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Biologic treatment eligibility and characteristics of Romanian patients with severe asthma: Real-world data from the RECOGNISE study

Dragos Nicolosu[1], Dragos Gabriel Ungureanu[2], Violeta Perlea[3], Corina-Elena Horodniceanu[4], Mirela Tudorache[5], Bogdan Mincu[6], Adriana Stoica[7,*], Gabriela Teodorescu[7]

[1]*Pneumology Department, "Victor Babes" Clinical Hospital of Infectious Diseases and Pneumophtisiology, Craiova, Romania*
[2]*Ambulatory Department, Pneumophthisiology Hospital, Bacau, Romania*
[3]*Ambulatory Diagnostic and Treatment "Academician Stefan Milcu" Medical Center, Bucharest, Romania*
[4]*Tuberculosis Dispensary, Pneumophtisiology Clinical Hospital, Iasi, Romania*
[5]*Ambulatory Department, "Sfantul Stefan" Pneumophthisiology Hospital, Bucharest, Romania*
[6]*Dr Bogdan Mincu Individual Medical Practice, Cluj-Napoca, Romania*
[7]*Medical Department, AstraZeneca Romania, Tipografilor 1A, MUSE Offices, floors 2 and 3, District 1, 013714, Bucharest, Romania*

Abstract

English:

Introduction: *Severe asthma remains refractory to optimised therapy with oral/systemic corticosteroids even after addressing contributing factors, impacting the patients' health-related quality of life (HRQoL) and increasing the risk for comorbidities and mortality. Several biologics are available for severe asthma treatment; however, their use remains heterogenous across Europe.*
Aims: *To generate real-world data on the characteristics of adult patients with severe asthma in Romania and their eligibility for biologics.*
Methods: *The European, non-interventional, multicenter RECOGNISE study (NCT03629782) evaluated patient characteristics, asthma medication and control, health care resource use, and HRQoL as assessed by St. George's Respiratory Questionnaire (SGRQ) in patients with severe asthma, as well as their eligibility for biologic treatment. We report data from the Romanian cohort.*
Results: *Of the 117 enrolled patients, 103 were included in the analyses. Almost all patients (90.29%) were treated by specialists. Most patients were female (64.08%) and had never smoked (83.50%). In all, 15 (14.56%) patients had chronic oral corticosteroids (OCS) use. Totally, 89 (86.41%) patients were assessed as eligible for biologic treatment by investigator's judgement (per label criteria: 79.61%). In the previous year, 77.53% and 78.57% of eligible and non-eligible patients, respectively, had exacerbations of severe asthma, and 53.33% and 15.91% were hospitalised. More eligible patients had poorly controlled asthma (92.13% vs 57.14%) and more impaired HRQoL (mean total SGRQ score: 63.2% vs 47.34%).*
Conclusion: *A large proportion of Romanian patients with severe asthma are eligible for biologic treatment. New strategies are needed to further increase the availability of biologics and to improve the management of severe asthma.*

Keywords

severe asthma • biologics • treatment eligibility • patient characteristics • real-world

Eligibilitatea pentru terapia biologică și caracteristicile pacienților cu astm sever din România: studiul RECOGNISE cu date din practica clinică curentă

Rezumat

Romanian:

Introducere: *Astmul bronșic sever este refractar la terapia optimizată cu corticosteroizi orali/sistemici, chiar și după adresarea factorilor contributori, determinând un impact negativ asupra calității vieții pacienților, creșterea morbidității și mortalității. Mai multe terapii biologice sunt disponibile pentru tratamentul astmului sever, dar utilizarea este heterogenă în Europa.*
Obiective: *Descrierea caracteristicilor pacienților adulți cu astm bronșic sever din practica clinică curentă din România și eligibilitatea acestora pentru terapie biologică.*

**Corresponding author: Adriana Stoica*
E-mail: adriana.stoica@astrazeneca.com

Metode: *Studiul european, non-intervențional, multicentric RECOGNISE (NCT03629782) a evaluat caracteristicile pacienților cu astm bronșic sever, medicația, controlul astmului, utilizarea resurselor de îngrijire a sănătății, calitatea vieții (St. George's Respiratory Questionnaire [SGRQ]) și eligibilitatea pacienților pentru terapie biologică. Raportăm aici datele cohortei din România.*
Rezultate: *Din 117 pacienți înrolați, 103 au fost incluși în analiză. Aproape toți pacienții (90.29%) erau tratați de către specialisti. Majoritatea pacienților au fost femei (64.08%) și nefumători (83.50%). Cincisprezece (14.56%) pacienți utilizau corticoterapie orală cronică. Investigatorii au evaluat ca eligibili pentru terapie biologică 89 (86.41%) de pacienți (conform indicației aprobate: 79.61%). În anul precedent, 77.53% și, respectiv, 78.57% dintre pacienții eligibili și neeligibili, au avut exacerbări de astm bronșic sever, iar 53.33% și 15.91% au fost spitalizați. Pacientii eligibili au prezentat un control mai scăzut al astmului (92.13% vs 57.14%) și calitatea vieții mai afectată (scor mediu total SGRQ: 63.2% vs 47.4%).*
Concluzie: *O proporție ridicată a pacienților cu astm bronșic sever din România sunt eligibili pentru terapie biologică. Sunt necesare noi strategii pentru a crește disponibilitatea terapiilor biologice și pentru a îmbunătăți managementul astmului sever în România.*

Cuvinte-cheie

astm sever • terapie biologică • eligibilitate pentru tratament • caracteristicile pacienților • practică clinică curentă

Introduction

Asthma is a common, non-communicable, chronic respiratory disease that affects up to 18% of the population in different countries [1,2], with an estimated 262 million cases worldwide in 2019 [3]. In 2019, in the European Union, asthma was estimated to affect around 6% of the population, ranging from ~2% in Romania and Bulgaria and ~9% in Finland [4]. Around 5%–10% of all asthma individuals suffer from severe asthma, although this proportion could be much larger [5,6]. Mild and moderate forms of asthma can be managed with appropriate treatment, but severe asthma remains refractory to optimised treatment even after addressing the contributing factors. Thus, it highly impacts the patients' health and quality of life (QoL) and increases the risk for comorbidities and mortality [1]. Although the proportion of cases is small, severe/poorly controlled asthma accounts for the greater part of the asthma-related economic burden [7].

