ORIGINAL ARTICLE

Association Between T2-related Comorbidities and Effectiveness of Biologics in Severe Asthma

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Abstract

Rationale: Previous studies investigating the impact of comorbidities on the effectiveness of biologic agents have been relatively small and of short duration and have not compared classes of biologic agents.

Objectives: To determine the association between type 2–related comorbidities and biologic agent effectiveness in adults with severe asthma (SA).

Methods: This cohort study used International Severe Asthma Registry data from 21 countries (2017–2022) to quantify changes in four outcomes before and after biologic therapy—annual asthma exacerbation rate, FEV_1% predicted, asthma control, and long-term oral corticosteroid daily dose—in patients with or without allergic rhinitis, chronic rhinosinusitis (CRS) with or without nasal polyps (NPs), NPs, or eczema/atopic dermatitis.

Measurements and Main Results: Of 1,765 patients, 1,257, 421, and 87 initiated anti–IL-5/5 receptor, anti-IgE, and anti–IL-4/13 therapies, respectively. In general, pre- versus post–biologic therapy improvements were noted in all four asthma outcomes assessed, irrespective of comorbidity status. However, patients with comorbid CRS with or without NPs experienced 23% fewer exacerbations per year (95% CI, 10–35%; $P < 0.001$) and had 59% higher odds of better post–biologic therapy asthma control (95% CI, 26–102%; $P < 0.001$) than those without CRS with or without NPs. Similar estimates were noted for those with comorbid NPs: 22% fewer exacerbations and 56% higher odds of better post–biologic therapy control. Patients with SA and CRS with or without NPs had an additional FEV_1% predicted improvement of 3.2% (95% CI, 1.0–5.3; $P = 0.004$), a trend that was also noted in those with comorbid NPs. The presence of allergic rhinitis or atopic dermatitis was not associated with post–biologic therapy effect for any outcome assessed.

Conclusions: These findings highlight the importance of systematic comorbidity evaluation. The presence of CRS with or without NPs or NPs alone may be considered a predictor of the effectiveness of biologic agents in patients with SA.

Keywords: allergic rhinitis; chronic rhinosinusitis; nasal polyposis

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

At a Glance Commentary

Scientific Knowledge on the Subject: Although the effectiveness of biologic agents in treating patients with asthma who have a type 2–related comorbidity is documented, the influence of comorbidities on the effectiveness of biologic therapy is less studied.

What This Study Adds to the Field: We investigated the association of four potentially type 2–related comorbidities on the effectiveness of biologic therapy *1*) overall and by class and *2*) measured across four asthma outcomes and *3*) directly compared biologic agent effectiveness in patients with and without a given comorbidity. We found that most patients treated with biologic therapy exhibited an improvement in each asthma-related outcome assessed, irrespective of the presence of a comorbidity. However, additional improvements in exacerbation rate, asthma control, and lung function were noted in patients with chronic rhinosinusitis with or without nasal polyps (NPs) and in those with NPs compared with those without NPs, even after adjusting for blood eosinophil count. Our findings suggest that patients with severe asthma and chronic rhinosinusitis with or without NPs or NPs alone may benefit more from biologic therapy than those without these comorbidities, emphasizing the need for systematic comorbidity evaluation and a multidisciplinary approach to the management of severe asthma.

Asthma is increasingly considered a multimorbidity syndrome rather than a discrete disease (1, 2). This is particularly true for severe asthma (SA), which tends to fall on the type 2 (T2)–high side of the asthma endotype spectrum (2, 3). T2-high asthma is associated with cytokines produced by T helper 2 cells, with pathogenesis orchestrated by IL-4, IL-5, and IL-13 predominantly, and can be predicted based on increased fractional exhaled NO and sputum/blood eosinophil count (4, 5). Most patients with SA have this type of asthma: 83.8% by recent estimates (6). Potentially T2-related comorbidities are the most common and include allergic rhinitis (AR), chronic rhinosinusitis (CRS) with or without nasal polyps (NPs), and eczema/atopic dermatitis (AD); nearly 70% of patients with SA have at least one T2 comorbidity (7). These comorbidities can impair quality of life, worsen asthma outcomes, and contribute to the overall socioeconomic burden of the disease, particularly in SA (2, 4, 8). Recent data from the Finnish Nationwide Allergy Barometer Survey indicate that the annual cost of managing patients with asthma with multimorbidity was 28% higher than that for patients with asthma alone (2).

Patients with an increased T2 comorbidity burden are also more likely to experience asthma exacerbations and less likely to achieve asthma control (8). The scope of that impact appears to be comorbidity-dependent (7). For example, recent data from the International Severe Asthma Registry (ISAR; the same dataset used in the present study) showed that having CRS with or without NPs was associated with 29% more asthma exacerbations and a 46% greater likelihood of receiving long-term oral corticosteroid (LTOCS) treatment compared with those without CRS with or without NPs (7). In the same study, patients with AR also experienced more frequent exacerbations than patients without AR (7). This relationship between comorbidities and asthma outcomes is bidirectional: treating comorbidities is associated with improved asthma outcomes (9–12).

