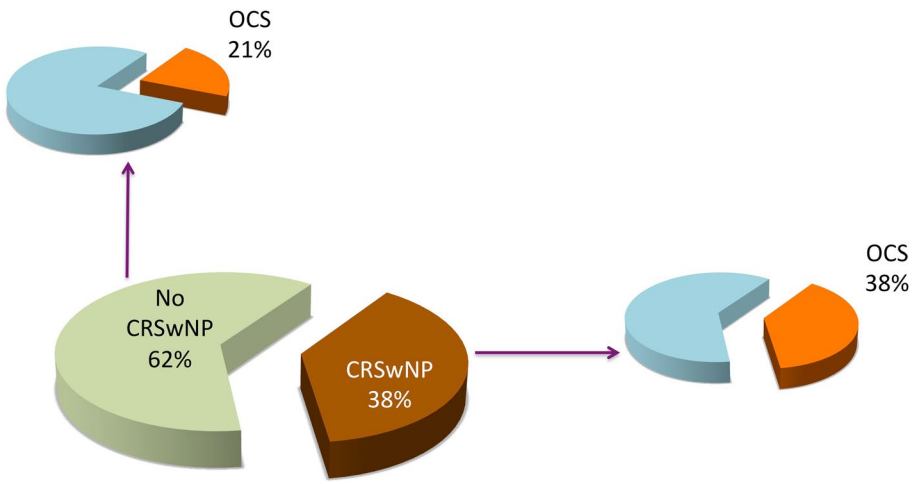


**Fig. 2** Proportion of patients with and without comorbid chronic rhinosinusitis with nasal polyps (CRSwNP), and of those exposed or not to oral corticosteroids (OCS)

patient was €4553. In patients with CRSwNP this cost (€5679) was significantly higher compared with the entire study cohort (difference of €1126) and patients without CRSwNP (difference of €1909). Corticosteroid use was associated with significantly higher disease-related costs compared with no corticosteroid use (Fig. 3). Patients with CRSwNP receiving oral corticosteroids had higher mean annual disease-related costs when compared with patients without CRSwNP receiving oral corticosteroids (difference of €1869, Fig. 4) and with the overall cohort receiving oral corticosteroids (difference of €1307).

## DISCUSSION

We have reported real-world data from the SANI registry which includes patients with severe asthma from Italian centers specialized in severe asthma treatment. The 669 patients included in the present analysis were from centers covering most Italian regions, providing a representative picture of severe asthma management across Italy. The study cohort was characterized by an elevated presence of concomitant CRS, with more than 40.0% of patients having CRSwNP.