Current guidelines define severe asthma as asthma requiring treatment with high-dose inhaled corticosteroids (ICS) and a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains 'uncontrolled' after at least several months of this optimised maximal therapy [8,9]. The Global Initiative for Asthma (GINA) recommends a clinical decision tree for the diagnosis and management of severe asthma, stipulating distinct and shared tasks for general practitioners and/or specialist care and respiratory specialists, and emphasising the need for collaboration between primary and secondary care [1]. Before deciding the treatment, specialists need to assess comorbidities, differential diagnoses and the clinical phenotype during high-dose ICS treatment or the lowest possible dose of oral corticosteroids (OCS) and evaluate any factors contributing to symptoms and/or exacerbations. For Type 2 inflammation phenotype (defined by the presence of blood eosinophils ≥150/μL, and/or fractional concentration of exhaled nitric oxide [FeNO] ≥20 ppb, and/or sputum eosinophils ≥2%, and/or asthma that is clinically allergen-driven and/or that requires maintenance OCS), add-on targeted biologic therapy is advocated for patients with exacerbations or poor symptom control on high-dose ICS-long-acting β_2-agonist (LABA). Recommended biologics are anti-immunoglobulin E (IgE) (omalizumab), anti-interleukin (IL) 5/anti-IL5 receptor (IL5R) (benralizumab, mepolizumab, and reslizumab), anti-IL4R (dupilumab) and anti-thymic stromal lymphopoietin (tezepelumab) agents, depending on patients' eligibility [1]. Response to the biologic is evaluated after at least 4 months and treatment is extended to 6–12 months if favourable, with further periodical review. Switching to another biologic is recommended in case of little/no response to the initial agent if the patient is still eligible for Type 2-targeted therapy. The European Academy of Allergy and Clinical Immunology (EAACI) also advocates the use of biologics currently approved in Europe (benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab), based on severe asthma phenotyping [10].

However, despite impressive advancements in the field of biologic therapies, the clinical management of severe asthma remains challenging. In Europe, the use of biologics is not uniform: a recent study found important differences between countries in the availability of biologics, authorised prescriber and the defined criteria and thresholds for eligibility or for continuing treatment [11]. These differences are maintained at a global level [12]. More information is needed about the characteristics of patients with severe asthma to account for the heterogeneity and potential overlapping of clinical phenotypes and any restrictions in terms of biologic treatment cost or availability.

The RECOGNISE study aimed to generate real-world data on the characteristics of adult patients with severe asthma

across Europe and their eligibility for biologics [13]. Here, we present a separate analysis of the Romanian population, for whom little information is available to date. In 2018, when the study was initiated, omalizumab was the only reimbursed biologic treatment available for severe asthma in Romania. Benralizumab and dupilumab were included after study end on the list of biologics approved for severe asthma, with partial or full reimbursement of the cost (May 2020, and February 2022, respectively).

Objectives

The primary objective was to describe the proportion of severe asthma patients eligible for referral for biologic therapy, together with their clinical and biologic characteristics. Secondary objectives included describing the percentage of patients objectively meeting label criteria for biologics and the agreement between objective measurement and the physician's assessment on eligibility for biologic therapy referral. Other secondary objectives were to describe the characteristics of patients with long-term OCS therapy (defined as treatment maintenance with OCS ≥50% of the previous year) and to assess the severity of asthma exacerbations and healthcare resource utilisation (HCRU) in patients with ≥2 OCS bursts in the previous year.

Materials and methods

Study design

We conducted a multicenter, observational, cross-sectional study among asthma patients screened in primary and secondary care settings in 12 European countries, between February 2018 and July 2020 (ClinicalTrials.gov NCT03629782). In Romania, 14 centres (11 practice centres and 3 clinics) participated in this study. Only the results for the Romanian cohort are described here.

We enrolled adult patients (age ≥18 years) with a confirmed diagnosis of severe asthma according to the ATS/ERS 2014 guidelines [8] (see Table 1 for case definitions) who signed an informed consent form and were able and willing to read and understand the instructions provided and complete the required questionnaires. At least one eosinophil count in the last year was required for enrolment in the study. Exclusion criteria included concomitant respiratory conditions (such as chronic obstructive pulmonary disease [COPD] as main diagnosis, bronchiectasis, idiopathic pulmonary fibrosis, pulmonary hypertension, α-1-antitrypsin-deficiency, and malignancy of any kind), concurrent use of biologics for asthma (except stable allergen immunotherapy), and concomitant participation in an ongoing randomised clinical trial.

Table 1. Case definitions used in the study.

Severe asthma	Asthma requiring high-dose ICS plus at least one additional controller(s) for 12 months among LABA, leukotriene modifier, theophylline (GINA Step 4/5) or continuous or near continuous OCS (i.e. maintenance OCS for ≥50% of the previous year) (controlled or uncontrolled).
Asthma exacerbation Category I Category II Category III	Worsening of asthma that led to one of the following: - use of systemic corticosteroids, or temporary increase in a stable OCS background dosage, for ≥3 days or a single injectable dose of corticosteroids; - emergency department or visit to an urgent care centre (<24 hr) because of asthma that needed systemic corticosteroids; - inpatient hospital stay (≥24 hr) because of asthma.

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; OCS, oral corticosteroids.
Notes: High-dose ICS was defined according to GINA guidelines [14].

The study consisted in a single visit, during which eligibility was assessed and the patients were enrolled. The investigator recorded the information in an electronic case report form: demographics, medical history and comorbidities, asthma exacerbations and associated HCRU and asthma-prescribed treatment class in the last 12 months, medication adherence, eosinophil measurements, any available IgE or forced expiratory volume in 1 second (FEV_1) measurement or information on history of atopy (from medical records). The patients completed patient-reported outcome measures for health-related QoL (HRQoL) and asthma control, using the St. George's Respiratory Questionnaire (SGRQ) [15] and the shortened version of the asthma control questionnaire (ACQ-6) [16].

The study was designed and conducted following the Declaration of Helsinki, the Good Pharmacoepidemiology Practices guidelines of the International Society for Pharmacoepidemiology, as well as local regulations. The study was approved by the National Bioethics Committee for Medicine and Medical Devices (approval 4 SNI/22.03.2018).

Statistical analysis

A minimum target of 100 patients per country was chosen to provide a reasonable sample size and to ensure that the descriptive data mandated by the primary and secondary endpoints are sufficiently precise and meaningful at the country/subgroup level. With this sample size, the estimated exact binomial 95% confidence interval (CI) for a proportion of a patient characteristic of 10% and 50% is 4.9%–17.6% and 38.8%–60.2%, respectively.

Statistical analyses were mainly descriptive and were performed on all eligible patients with documented ICS therapy with additional controller for ≥12 months before enrolment, overall and stratified by eligibility for biologic treatment or by chronic OCS use. *P*-values for subgroups comparisons were

calculated using the Kruskal–Wallis test or Fisher's exact test, but were not corrected for multiple testing. Results were expressed as medians with ranges or percentages with 95% CIs, as applicable.