Although there is documented effectiveness of biologic agents in treating patients with asthma who have a potential T2-related comorbidity (13–17), the influence of comorbidities on biologic agent effectiveness is less well studied. A *post hoc* analysis of the PROXIMA (Patient-Reported Outcomes and Xolair® In the Management of Asthma) study showed that patients with SA and comorbid CRS with NPs had a greater response to omalizumab in terms of improvement in asthma control, lung function, and annual exacerbation rate than those without CRS with NPs (35.7% vs. 23.0%) (18). The effectiveness of benralizumab was similarly positively associated with the presence of CRS with NPs; more patients with CRS with NPs than without experienced a more clinically relevant improvement in asthma control (92.4% vs. 79.3%), suspension of oral corticosteroid treatment (76.6% vs. 61.8%), and time free of exacerbations despite oral corticosteroid discontinuation (70.2% vs. 52.9%) (19). Indeed, NPs are already noted by the Global Initiative for Asthma (GINA) strategy document as a factor that may predict a positive response to anti–IL-5/IL-5 receptor (IL-5R) therapy (4), a finding supported by recent evidence (20, 21). However, these studies included relatively small numbers of patients, assessed only one asthma comorbidity pattern, and did not compare across biologic agent classes (although the EVEREST [EValuating trEatment RESponses of Dupilumab Versus Omalizumab in Type 2 Patients] study comparing omalizumab and dupilumab is currently in progress) (22).

The aim of our study was to determine the association between a range of potentially T2-related comorbidities and the effectiveness of biologic agents across multiple asthma domains in adult patients with SA.

Methods

Study Design and Data Source

This was a registry-based cohort study using data from ISAR (https://isaregistries.org/), the largest adult SA registry in the world, with data from more than 17,000 patients from 25 countries (23). The registry has been described elsewhere (*see* online supplement) (24). Here, we included data from 21 countries (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Italy, Japan, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, South Korea, Spain, Taiwan, the United Arab Emirates, the United Kingdom, and the United States) collected between May 1, 2017, and January 24, 2022. Study entry corresponded to the date of initiation of first biologic therapy. Asthma-related outcomes were assessed before and after biologic therapy, and a minimum of 24 weeks of follow-up (48 wk for asthma exacerbations) was required (Figure 1).

Patients

All patients in the present study were enrolled into ISAR and were required to have

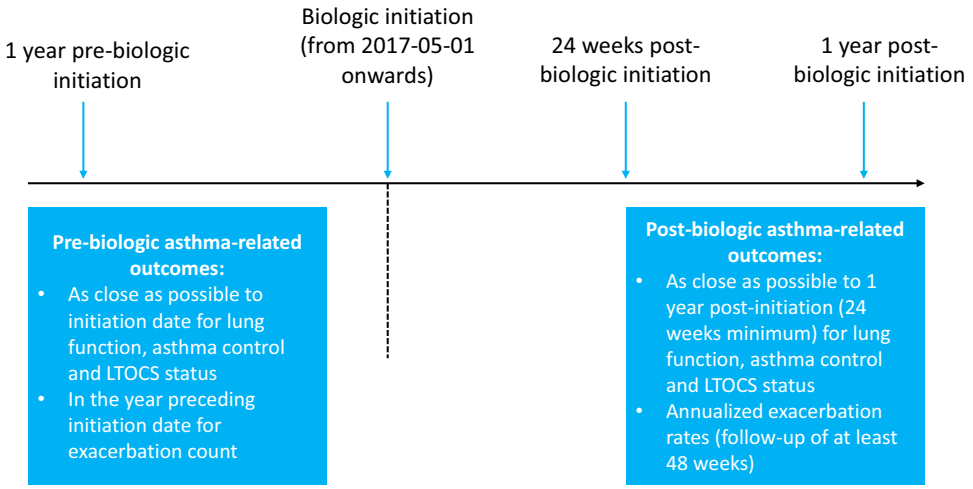

Figure 1. Study design. LTOCS = long-term oral corticosteroid.

SA (defined as asthma requiring treatment at GINA 2018 Step 5 or remaining uncontrolled at GINA Step 4) (25). They were also required to have initiated treatment with a biologic agent on or after May 1, 2017 (the date of the ISAR launch). We excluded patients who were younger than 18 years of age at the time of biologic agent therapy initiation or whose age was missing from the records and those who had bronchial thermoplasty, missing data for all four comorbidities considered (as detailed later), or missing eligible paired pre– and post–biologic therapy data for all four asthma outcomes considered (as detailed later) (Figure 1). Eligible patients were included irrespective of their biomarker profiles.

Comorbidity Variables

We focused on four potentially T2-related physician-reported comorbidities collected in all contributing countries: AR, CRS with or without NPs, NPs, and eczema/AD. Presence or absence of these comorbidities was assessed by physicians during routine clinical care visits (Table E1 in the online supplement). Because data were not complete across all visits, and to maximize data availability for our analysis, a history of T2-related comorbidities was assumed at study entry (i.e., biologic therapy initiation) regardless of the visit when it was reported. However, the comorbidities were reported for the first time after study entry in $<5\%$ of the cases.

Asthma-related Outcome Variables

Pre– and post–biologic therapy values were assessed for severe exacerbation rate, postbronchodilator FEV_1% predicted, asthma control, and LTOCS daily dose (Figure 1 and Table E2). A severe exacerbation was defined as an asthma-related hospital attendance/admission, asthma-related emergency room attendance, and/or worsening of asthma requiring an acute oral corticosteroid course of at least 3 days (collectively henceforth referred to as exacerbations). LTOCS was defined as daily use of oral corticosteroids as a background therapy for more than 3 months. Asthma control was assessed using GINA 2020 criteria and categorized as well controlled, partly controlled, or uncontrolled. If contributing countries used the Asthma Control Questionnaire or the Asthma Control Test to assess asthma control, conversions were made to fit the GINA categories (*see* Table E2).