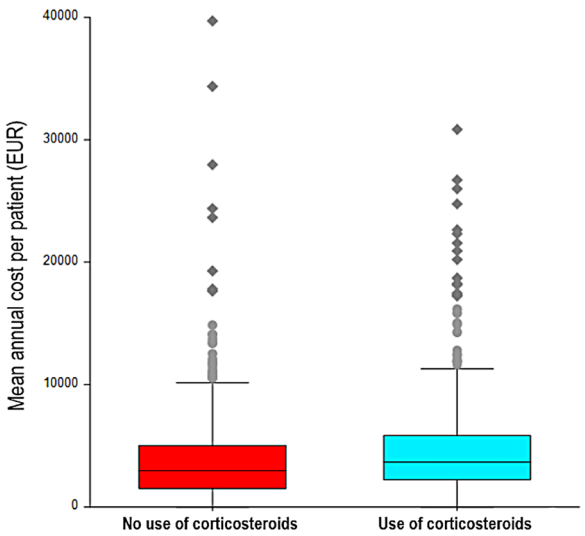


**Fig. 3** Mean annual asthma-related costs per patient in users and non-users of corticosteroids. *EUR* Euro

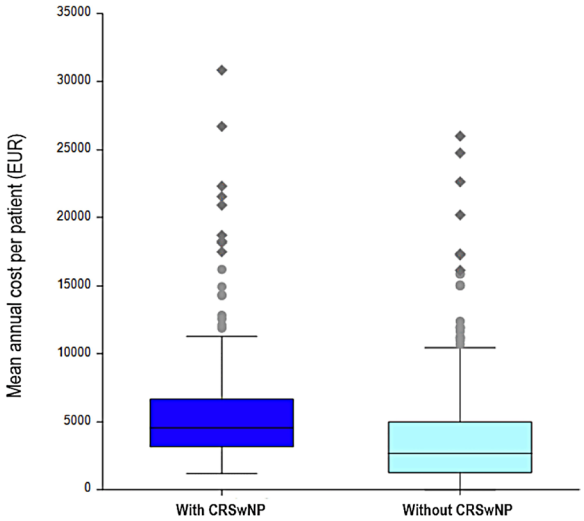


**Fig. 4** Mean annual asthma-related costs per patient in users of corticosteroids with CRSwNP and without CRSwNP. *CRSwNP* chronic rhinosinusitis with nasal polyps, *EUR* Euro

CRSwNP often coexists with severe asthma and the prevalence data in the current study overlaps with data reported previously [3, 8, 10, 28]. For example, an analysis of the Italian web-based registry, RItA, which included 493 adult patients with severe/uncontrolled asthma, reported that allergic rhinitis was present in 62.3% of patients, sinusitis in 37.9%, and nasal polyposis in 30.2% [28]. A separate analysis of the Belgian Severe Asthma Registry has also reported that rhinitis/chronic rhinosinusitis and nasal polyposis are among the most common comorbidities in patients with severe asthma, with a prevalence of 49.0% and 19.0%, respectively [29]. An earlier analysis of the SANI registry found that patients with CRSwNP experienced significantly more asthma exacerbations per year and used oral corticosteroids for longer periods compared with patients without CRSwNP [11].

In the current analysis of asthma-related expenditures, mean annual costs per patient were significantly higher in patients with severe asthma and CRSwNP compared with patients with severe asthma without CRSwNP. Furthermore, use of corticosteroids in the year preceding enrolment into the SANI registry was associated with a significant increase in costs

compared with no corticosteroid use. The most relevant increase in costs was seen in patients with CRSwNP receiving oral corticosteroids. Overall, these results support the findings of a previous economic analysis of the SANI registry, which assessed the costs associated with oral corticosteroid-related adverse event management [32]. In that analysis, patients with severe asthma who needed treatment intensification with oral corticosteroids incurred a 45.0% increase in annual costs compared with patients with mild-to-moderate asthma [32]. More specifically, the analysis considered the total annual costs associated with the five most common oral corticosteroid-related comorbidities (i.e., diabetes, obesity, fractures, glaucoma, and chronic kidney disease) [32], which were associated with total annual costs of €92.7 million in patients with severe asthma, which was €26.3 million higher than in patients with moderate asthma and €41.5 million higher than in those without asthma [32].

The association between asthma severity and increased healthcare expenditure is well documented in the literature [6, 7, 17–19, 32–35]. In a Canadian study assessing the impact of insufficient asthma control on costs, a 10.0% reduction in the prevalence of uncontrolled asthma was predicted to reduce asthma-related costs by 18.0% over the next 20 years [22]. Less well understood is what drives the increase in healthcare costs associated with severe asthma. Maintenance therapy with oral corticosteroids has emerged as a predictor of increased economic burden in severe asthma [33]. A systematic literature review of studies assessing systemic corticosteroid use for asthma management revealed that oral/systemic corticosteroids are the most commonly used treatment, especially in patients with severe asthma; however, use is typically short term [17]. However, patients with repeated short-term use or those receiving low doses of systemic corticosteroids have an increased risk of developing acute and chronic adverse events affecting multiple systems compared with patients who do not use oral/systemic corticosteroids [17]. Finally, the systematic review confirmed that extended exposure to oral/systemic corticosteroids was associated with greater healthcare expenditures and resource use.