The agreement between objective measurement and physician assessment on eligibility for biologic therapy referral was assessed in terms of percentages of patients (with Wald 95% CIs). The hypothesis that the true value of the proportion of patients who are assessed eligible by the physician in agreement with objective measures was higher than 50% was evaluated using the right-sided binomial test *P*-value.

All analyses were performed using version 9.4 (SAS Institute Inc.).

Results

Of the 118 patients screened, 117 were enrolled and 103 were included in the analyses. Documented ICS therapy with an additional controller for ≥12 months before enrolment was not available for 13 patients, who were therefore excluded from the analyses. Most patients (73/103, 70.87%) were treated by a pulmonologist, 20/103 (19.42%) by an allergist and for 10/103 (9.71%) this information was missing.

Eighty-nine (86.41%) patients were considered by their treating physician as eligible for referral for biologics. Reasons for referral were high risk for 12 (11.65%) patients, corticosteroid treatment (high dose, long-term use and/or side effects) for 11 (10.68%) patients and add-on specialist treatment for 66 (64.08%) patients. When eligibility was assessed based on objective measures (label criteria), 82 (79.61%) were still eligible for biologics. The overall agreement between the physician's assessment and objective measures was 83% (Wald 95% CI: 76–90; *P*-value <0.0001).

Patients' characteristics are summarised in Table 2. Most patients were female (66/103; 64.08%) and diagnosed at adult age (median 46 years). The median age at diagnosis for patients eligible for biologics tended to be higher than in those considered non-eligible (48 [range 4–78] years vs 34 [range 16–73] years). More patients had never smoked (82.02% vs 92.86%) in the eligible versus the non-eligible subgroup (Table 2). However, no between-subgroup differences were statistically significant.

Median total blood eosinophil counts for patients with available data tended to be higher in the eligible than in the non-eligible subgroup (300.00 cells/μL [range: 2.00–1770.00] vs 80.00 [range: 70.00–90.00]). However, no statistically significant difference was found for any of the blood and lung parameters assessed. Patients eligible for biologics also tended to have more chronic OCS use (16.85% vs 0%) or short courses of systemic corticosteroids than those non-eligible. Significantly more patients eligible for biologics compared to non-eligible patients had a history of atopy (55.06% vs 7.14%; *P*-value = 0.0009) (Table 2).

All patients with medication data available were receiving asthma medication at the study visit and in the prior year. Of these, 37/103 (35.92%; 95% CI: 26.70–45.97) were receiving only asthma medication at the time of the study visit: 33/89 (37.08%; 95% CI: 27.07–47.97) patients eligible and 4/14 (28.57%; 95% CI: 8.39–58.10) patients non-eligible for biologics. The use of drugs for obstructive airway diseases tended to be more pronounced in patients eligible for biologic treatment than those not eligible (Figure 1).

The proportion of patients with OCS-related comorbidities was low in both subgroups (Table 2); no statistically significant differences were observed. Among patients with available data, the median Charlson Comorbidity Index (CCI) and age-adjusted CCI (ACCI) were low, with most patients (80.89% of biologics-eligible and 85.71% of non-eligible patients) having ACCI scores between 0 and 3 (Table 3).

Exacerbations of severe asthma in the previous year were reported in 69/89 (77.53%) of patients eligible for any biologics and 11/14 (78.57%) of non-eligible patients. The proportion of patients with category II and III exacerbations tended to be higher among those biologics-eligible versus non-eligible patients (Table 4), but this difference was not statistically significant.

Almost all patients (98.88% of biologics-eligible and 100% of non-eligible patients) had visits to a physician in the year prior to the study visit. The proportion of patients with hospitalisations, emergency visits or sick leave tended to be higher in the subgroup eligible for biologics (Table 5).

Reduced HRQoL and poor asthma control were reported in both subgroups, with slightly higher scores (indicating greater impairment) and a higher proportion of patients with poorly controlled asthma observed in patients eligible for biologics than in non-eligible patients (Figure 2).

Totally, 15 (14.56%) patients had chronic OCS use. The proportion of females, non-employed participants and non-smokers tended to be higher in the subgroup with chronic OCS use. Clinical characteristics were overall similar between the two subgroups (Table S1 in Supplementary Material). A higher proportion of patients with chronic OCS received leukotriene receptor antagonists and selective β_2-adrenoreceptor agonists for their asthma treatment (Figure S1 in Supplementary Material). Fewer patients with chronic OCS use (66.7%) had ACCI scores ≤3 than among the subgroup with no chronic OCS use (84.09% of patients) (Table S2 in Supplementary Material). Exacerbations of severe asthma tended to be more frequent among patients with chronic OCS use (100% vs 73.86%) (Table S3 in Supplementary Material). Patients with chronic OCS use also tended to have a higher HCRU (Table S4 in Supplementary Material) and reported a

Table 2. Demographic and clinical characteristics of patients at study visit, by eligibility for biologic treatment and overall.

	Eligible for biologics (N = 89)	Non-eligible for biologics (N = 14)	Overall (N = 103)
Demographic characteristics			
Median age at diagnosis, years (range)	48 (4–78)	34 (16–73)	46 (4–78)
Mean age at diagnosis ± SD, years	44.0.90 ± 16.89	39.14 ± 15.88	44.12 ± 16.80
Female, % (95% CI)	60.67 (49.75–70.87)	85.71 (57.19–98.22)	64.08 (54.03–73.30)
Male, % (95% CI)	39.33 (29.13–50.25)	14.29 (1.78–42.81)	35.92 (26.70–45.97)
White, % (95% CI)	100 (95.94–100)	100 (76.84–100)	100 (96.48–100)
Employment status, % (95% CI)			
Full-time	24.72 (16.19–35.00)	28.57 (8.39–58.10)	25.24 (17.20–34.76)
Part-time	2.25 (0.27–7.88)	-	1.94 (0.24–6.84)
Not employed	73.03 (62.58–81.90)	71.43 (41.90–91.61)	72.82 (63.16–81.12)
Work type, % (95% CI)			
Physical	5.62 (1.85–12.63)	7.14 (0.18–33.87)	5.83 (2.17–12.25)
Intellectual	21.35 (13.37–31.31)	21.43 (4.66–50.80)	21.36 (13.90–30.53)
Smoking status, % (95% CI)			
Former smoker	13.48 (7.17–22.37)	-	11.65 (6.17–19.47)
Current smoker	4.49 (1.24–11.11)	7.14 (0.18–33.87)	4.85 (1.59–10.97)
Never smoked	82.02 (72.45–89.36)	92.86 (66.13–99.82)	83.50 (74.89–90.08)
Clinical characteristics			
Median blood eosinophil count*, cells/μL (range)	300.00 (2.00–1770.00)	80.00 (70.00–90.00)	220.00 (2.00–1770.00)
Median blood eosinophil count*, % (range)	3.25 (0.1–23)	3.25 (0.5–16)	3.25 (0.1–23)
Median total WBC count*, cells/μL (range)	7645 (3900–18,300)	9000.5 (5600–18,600)	7685 (3900–18,600)
Median IgE count**, IU/mL (range)	268.95 (50.3–949.5)	200 (200–200)	242.8 (50.3–949.5)
Pre-bronchodilator FEV_1 in the last 12 months, mL (range)	1120 (370–4400)	1260 (790–4340)	1160 (370–4400)
Chronic OCS use, % (95% CI)	16.85 (9.75–26.27)	-	14.56 (8.39–22.88)
Short courses of systemic corticosteroids for ≥3 days, % (95% CI)	75.28 (65.00–83.81)	85.71 (57.19–98.22)	76.7 (67.34–84.46)
Medication adherence, % (95% CI)	100 (95.94–100.00)	92.86 (66.13–99.82)	99.03 (94.71–99.98)
History of atopy***, % (95% CI)	55.06 (44.14–65.62)	7.14 (0.18–33.87)	48.54 (38.58–58.60)