Pre–biologic therapy exacerbation rates were assessed as the number of asthma exacerbation events in the 12 months preceding study entry. Post–biologic therapy exacerbation rate computation used the number of events that occurred in the entire follow-up period (minimum 48 wk required) and were annualized. For lung function, asthma control, and LTOCS daily dose, pre–biologic therapy variables were constructed using information as close as available to the date of biologic therapy initiation. Post–biologic therapy variables used information available as close as available to 1 year after the initiation of biologic therapy ($\geq$24 wk of follow-up required).

Statistics

The statistical analysis plan was predefined. R version 4.1.0 (R Foundation for Statistical Computing) was used to conduct all statistical analyses (26). For each asthma-related outcome, we quantified the difference between pre– and post–biologic therapy values between patients with and without a comorbidity by fitting appropriate multivariable models with the post–biologic therapy variable as the dependent variable and comorbidity status, age, sex, and the pre–biologic therapy outcome variable as independent variables. Results are expressed as the average relative pre– versus post–biologic therapy differences in patients with a comorbidity compared with patients without the same comorbidity for any given pre–biologic therapy measure (i.e., conditioning on pre–biologic therapy measure). The impact of each of the comorbidities was assessed singly. Reference groups were patients without the single comorbidity of interest, but patients could have one or more comorbidities (e.g., the reference group for AR comprised patients without reported AR, but they could have CRS, NPs, and/or AD).

Exacerbation rates were modeled by negative binomial regressions. Lung function and LTOCS daily dose were modeled using multiple linear regressions. For LTOCS daily dose, the analysis was restricted to patients receiving LTOCS treatment at the time of biologic therapy initiation, and doses were log-transformed to normalize the variables. For asthma control, we used ordinal logistic regressions. As a *post hoc* analysis, whenever associations were detected, we tested the effect of adjusting for blood eosinophil count (BEC), smoking status, pre–biologic therapy exacerbation rate, LTOCS use, and age at

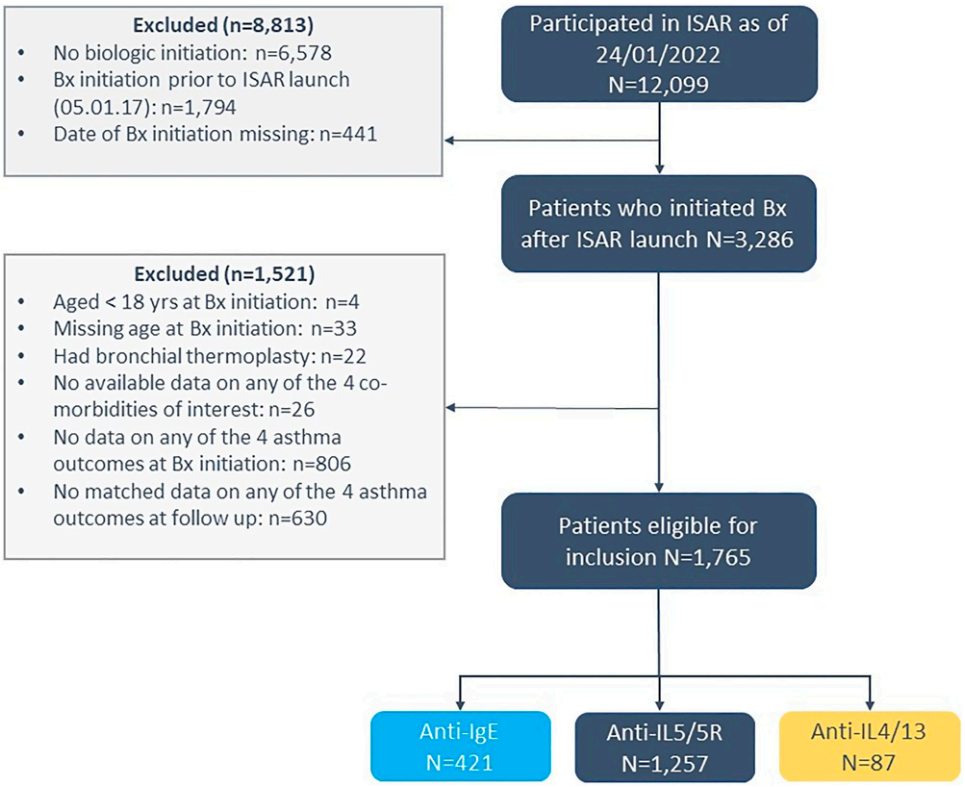

Figure 2. Subject disposition. Includes 609 patients who did not receive long-term oral corticosteroid treatment at the initiation of biologic therapy and had no available data on any of the other three asthma-related outcomes. Bx = biologic; IL-5R = interleukin 5 receptor; ISAR = International Severe Asthma Registry.

asthma onset. Analyses were first conducted in all patients initiating any type of anti-T2 biologic agent (anti-IgE, anti–IL-5/5R, or anti–IL-4/13) and repeated in patients initiating anti-IgE or anti–IL-5/5R therapies separately. Separate analysis in patients initiating anti–IL-4/13 therapy was not conducted because of the low number of participants in this subgroup. All statistical comparisons were two-sided.

Results

Subject Disposition

As of January 24, 2022, ISAR contained data from 25 countries including 12,099 adult patients with SA (Figure 2). In the present study, a total of 1,765 patients from 21 countries were eligible for inclusion, of whom 1,257 initiated anti–IL-5/5R therapy, 421 initiated anti-IgE therapy, and 87 initiated anti–IL-4/13 therapy.