The ongoing extensive use of oral corticosteroids, despite the availability of effective targeted therapies (e.g., biologics), may be partially explained by their low acquisition costs and easy accessibility; most physicians are familiar with corticosteroids and these medications have been long held in asthma guidelines. However, it should be noted that the latest GINA guidelines for the treatment of severe asthma (type 2 inflammation phenotype) recommend add-on therapy with type 2 biologics (anti-immunoglobulin E, anti-interleukin [IL]5/anti-IL5 receptor [IL5R], anti-IL4R, anti-thymic stromal lymphopoietin) as a first choice if available/affordable, followed by higher dose inhaled corticosteroids and non-biologic add-on therapies. Add-on low-dose oral corticosteroids are now a last-resort option to be used alongside strategies that minimize side effects [1].

The need for corticosteroid-sparing strategies is now widely recognized across many therapeutic areas, as highlighted by the recent development of the Glucocorticoid Toxicity Index by an international group of experts in corticosteroid use and outcome measures [36]. The aim of this tool is to evaluate corticosteroid-related toxicity and to assess the ability of other medications to improve treatment tolerability and safety and thus act as corticosteroid-sparing agents. This tool was designed for use in randomized clinical trials evaluating the efficacy and safety of biologics and is currently used in this setting only [37]. In clinical practice, it is conceivable that assessing the ability to prevent oral corticosteroid-requiring exacerbations or reducing the use of oral corticosteroids will soon become part of the variables used to evaluate responses to targeted therapies. Efforts towards the implementation of these strategies for severe asthma management in clinical practice are ongoing [37].

The main limitations of our study are that: (1) the diagnosis of CRSwNP could be underestimated, since the data were collected in a real-life setting and it is plausible that not all patients underwent to an objective endoscopic ENT evaluation; (2) the pharmacoeconomic evaluations were performed using the Italian DRG costs which could be different from healthcare-related costs in other countries; and (3) the analysis should be regarded as an estimation of costs and not

directly measured expenditure, assuming mean annual costs based on national tariffs and the frequency of the events. Despite these limitations, we believe that our results clearly show that severe asthma, when associated with CRSwNP, has a substantial impact on healthcare costs, mainly due to the overuse of systemic corticosteroids.

## CONCLUSIONS

The present analysis of the SANI registry provides additional evidence of the heavy economic impact in patients with severe asthma, especially when associated with corticosteroid use. Difficult-to-treat groups like those with concomitant CRSwNP have the highest costs, confirming that the economic impact worsens as asthma control decreases. Our study clearly showed that the concomitant presence of CRSwNP is an additional and relevant factor increasing the health-related costs due to the use of systemic corticosteroids. As a consequence, patients with severe asthma and comorbid conditions, such as CRSwNP, deserve a real multidisciplinary approach aiming to achieve the best control possible of both diseases, and therefore a reduced need of using oral corticosteroids [38]. Moreover, our results suggest that a careful analysis of costs, benefits, and adverse event profiles is required when making decisions about the intensification of severe asthma treatment with corticosteroids or targeted therapies. In this respect, biologics are a potentially fruitful corticosteroid-sparing strategy for severe asthma with CRSwNP and the high acquisition costs of these agents might be counterbalanced by a more favorable safety profile and reduced expenses for the management of adverse events. Real-world data from SANI and other registries are crucial for these analyses and will be useful for defining the corticosteroid-sparing potential of novel therapies.

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***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### *Declarations*

***Conflict of Interest.*** Enrico Heffler reports receiving grants and personal fees from Sanofi, Regeneron, AstraZeneca, Novartis, GlaxoSmithKline, Chiesi, Stallergenes-Greer, Almirall, Celltrion Healthcare, and Bosch. Francesco Blasi reports receiving grants and personal fees

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***Ethical Approval.*** The SANI registry study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All patients signed an informed consent. The collected data were anonymized (all identifiers have been irreversibly removed). The protocol was approved by the Central Ethics Committee (Comitato Etico Area Vasta Nord-Ovest Toscana; protocol number: study number 1245/2016, protocol number: 73714) and all other centers' local ethics committees. The permission to access and use the data from the registry was granted by the registry owners.



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