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IU, international units; N, number of patients included in the analyses; OCS, oral corticosteroids; SD, standard deviation; WBC, white blood cell count.
Notes: For repeated evaluations of a given characteristic, the most recent (including at time of enrolment) was selected.
*Data for total eosinophil count (cells/μL) were available for 27 patients eligible for biologic treatment and 2 patients non-eligible for biologic treatment; for the other patients included in the analyses, blood eosinophil (%) data were available.
**Data were available for eight patients eligible for biologic treatment and one patient non-eligible for biologic treatment.
***A statistically significant difference between patients eligible and non-eligible for biologic treatment was observed (Fisher's exact test *P*-value 0.0009).

higher impact of the disease on their health status (Figure S2A in Supplementary Material). Asthma control was poor in both subgroups (Figure S2B in Supplementary Material).

Discussions and Conclusions

This is the first real-world study conducted in Romania to evaluate the eligibility for biologic treatment in adult patients with severe asthma. We found that a large proportion of this population was considered eligible for referral for biologic treatment, as assessed by treating physicians and based on label criteria (around 86% and 80%, respectively). This proportion is higher than that observed in a large multi-national observational study in patients ≥12 years of age treated in primary and secondary care settings (IDEAL study), where the eligibility for biologics among severe asthma patients varied from 34% to 41% for omalizumab only and from 24% to 35% for any biologic, depending on the criteria used [18]. Higher eligibility for biologics was reported in an observational study in Canada (78% for any biologic therapy) [19] and 1 in Brazil (60% for any biologic but only 35% for omalizumab) [20]. The proportion observed in the Romanian patients was also closer to that observed in the overall population of the RECOGNISE

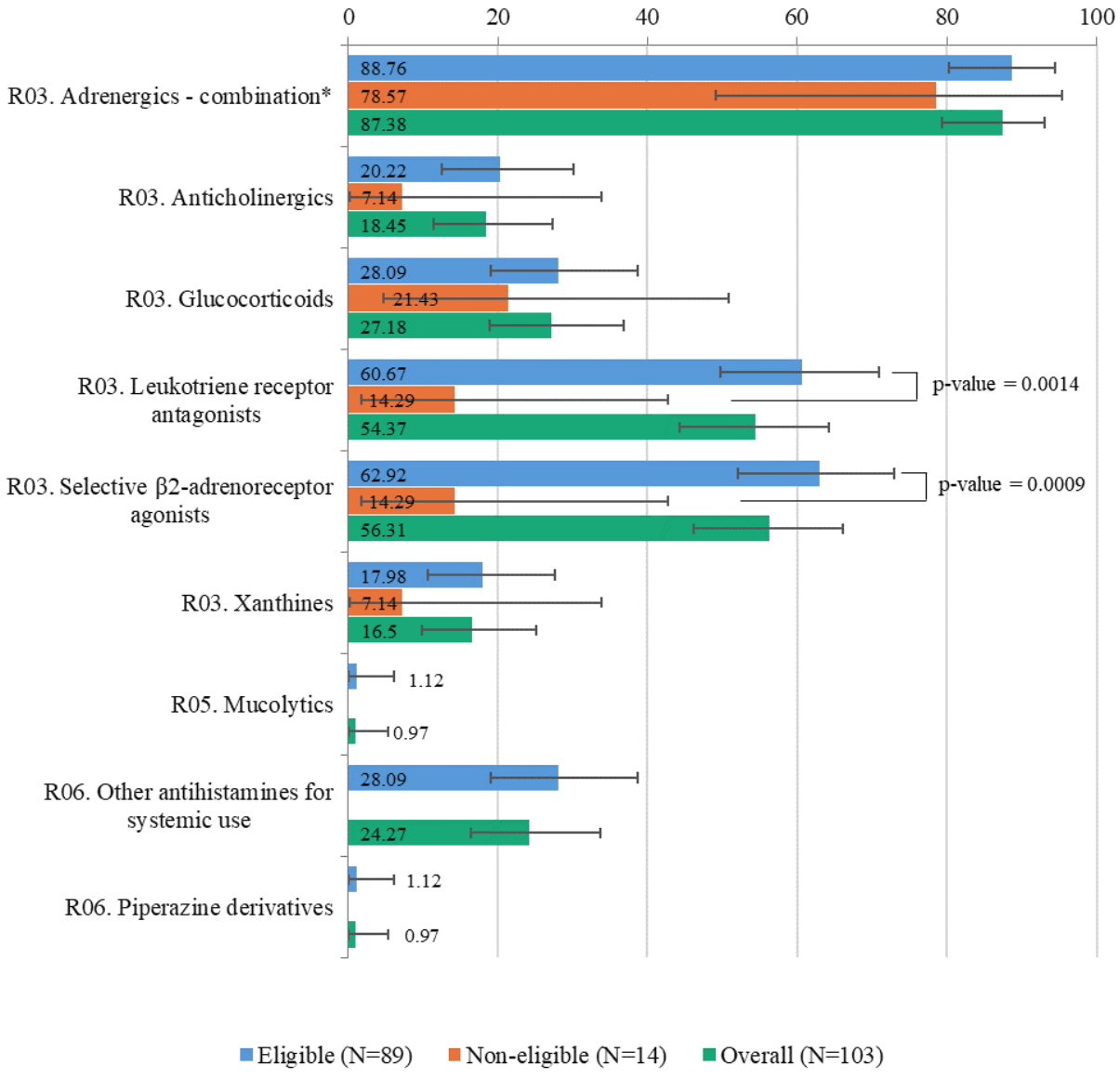

Figure 1. Proportion of patients receiving respiratory system drugs (according to the ATC Classification System – Level 2), by eligibility for biologic treatment and overall. N, number of patients with available data receiving asthma medication at study visit and in the prior 12 months.
Notes: The following therapeutic subgroups were included: R03 – Drugs for obstructive airway diseases, R05 – Cough and cold preparations, R06 – Antihistamines for systemic use. *P*-values (Fisher's exact test) are shown for statistically significant differences between subgroups. *Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics. ATC, anatomical therapeutic chemical.