Baseline Characteristics

Patients were predominantly female (60.6%), aged 50 years or older (65.7%), and never- or ex-smokers (97.4%) with asthma onset after 12 years of age (79.7%) and asthma phenotype characterized as eosinophilic (6) (95.8%) (Table 1). At biologic therapy initiation, most patients had multiple exacerbations in the past year (41.6% with at least three), reduced lung function (61.6% with FEV1% predicted $<$80%), and uncontrolled asthma (65.4%). Almost half of the patients (48.7%) were receiving LTOCS treatment, and the highest median BEC, blood IgE, and fractional exhaled NO concentrations were 520 cells/μl, 180 IU/ml, and 40 ppb, respectively (Table 1). Those who initiated anti–IL-5/5R therapy tended to have more severe disease than those in the anti-IgE therapy group, and those who initiated anti–IL-4/13 therapy tended to have the least severe disease. The most common potentially T2-related comorbidity was AR (60.7%), followed by CRS with or without NPs (56.4%), NPs (36.2%), and eczema/AD (13.9%), with 83.5% of patients having one or more of these comorbidities (Tables 1 and E3). Although the number of comorbidities was comparable between biologic agent groups, those who initiated anti-IgE therapy tended to have a higher prevalence of AR than their counterparts who initiated an anti–IL-5/5R or anti–IL-4/13 therapy, whereas those who initiated anti–IL-5/5R or anti–IL-4/13 therapy were more likely to have CRS with or without NPs or NPs alone (Table 1). Prevalence of comorbidities by country and overlap between comorbidities are provided in the online supplement (Figure E1 and Table E3).

Patients with AR or AD were more commonly female and younger at asthma onset than patients without AR or AD, whereas patients with CRS and NPs were more commonly male and older at asthma onset than patients without CRS or NPs. BEC was also higher in patients with CRS and NPs than in patients without these comorbidities (Table 2).

Association between Potentially T2-related Comorbidities and Biologic Therapy Effectiveness

In general, patients showed improvement after biologic therapy in terms of exacerbation rate, lung function, asthma control, and LTOCS daily dose irrespective

Table 1. Baseline Patient Characteristics

Characteristic No. of patients	Total 1,765	Anti–IL-5/5R 1,257	Anti-IgE 421	Anti–IL-4/13 87
Demographic				
Female sex	1,070 (60.6%)	754 (60.0%)	257 (61.0%)	59 (67.8%)
Age at enrollment, yr				
18–29	119 (6.7%)	61 (4.9%)	47 (11.2%)	11 (12.6%)
30–39	173 (9.8%)	100 (8.0%)	61 (14.5%)	12 (13.8%)
40–49	314 (17.8%)	210 (16.7%)	86 (20.4%)	18 (20.7%)
50–59	533 (30.2%)	392 (31.2%)	116 (27.6%)	25 (28.7%)
60–69	430 (24.4%)	344 (27.4%)	73 (17.3%)	13 (14.9%)
70–79	171 (9.7%)	132 (10.5%)	33 (7.8%)	6 (6.9%)
⩾80	25 (1.4%)	18 (1.4%)	5 (1.2%)	2 (2.3%)
Median (Q1–Q3)	55 (45–63)	56 (48–64)	51 (39–60)	51 (38–59)
Smoking status	*n* = 1,570	*n* = 1,146	*n* = 345	*n* = 79