study (75%) [13], and very similar to that observed in the RECOGNISE Greek population (87%) [21]. This higher proportion of patients considered eligible for biologics by Romanian physicians might be driven by the fact that they were all specialists, with most being either pulmonologists or allergists. Similarly, in the RECOGNISE Greek population, 88% of patients were evaluated by specialists [21]. In addition, omalizumab had been in use for severe asthma for more than 5 years at the time of the study and the specialists likely had extensive experience with this agent. In a survey conducted in Romania in 2019 (SABATINO) that evaluated patients' and physicians' perspectives on asthma and its therapy, the use of biologics was reported in only 9.2% of severe asthma cases [22]. Results from this survey and our study seem to indicate a gap between patient eligibility – at least as assessed in our study – and the actual use of biologics in severe asthma

Table 3. Prevalence of treated and untreated comorbidities associated with OCS use and CCI, by eligibility for biologic treatment and overall.

	Eligible for biologics (N = 89)	Non-eligible for biologics (N = 14)	Overall (N = 103)
Comorbidities, % (95% CI)			
Cataracts, untreated	4.49 (1.24–11.11)	-	3.88 (1.07–9.65)
Gastrointestinal disorders (including ulcers), treated	4.49 (1.24–11.11)	-	3.88 (1.07–9.65)
Osteoporosis, treated	-	7.14 (0.18–33.87)	0.97 (0.02–5.29)
Osteoporosis, untreated	4.49 (1.24–11.11)	-	3.88 (1.07–9.65)
Congestive heart failure, treated	5.62 (1.85–12.63)	7.14 (0.18–33.87)	5.83 (2.17–12.25)
COPD, untreated	-	14.29 (1.78–42.81)	1.94 (0.24–6.84)
Other (not captured by OCS or CCI score), treated	44.94 (34.38–55.86)	35.71 (12.76–64.86)	43.69 (33.94–53.82)
Other (not captured by OCS or CCI score), untreated	11.24 (5.52–19.69)	-	9.71 (4.75–17.13)
CCI*, median (range)	0 (0–4)	0 (0–1)	0 (0–4)
ACCI*, median (range)	2 (0–7)	1 (0–4)	2 (0–7)
ACCI scores, % (95% CI)**			
0–1	32.58 (23.02–43.34)	50.00 (23.04–76.96)	34.95 (25.82–44.98)
2–3	48.31 (37.59–59.16)	35.71 (12.76–64.86)	46.60 (36.71–56.70)
4–5	11.24 (5.52–19.69)	7.14 (0.18–33.87)	10.68 (5.45–18.31)
≥6	1.12 (0.03–6.10)	-	0.97 (0.02–5.29)
Estimated 10-year survival rate*, median (range)	90.15 (0.01–98.30)	95.87 (53.39–98.30)	90.15 (0.01–98.3)

ACCI, age-adjusted CCI; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; N, number of patients included in the analyses; OCS, oral corticosteroids.
Notes: The CCI score included 19 different medical conditions and each comorbid condition ranges from 1 to 6 points to sum an index score. The ACCI scores were calculated with additional points added for age. Each decade over the age of 50 years is assigned a comorbidity score of 1 [17]. The 10-year survival rate was calculated using a theoretical low-risk population whose 10-year survival is 98.3%, as $(0.983 \times e^{0.9 \times ACCI}) \times 100$.
*Data were available for 83 patients eligible for biologic treatment and 13 patients non-eligible for biologic treatment.
**Percentage of patients in each score category from the number of patients with available ACCI scores.

patients in Romania, likely due to an underestimation by the specialists and overestimation by the patients of the level of asthma control. In SABATINO, a quarter of patients with severe asthma admitted they used maintenance therapy (including biologics) only when symptomatic; this suggests low medication adherence, which was attributed to concerns about the side effects, dose and appropriateness of therapy especially in the absence of symptoms and despite a self-reported good knowledge of the treatment [22]. However, in our study, severe asthma medication adherence was assessed as being high in patients both eligible and non-eligible for biologics.

The patients' demographic characteristics were in line with those observed for other severe asthma populations [13,18,20,21,23,24]. Most patients were female, as previously reported for the entire RECOGNISE cohort [13] or the population of the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) project, consisting of adult patients from 11 European countries [24]. Conversely, more females than males were considered eligible for biologics. Most patients (>83%) had never smoked; this proportion was slightly higher than that observed in other European or global populations [21,23–25]. Both subgroups were heavily treated for asthma, with significantly more patients eligible for biologics receiving leukotriene receptor antagonists and LABA. Prior chronic OCS use was low in both groups, and consequently, <50% of patients had comorbidities associated with OCS treatment. As in the overall RECONGNISE study population [13], a significantly higher proportion of patients eligible for biologic therapy had a history of atopy.

We found an overall poor asthma control in the entire cohort, with exacerbations present in both the eligible and non-eligible patients for biologic treatment, in line with reports from other studies [20,21,25,26], although this comparison is likely hindered due to differences in the definitions used for exacerbation across studies. Serious exacerbations, requiring hospital stay ≥24 hr were more frequent among patients eligible for biologics. ACQ-6 scores also indicated not well-controlled asthma for the majority of patients in our study, especially for those eligible for treatment with biologics. The proportion of patients with poor asthma control according to ACQ-6 was higher in our study (>90%) than in

Table 4. Summary of exacerbations of severe asthma in the 12 months prior to the study visit, by eligibility for biologic treatment and overall.

	Eligible for biologics (N = 89)	Non-eligible for biologics (N = 14)	Overall (N = 103)
Patients with exacerbations, % (95% CI)	77.53 (67.45–85.70)	78.57 (49.20–95.34)	77.67 (68.40–85.29)
Category I	69.66 (59.01–78.97)	71.43 (41.90–91.61)	69.9 (60.08–78.55)
Category II	22.47 (14.30–32.55)	7.14 (0.18–33.87)	20.39 (13.09–29.46)
Category III	12.36 (6.33–21.04)	7.14 (0.18–33.87)	11.65 (6.17–19.47)
Median number of exacerbations	2 (1–7)	1 (1–2)	2 (1–7)
Category I	1 (1–5)	1 (1–2)	1 (1–5)
Category II	1 (1–3)	1 (1–1)	1 (1–3)
Category III	1 (1–3)	1 (1–1)	1 (1–3)

CI, confidence interval; N, number of patients included in the analyses.

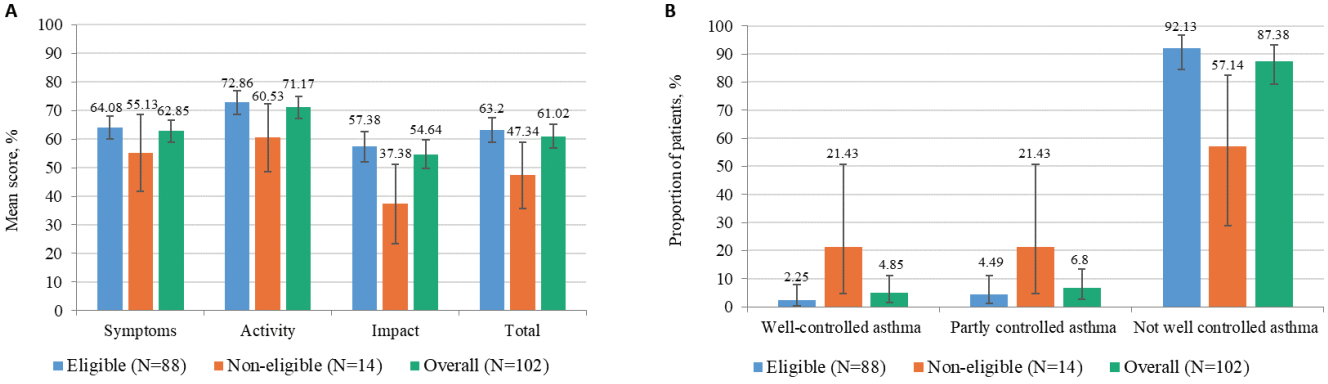

Figure 2. Patient-reported reduced HRQoL and asthma control, by eligibility for biologic treatment (part A) and overall (part B). N, number of patients included in the analyses.
Notes: Error bars represent 95% CIs. SGRQ domain and total scores are presented. Mean scores could vary from 0% (best possible health status, less impairment) to 100% (worst possible health status, greater impairment). Well-controlled, partly controlled and not well-controlled asthma categories corresponded to mean total ACQ-6 scores of ≤0.75, >0.75–<1.5 and ≥1.5, respectively. ACQ-6, asthma control questionnaire; CI, confidence interval; HRQoL, health-related quality of life; SGRQ, St. George's Respiratory Questionnaire.

Table 5. Summary of HCRU in the 12 months prior to the study visit, by eligibility for biologic treatment and overall.

	Eligible for biologics (N = 89)	Non-eligible for biologics (N = 14)	Overall (N = 103)
Patients with visits to physician, % (95% CI)	98.88 (93.90–99.97)	100 (76.84–100)	99.03 (94.71–99.98)
General practitioner	83.15 (73.73–90.25)	92.86 (66.13–99.82)	84.47 (76.00–90.85)
Specialist	98.88 (93.90–99.97)	100 (76.84–100)	99.03 (94.71–99.98)
Asthma specialist	98.88 (93.90–99.97)	100 (76.84–100)	99.03 (94.71–99.98)
Other specialist	31.46 (22.03–42.17)	14.29 (1.78–42.81)	29.13 (20.59–38.90)
Patients with at least one type of HCRU, % (95% CI)	41.57 (31.21–52.51)	21.43 (4.66–50.80)	38.83 (29.39–48.94)
Hospitalisation	22.47 (14.30–32.55)	14.29 (1.78–42.81)	21.36 (13.90–30.53)
Emergency visit	20.22 (12.45–30.07)	14.29 (1.78–42.81)	19.42 (12.28–28.38)
Sick leave	5.62 (1.85–12.63)	-	4.85 (1.59–10.97)

CI, confidence interval; HCRU, healthcare resource utilisation; N, number of patients included in the analyses.
Note: Multiple answers were possible.

the overall (84%) [13] and the Greek (76%) [21] RECOGNISE population or in a Brazilian study (56%) [20]. The HRQoL of patients eligible for biologics seemed to be more impacted than for those not eligible as indicated by SGRQ total scores, consistent with observations from the IDEAL study [18]. In our study, hospitalisations and emergency visits were more frequent in patients eligible for biologics, indicating a higher HCRU than in non-eligible patients with severe asthma.

Biologic treatment of severe asthma in a clinical trial setting has already been shown to have high efficacy and clinical benefits, including a reduction in the frequency of exacerbations and hospital visits due to asthma, leading to improved HRQoL and a potential decrease in costs related to HCRU [27]. These results have also been confirmed in real-world settings [28,29]. Given the large portion of Romanian patients with severe asthma considered eligible for biologic therapy, its consistent use has the potential to have important implications in reducing the societal and economic burden of the disease. New strategies are needed to make more biologics available to Romanian patients and educate the latter on the importance of treatment adherence.

This study has several limitations. Only one biologic agent (omalizumab) was approved for the treatment of severe asthma in Romania during the study conduct, and this situation persisted for most of the study duration, therefore referral for other biologics was not evaluated and may have impacted the results. In Romania, all patients were treated in secondary care settings, due to the particularities of the healthcare system. By contrast, in other European countries from the study, more biologics were available and severe asthma was also managed in primary care settings. These preclude generalisation of our results. Also, evaluation of adherence to asthma medication was based on the patients' recall, which might have introduced some bias towards higher reported adherence.

In conclusion, poor asthma control was observed among Romanian patients with severe asthma, despite heavy treatment. As shown by these findings, a large proportion of patients with severe asthma could benefit from biologic treatment. Presumably, with more biologics currently available, more patients receive such innovative treatment. New strategies are needed to further increase biologics availability and improve the management of severe asthma.

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Author Contributions

DN, DU, VP, CEH, MT, BM: participation to study data collection and interpretation; participation to paper writing or reviewing; endorsement of publishing the final version.GT, AS: participation to study data interpretation; participation to paper writing or reviewing; endorsement of publishing the final version.

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Table S1. Demographic and clinical characteristics of patients at study visit, by chronic OCS use.