Current	41 (2.6%)	23 (2.0%)	18 (5.2%)	0
Former	457 (29.1%)	344 (30.0%)	88 (25.5%)	25 (31.6%)
Never	1,072 (68.3%)	779 (68.0%)	239 (69.3%)	54 (68.4%)
Age at asthma onset	*n* = 1,327	*n* = 965	*n* = 319	*n* = 43
<12 yr	270 (20.3%)	168 (17.4%)	89 (27.9%)	13 (30.2%)
⩾12 yr	1,057 (79.7%)	797 (82.6%)	230 (72.1%)	30 (69.8%)
Prebiologic asthma-related outcome				
LTOCS	860 (48.7%)	687 (54.7%)	149 (35.4%)	24 (27.6%)
Exacerbation rate	*n* = 1,651	*n* = 1,183	*n* = 384	*n* = 84
0	367 (22.2%)	227 (19.2%)	104 (27.1%)	36 (42.9%)
1	312 (18.9%)	209 (17.7%)	80 (20.8%)	23 (27.4%)
2	286 (17.3%)	194 (16.4%)	79 (20.6%)	13 (15.5%)
⩾3	686 (41.6%)	553 (46.7%)	121 (31.5%)	12 (14.3%)
Postbronchodilator FEV_1, % predicted	*n* = 1,488	*n* = 1,076	*n* = 335	*n* = 77
<80%	916 (61.6%)	668 (62.1%)	202 (60.3%)	46 (59.7%)
Median (Q1–Q3)	74 (59–88)	74 (59–89)	75 (60–87)	74 (59–87)
FEV_1/FVC	*n* = 1,460	*n* = 1,055	*n* = 328	*n* = 77
<0.70	814 (55.8%)	606 (57.4%)	166 (50.6%)	42 (54.5%)
Median (Q1–Q3)	0.68 (0.58–0.76)	0.68 (0.57–0.75)	0.70 (0.60–0.79)	0.68 (0.57–0.75)
Asthma control*	*n* = 1,338	*n* = 980	*n* = 298	*n* = 60
Well controlled	176 (13.2%)	107 (10.9%)	57 (19.1%)	12 (20.0%)
Partly controlled	287 (21.4%)	209 (21.3%)	63 (21.1%)	33 (55.0%)
Uncontrolled	875 (65.4%)	664 (67.8%)	178 (59.7%)	15 (25.0%)
Biomarkers				
Highest BEC, cells/μL	*n* = 1,455	*n* = 1,084	*n* = 303	*n* = 68
Median (Q1–Q3)	520 (300–880)	600 (390–940)	300 (200–595)	400 (225–600)
Highest blood IgE, IU/mL	*n* = 1,306	*n* = 926	*n* = 323	*n* = 57
Median (Q1–Q3)	180 (70–465)	151 (59–393)	283 (130–636)	135 (41–724)
Highest F_{ENO}, ppb	*n* = 1,033	*n* = 794	*n* = 185	*n* = 54
Median (Q1–Q3)	40 (22–77)	45 (24–82)	26 (14–50)	46 (19–80)
Potentially T2-related comorbidities				
Allergic rhinitis	*n* = 1,254,254	*n* = 826,826	*n* = 344,344	*n* = 84
Ever	761 (6,060.7%)	464 (5,656.2%)	246 (7,171.5%)	51 (60.7%)
Chronic rhinosinusitis*	*n* = 1,716	*n* = 1,220	*n* = 410	*n* = 86
Ever	968 (56.4%)	739 (60.6%)	179 (43.7%)	50 (58.1%)
Nasal polyposis	*n* = 1,756	*n* = 1,251	*n* = 419	*n* = 86
Ever	636 (36.2%)	504 (40.3%)	97 (23.2%)	35 (40.7%)
Eczema/atopic dermatitis	*n* = 1,753	*n* = 1,249	*n* = 417	*n* = 87
Ever	243 (13.9%)	144 (11.5%)	71 (17.0%)	28 (32.2%)
Count of comorbidities	*n* = 1,208,208	*n* = 792,792	*n* = 334,334	*n* = 82
0	199 (1,616.5%)	136 (1,717.2%)	54 (1,616.2%)	9 (11.0%)
1	319 (2,626.4%)	187 (2,323.6%)	109 (3,232.6%)	23 (28.0%)
2	338 (28.0%)	224 (28.3%)	90 (2,626.9%)	24 (29.3%)
3	294 (2,424.3%)	205 (2,525.9%)	71 (2,121.3%)	18 (22.0%)
4	54 (44.8%)	40 (55.1%)	10 (33.0%)	8 (9.8%)
Eosinophilic phenotype gradient†	*n* = 1,592	*n* = 1,257	*n* = 269	*n* = 66
Grade 0: unlikely/noneosinophilic	2 (0.1%)	0	1 (0.4%)	1 (1.5%)
Grade 1: least likely	24 (1.5%)	0	19 (7.1%)	5 (7.6%)
Grade 2: likely	41 (2.6%)	0	38 (14.1%)	3 (4.5%)
Grade 3: most likely	1,525 (95.8%)	1,257 (100%)	211 (78.4%)	57 (86.4%)