	Chronic OCS use (N = 15)	No chronic OCS use (N = 88)
Demographic characteristics		
Median age at diagnosis, years (range)	47 (22–74)	46 (4–78)
Female, % (95% CI)	86.67 (59.54–98.34)	
Male, % (95% CI)	13.33 (1.66–40.46)	39.77 (29.49–50.77)
Employment status, % (95% CI)		
Full-time	13.33 (1.66–40.46)	27.27 (18.32–37.81)
Part-time	-	2.27 (0.28–7.97)
Not employed	86.67 (59.54–98.34)	70.45 (59.78–79.71)
Work type, % (95% CI)		
Physical	-	6.82 (2.54–14.25)
Intellectual	13.33 (1.66–40.46)	22.73 (14.47–32.89)
Smoking status, % (95% CI)		
Former smoker	-	13.64 (7.25–22.61)
Current smoker	-	5.68 (1.87–12.76)
Never smoked	100 (78.20–100)	80.68 (70.88–88.32)
Clinical characteristics		
Median blood eosinophil count*, cells/μL (range)	-	220 (2–1770)
Median blood eosinophil count**, % (range)	3.1 (1.1–23)	3.6 (0.1–22)
Median total WBC count**, cells/μL (range)	7670 (4200–12,280)	7700 (3900–18,600)
Median IgE count***, IU/mL (range)	224.8 (50.3–949.5)	242.8 (200–343)
Pre-bronchodilator FEV_1 in the last 12 months, mL (range)	950 (570–2700)	1255 (370–4400)
Short courses of systemic corticosteroids for ≥3 days, % (95% CI)	100 (78.20–100)	72.73 (62.19–81.68)
Medication adherence, % (95% CI)	100 (78.20–100)	98.86 (93.83–99.97)
History of atopy, % (95% CI)	100 (78.20–100)	39.77 (29.49–50.77)

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IU, international units; N, number of patients included in the analyses; OCS, oral corticosteroids; WBC, white blood cell count.
Notes: For repeated evaluations of a given characteristic, the most recent (including at time of enrolment) was selected.
*Data were available for 29 patients with no chronic OCS use.
**Data were available for 15 patients with chronic OCS use and 59 patients with no chronic OCS use.
***Data were available for four patients with chronic OCS use and five patients with no chronic OCS use.

Table S2. Prevalence of treated and untreated comorbidities associated with OCS use and CCI, by chronic OCS use.

	Chronic OCS use (N = 15)	No chronic OCS use (N = 88)
Comorbidities, % (95% CI)		
Cataracts, untreated	6.67 (0.17–31.95)	3.41 (0.71–9.64)
Gastrointestinal disorders (including ulcers), treated	-	4.55 (1.25–11.23)
Osteoporosis, treated	-	1.14 (0.03–6.17)
Osteoporosis, untreated	6.67 (0.17–31.95)	3.41 (0.71–9.64)
Congestive heart failure, treated	-	6.82 (2.54–14.25)
COPD, untreated	-	2.27 (0.28–7.97)
Other (not captured by OCS or CCI score), treated	73.33 (44.90–92.21)	38.64 (28.44–49.62)
Other (not captured by OCS or CCI score), untreated	6.67 (0.17–31.95)	10.23 (4.78–18.53)
CCI*, median (range)	0 (0–2)	0 (0–4)
ACCI*, median (range)	2 (0–5)	2 (0–7)
ACCI scores, % (95% CI)**		
0–1	20.00 (4.33–48.09)	37.5 (27.40–48.47)
2–3	46.67 (21.27–73.41)	46.59 (35.88–57.54)
4–5	20.00 (4.33–48.09)	9.09 (4.01–17.13)
≥6	-	1.14 (0.03–6.17)
Estimated 10-year survival rate*, median (range)	90.15 (21.36–98.30)	95.87 (0.01–98.30)

ACCI, age-adjusted CCI; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; N, number of patients included in the analyses; OCS, oral corticosteroids.
Notes: The CCI score included 19 different medical conditions and each comorbid condition ranges from 1 to 6 points to sum an index score. The ACCI scores were calculated with additional points added for age. Each decade over the age of 50 years is assigned a comorbidity score of 1 [17]. The 10-year survival rate was calculated using a theoretical low-risk population whose 10-year survival is 98.3%, as $(0.983 \times e^{0.9 \times ACCI}) \times 100$.
*Data were available for 13 patients with chronic OCS use and 83 patients with no chronic OCS use.
**Percentage of patients in each score category from the number of patients with available ACCI scores.

Table S3. Summary of exacerbations of severe asthma in the 12 months prior to the study visit, by chronic OCS use.

	Chronic OCS use (N = 15)	No chronic OCS use (N = 88)
Patients with exacerbations, % (95% CI)	100 (78.20–100)	73.86 (63.41–82.66)
Category I	73.33 (44.90–92.21)	69.32 (58.58–78.71)
Category II	66.67 (38.38–88.18)	12.50 (6.41–21.27)
Category III	40.00 (16.34–67.71)	6.82 (2.54–14.25)
Median number of exacerbations (range)	3 (1–5)	1 (1–7)
Category I	2 (1–4)	1 (1–5)
Category II	1.5 (1–3)	1 (1–2)
Category III	1 (1–3)	1 (1–2)

CI, confidence interval; N, number of patients included in the analyses; OCS, oral corticosteroids.

Table S4. Summary of HCRU in the 12 months prior to the study visit, by chronic OCS use.

	Chronic OCS use (N = 15)	No chronic OCS use (N = 88)
Patients with visits to physician, % (95% CI)	100 (78.20–100)	98.86 (93.83–99.97)
General practitioner	93.33 (68.05–99.83)	82.95 (73.45–90.13)
Specialist	100 (78.20–100)	98.86 (93.83–99.97)
Asthma specialist	100 (78.20–100)	98.86 (93.83–99.97)
Other specialist	46.67 (21.27–73.41)	26.14 (17.34–36.59)
Patients with at least one type of HCRU, % (95% CI)	93.33 (68.05–99.83)	29.55 (20.29–40.22)
Hospitalisation	53.33 (26.59–78.73)	15.91 (8.98–25.25)
Emergency visit	60.00 (32.29–83.66)	12.5 (6.41–21.27)
Sick leave	13.33 (1.66–40.46)	3.41 (0.71–9.64)

CI, confidence interval; HCRU, healthcare resource utilisation; N, number of patients included in the analyses; OCS, oral corticosteroids.
Note: Multiple answers were possible.