Definition of abbreviations: BEC = blood eosinophil count; IL-5R = interleukin 5 receptor; F_{ENO} = fractional exhaled nitric oxide; LTOCS = long-term oral corticosteroid.

Figure 1 shows assessment time points for outcome variables.

*With or without nasal polyps.

†Per Global Initiative for Asthma 2022 criteria (6).

Table 2. Patient Characteristics and Changes before versus after Biologic Therapy by Comorbidity Status

	Allergic Rhinitis		Chronic Rhinosinusitis		Nasal Polyposis		Eczema/Atopic Dermatitis	
Characteristic **No. of patients**	**Ever** **761**	**Never** **493**	**Ever** **968**	**Never** **748**	**Ever** **636**	**Never** **1,120**	**Ever** **243**	**Never** **1,510**
Female sex	479 (62.9%)	275 (55.8%)	573 (59.2%)	468 (62.6%)	354 (55.7%)	711 (63.5%)	159 (65.4%)	907 (60.1%)
Median age, yr (Q1–Q3)	54 (44–62)	57 (50–66)	55 (46–63)	54 (44–63)	54 (46–63)	55 (44–64)	54 (41–64)	55 (46–63)
Smoking status	*n* = 643	*n* = 431	*n* = 854	*n* = 670	*n* = 562	*n* = 1,004	*n* = 206	*n* = 1,355
Current	18 (2.8%)	13 (3.0%)	18 (2.1%)	22 (3.3%)	10 (1.8%)	31 (3.1%)	6 (2.9%)	35 (2.6%)
Former	191 (29.7%)	135 (31.3%)	240 (28.1%)	197 (29.4%)	163 (29.0%)	292 (29.1%)	60 (29.1%)	391 (28.9%)
Never	434 (67.5%)	283 (65.7%)	596 (69.8%)	451 (67.3%)	389 (69.2%)	681 (67.8%)	140 (68.0%)	929 (68.6%)
Age at asthma onset	*n* = 558	*n* = 283	*n* = 719	*n* = 562	*n* = 531	*n* = 788	*n* = 175	*n* = 1,146
<12 yr	13 (20.3%)	37 (13.1%)	123 (17.1%)	131 (23.3%)	83 (15.6%)	187 (23.7%)	61 (34.9%)	208 (18.2%)
Highest BEC, cells/μL	*n* = 596	*n* = 412	*n* = 800	*n* = 624	*n* = 531	*n* = 922	*n* = 191	*n* = 1,257
Median (Q1–Q3)	540 (300–900)	600 (341–915)	600 (350–950)	449 (270–780)	666 (400–1,000)	500 (300–800)	500 (295–800)	540 (300–900)
Positive test to any allergen*	*n* = 592	*n* = 326	*n* = 740	*n* = 640	*n* = 516	*n* = 899	*n* = 178	*n* = 1,234
Yes	445 (75.2%)	182 (55.8%)	431 (58.2%)	440 (68.7%)	285 (55.2%)	614 (68.3%)	139 (78.1%)	759 (61.5%)
Exacerbation rate	*n* = 559	*n* = 363	*n* = 719	*n* = 541	*n* = 463	*n* = 818	*n* = 189	*n* = 1,092
Before biologics	2.24 ± 2.34	2.16 ± 2.23	2.65 ± 2.77	3.37 ± 3.74	2.88 ± 3.02	3.05 ± 3.40	1.97 ± 2.00	3.15 ± 3.39
After biologics	0.65 ± 1.21	0.65 ± 1.04	0.75 ± 1.25	1.13 ± 1.62	0.77 ± 1.21	1.01 ± 1.55	0.72 ± 1.35	0.96 ± 0.46
Change	−1.59 ± 2.54	−1.51 ± 2.33	−1.89 ± 2.74	−2.24 ± 3.51	−2.11 ± 2.82	−2.04 ± 3.30	−1.25 ± 2.30	−2.19 ± 3.22
P value†	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
FEV_1% predicted	*n* = 313	*n* = 267	*n* = 493	*n* = 386	*n* = 306	*n* = 573	*n* = 101	*n* = 776
Before biologics	76.4 ± 21.7	72.2 ± 23.3	75.8 ± 22.5	71.0 ± 22.6	76.4 ± 22.1	72.2 ± 22.9	73.9 ± 22.5	73.6 ± 22.7
After biologics	80.1 ± 22.6	76.6 ± 23.2	79.5 ± 23.3	73.0 ± 22.1	79.7 ± 23.0	75.1 ± 22.8	75.6 ± 21.7	76.8 ± (23.1)
Change	+3.7 ± 17.9	+4.4 ± 16.0	+3.8 ± 17.1	+2.0 ± 17.1	+3.3 ± 17.1	+2.9 ± 17.1	+1.7 ± 13.7	+3.1 ± 17.5
P value†	<0.001	<0.001	<0.001	0.023	0.001	<0.001	0.210	<0.001
Asthma control	*n* = 430	*n* = 237	*n* = 570	*n* = 450	*n* = 414	*n* = 629	*n* = 118	*n* = 923
Before biologics								
Uncontrolled	65.6%	57.8%	65.8%	69.6%	65.2%	70.3%	71.2%	67.8%
Partly controlled	22.6%	23.2%	21.2%	18.9%	21.3%	18.6%	19.5%	19.7%
Well controlled	11.9%	19.0%	13.0%	11.6%	13.5%	11.1%	9.3%	12.5%
After biologics								
Uncontrolled	25.6%	27.0%	30.2%	42.4%	29.5%	39.6%	39.0%	35.2%
Partly controlled	31.9%	29.1%	26.5%	25.3%	24.9%	27.2%	33.1%	25.4%
Well controlled	42.6%	43.9%	43.3%	32.2%	45.7%	33.2%	28.0%	39.4%
P value†	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
LTOCS use	283 (37.2%)	202 (41.0%)	445 (46.0%)	383 (51.2%)	312 (49.1%)	543 (48.5%)	243 (33.3%)	772 (51.1%)
LTOCS dose‡	*n* = 128	*n* = 74	*n* = 243	*n* = 262	*n* = 196	*n* = 332	*n* = 42	*n* = 485
Before biologics	13.2 ± 10.9	15.5 ± 15.4	12.2 ± 10.0	13.2 ± 10.6	12.0 ± 9.3	13.1 ± 10.7	10.5 ± 10.1	12.8 ± 10.2
After biologics	11.7 ± 9.9	13.9 ± 14.7	10.5 ± 9.5	11.0 ± 10.1	9.8 ± 8.3	11.4 ± 10.4	8.8 ± 9.0	10.9 ± 9.8
Change	−1.4 ± 7.6	−1.6 ± 11.7	−1.7 ± 6.9	−2.2 ± 7.6	−2.2 ± 7.2	−1.7 ± 7.1	−1.7 ± 8.9	−1.9 ± 7.0
P value†	0.020	0.204	<0.001	<0.001	<0.001	<0.001	0.116	<0.001

Definition of abbreviations: BEC = blood eosinophil count; LTOCS = long-term oral corticosteroid.
Data presented as mean ± SD where applicable.
*Not available for all patients or for all allergens.
†Comparisons were made for before versus after biologic therapy with a paired Wilcoxon test for exacerbations and LTOCS dose, paired *t* test for FEV_1% predicted, and McNemar test (nominal symmetry test) for asthma control.
‡Mean daily dose ± SD in users before biologic therapy.

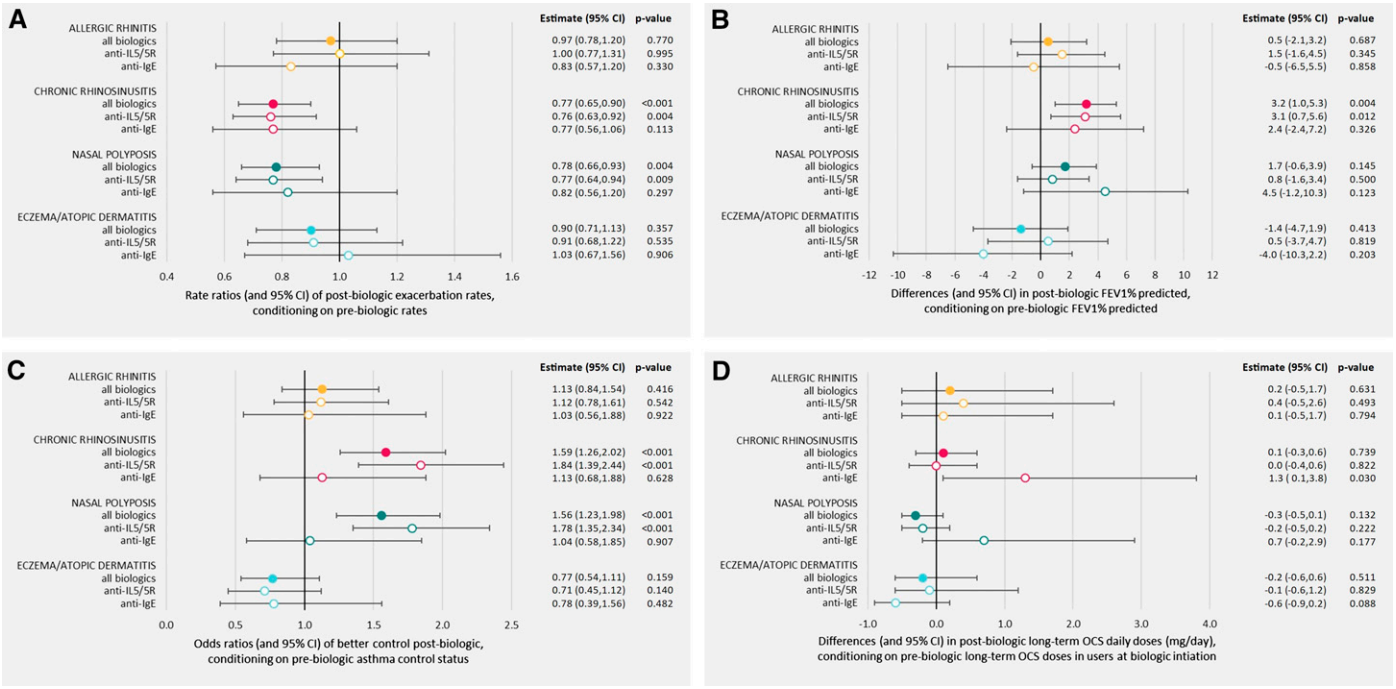

Figure 3. Association between potentially type 2–related comorbidity and post–biologic therapy asthma-related outcomes adjusted for pre–biologic therapy status, age, and sex: (*A*) exacerbation rates, (*B*) lung function, (*C*) asthma control, and (*D*) long-term oral corticosteroid daily dose. The reference group is patients without the comorbidity of interest. IL-5R = interleukin 5 receptor; OCS = oral corticosteroid; ppFEV$_1$ = FEV$_1$% predicted.

of comorbidity status (Table 2). We found evidence that patients with some comorbidities experienced additional improvement (Figure 3).

NPs. Patients with NPs experienced greater post–biologic therapy improvements in exacerbation rate and asthma control outcomes compared with patients without NPs (Figures 3A and 3C). Conditioning on pre–biologic therapy values, patients with NPs experienced 22% fewer exacerbations per year (95% CI, 7–34%; $P = 0.004$). As a specific example, for women aged 55 years and with three exacerbations per year before biologic therapy initiation, the predicted numbers of post–biologic therapy exacerbations were 0.65 per year in patients with NPs and 0.83 per year in patients without NPs. Patients with NPs also had 56% higher odds of better post–biologic therapy asthma control (95% CI, 23–98%; $P < 0.001$). In terms of predicted probabilities, women with NPs aged 55 years with uncontrolled asthma at biologic therapy initiation had a 29% probability of improving to partly controlled asthma and a 33% probability of improving to well-controlled asthma. The respective probabilities for those without NPs were 27% and 24%. Adjusting for BEC attenuated the association for exacerbations (rate ratio, 0.86; 95% CI, 0.72–1.02; $P = 0.092$) and for asthma control (odds ratio, 1.37; 95% CI, 1.06–1.77; $P = 0.015$), although the trends remained. Adjusting for pre–biologic therapy exacerbation rate, LTOCS, smoking status, or age at asthma onset did not impact the estimates (data not shown). A trend of stronger post–biologic therapy improvement in lung function was also apparent in patients with NPs compared with patients without NPs (Figure 3B), which was attenuated when adjusted for BEC (+1.00 FEV$_1$% predicted; 95% CI, −1.3 to 3.3; $P = 0.399$). No association with NPs was detected for differential post–biologic therapy improvement in LTOCS daily dose (Figure 3D).