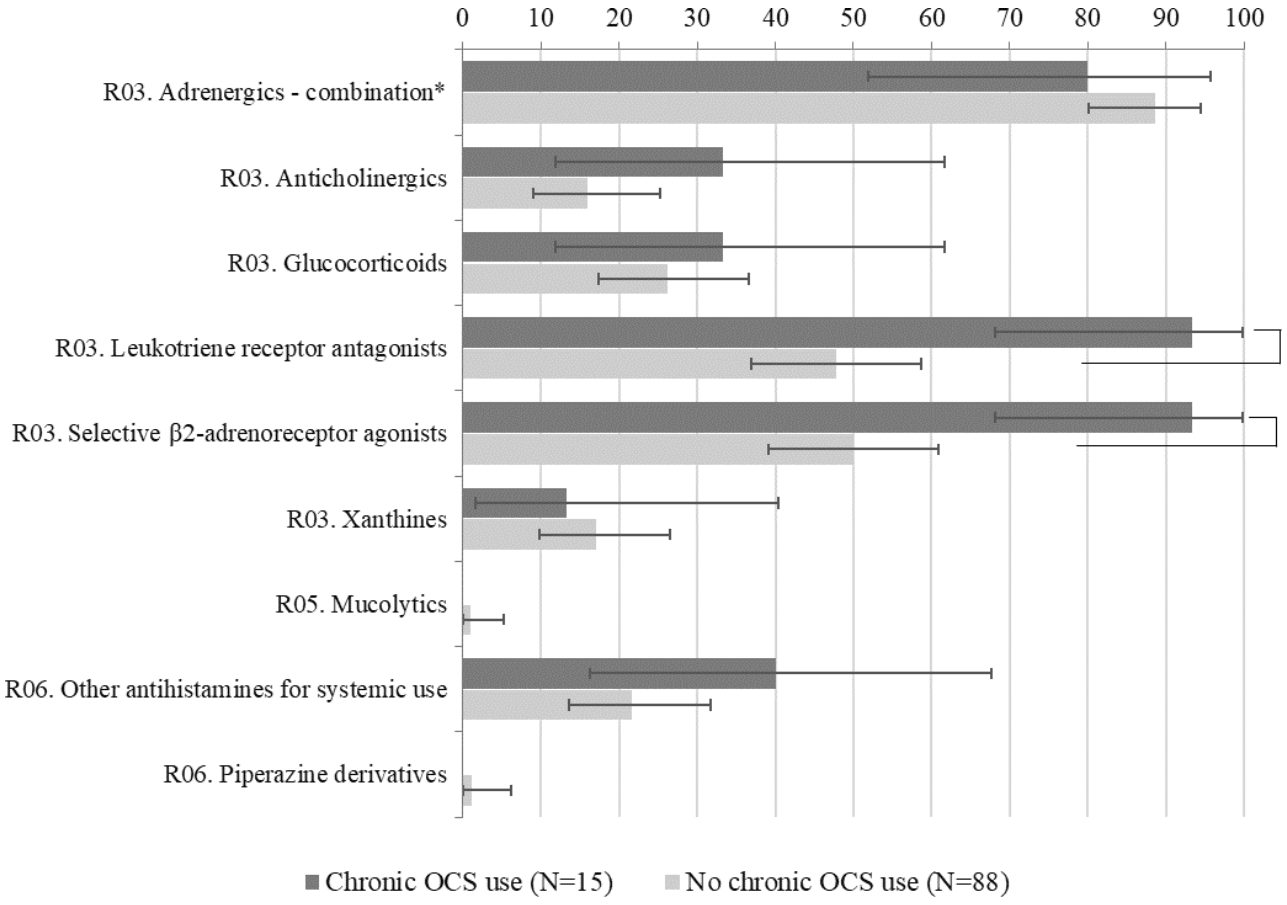

Figure S1. Proportion of patients receiving respiratory system drugs (according to the ATC Classification System – Level 2), by OCS use. OCS, oral corticosteroids; N, number of patients with available data receiving asthma medication at study visit and in the prior 12 months. *Notes*: The following therapeutic subgroups were included: R03- Drugs for obstructive airway diseases, R05- Cough and cold preparations, R06- Antihistamines for systemic use. *P*-values (Fisher's exact test) are shown for statistically significant differences between subgroups. *Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics. ATC, anatomical therapeutic chemical; OCS, oral corticosteroids.

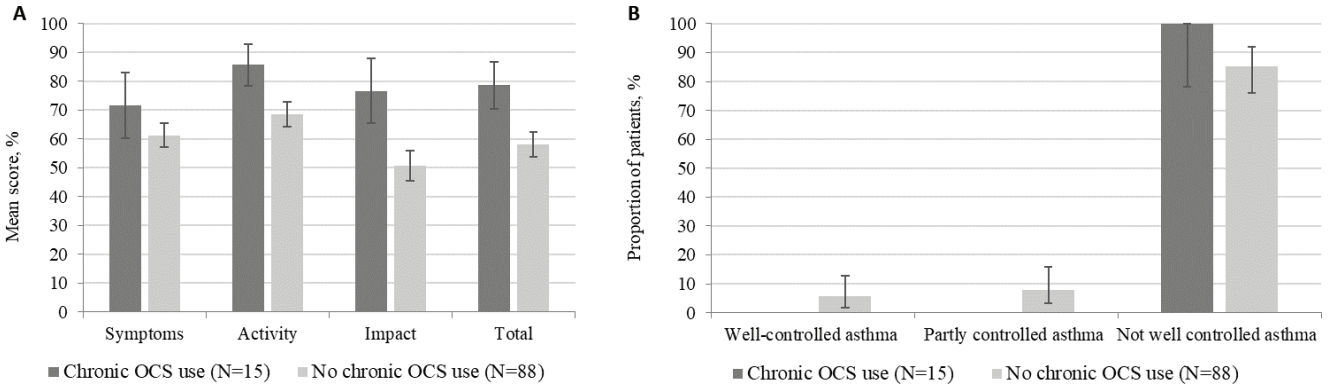

Figure S2. Patient-reported reduced HRQoL (part A) and asthma control (part B), by OCS use. OCS use; N, number of patients included in the analyses. *Notes*: Error bars represent 95% CIs. SGRQ domain and total scores are presented. Mean scores could vary from 0% (best possible health status, less impairment) to 100% (worst possible health status, greater impairment). Data for SGRQ outcomes were available for 15 patients with chronic OCS use and 87 patients with no OCS use. Well-controlled, partly controlled, and not well controlled asthma categories corresponded to mean total ACQ-6 scores of ≤0.75, >0.75–<1.5, and ≥1.5, respectively. ACQ-6, asthma control questionnaire; CI, confidence interval; HRQoL, health-related quality of life; OCS, oral corticosteroids; SGRQ, St. George's Respiratory Questionnaire.