CRS with or without NPs. Of 968 patients with reported CRS, 966 had information on NPs, and 621 (64%) had NPs reported. Irrespective of NP status, the associations between CRS and greater improvement in exacerbations and asthma control were in the same range as those observed for NPs. Patients with comorbid CRS with or without NPs experienced 23% fewer exacerbations per year (95% CI, 10–35%; $P < 0.001$) and had 59% higher odds of better post–biologic therapy asthma control (95% CI, 26–102%; $P < 0.001$) than those without CRS with or without NPs (Figures 3A and 3C). Adjusting for BEC had no impact on the estimate for exacerbations (rate ratio, 0.77; 95% CI, 0.65–0.91; $P = 0.002$) but slightly attenuated the association with better asthma control (odds ratio, 1.38; 95% CI, 1.07–1.78; $P = 0.013$). Adjusting for pre–biologic therapy exacerbation rate, LTOCS, smoking status, or age at asthma onset did not impact the estimates (data not shown). When excluding patients with reported NPs from the analysis, estimates remained in the same ranges: 0.81 (95% CI, 0.66–1.00; $P = 0.053$) for exacerbations and 1.40 (95% CI, 1.00–1.97; $P = 0.051$) for asthma control.

A stronger improvement in lung function was also detected in patients with CRS with or without NPs compared with patients without them (Figure 3C). Conditioning on pre–biologic therapy FEV1% predicted, patients with CRS with or without NPs had an extra FEV1% predicted improvement of 3.2% (95% CI, 1.0–5.3; $P = 0.004$). This positive association was attenuated when adjusted for BEC (+2.1;

95% CI, −0.2 to 4.3; $P = 0.076$), but was augmented when patients with NPs were excluded from the analysis (+3.7; 95% CI, 3.7–6.5; $P = 0.009$). Overall, the presence of CRS with or without NPs was not associated with a greater post–biologic therapy reduction in LTOCS (difference, 0.1; 95% CI, −0.3 to 0.6). However, patients with CRS with or without NPs who initiated anti-IgE therapy tended to experience a smaller decrease in daily LTOCS dose than patients without CRS with or without NPs (Figure 3D). In LTOCS users and conditioning on pre–biologic therapy dose, patients with CRS with or without NPs treated with anti-IgE therapy were, on average, prescribed 1.3 mg/d more (95% CI, 0.1–3.8; $P = 0.030$) than patients without CRS with or without NPs.

AR and eczema/AD. AR and AD were not associated with biologic agent effectiveness for any outcome assessed (Figures 3).

Heterogeneity between anti-IgE and anti–IL-5/5R therapy results. In general, there were no apparent differences between the estimates seen for anti-IgE and anti–IL-5/5R therapies except for asthma control, in which the positive associations with CRS and NPs seemed to be restricted to patients initiating anti–IL-5/5R therapy ($P = 0.08$ and $P = 0.012$ for heterogeneity for CRS with or without NPs and NPs alone, respectively).

Discussion

The effectiveness of biologic agents in treating SA with a T2-related comorbidity is well established (27, 28). What is less well known is whether the presence of a T2-related comorbidity influences the effectiveness of biologic agents. We investigated the association of a range of potentially T2-related comorbidities on the effectiveness of biologic agents *1*) overall and by class and *2*) measured across four asthma outcomes and *3*) directly compared biologic agent effectiveness in patients with and without a given comorbidity. We found that most patients treated with biologic therapy exhibited an improvement in each asthma-related outcome assessed, irrespective of the presence of a comorbidity (83.5% had at least one potentially T2-related comorbidity). However, additional improvements in exacerbation rate, asthma control, and lung function were noted in patients with CRS with or without NPs and in those with NPs alone compared with patients without these comorbidities. This was likely because these comorbidities are proxies for T2 asthma, the target of anti-T2 biologic agents. Assessment for the presence of potentially T2-related comorbidities is already recommended by GINA (4), is easily done during routine asthma review, and should help inform clinical decisions.

Most studies investigating the additional positive impact of potentially T2-related comorbidities on the effectiveness of biologic agents have focused on anti–IL-5/5R therapies and NPs alone or CRS with NPs (19, 27, 29, 30). For example, the presence of CRS with NPs increased the effectiveness of benralizumab in patients with SA, with more of these patients achieving a clinically relevant improvement in asthma control (92.4% vs. 79.3%) and experiencing a significantly greater improvement in FEV1% predicted (23.1% vs. 13.0%) than those without CRS with NPs (19). By contrast, others found that comorbid SA and CRS with NPs was associated with a lower risk of exacerbations or a lower number of exacerbations in patients treated with anti–IL-5 (30, 31) or anti–IL-4/13 therapies (21), but this additional effectiveness in those with CRS with NPs was not seen for asthma control or lung function domains (30). Improvement in lung function following omalizumab treatment has been found to be more likely in patients with asthma and CRS than in those without (32). In our study, a greater anti–IL-5/5R therapy–associated reduction in exacerbation rates also occurred in patients with CRS with or without NPs or NPs alone. Although there was no difference in lung function improvement in patients with NPs compared with patients without NPs, additional lung function improvement was noted in patients with CRS with or without NPs compared with patients without these comorbidities. Additionally, patients with CRS or NPs had higher odds of having better controlled asthma after anti–IL-5/5R treatment than patients without CRS or NPs, a trend that was not observed in patients treated with anti-IgE therapy. This enhanced effect of anti–IL-5/5R agents in these patients is consistent with the fact that NPs and CRS are highly associated with eosinophilic inflammation of the upper airway (particularly in the United States, Europe, and Australia) (33, 34), which tends to correlate with inflammation of the lower airway (35). Indeed, the recent European Position Paper on CRS and NP (EPOS2020) guidelines suggest splitting CRS without NP into eosinophilic CRS and noneosinophilic CRS (36).

The effectiveness of biologic agents in treating patients with asthma and comorbid AR or AD is well documented (13, 37, 38). We also found that biologic therapy was associated with reduced exacerbation rate and LTOCS dose and improved lung function and asthma control in those with and without AR and AD. However, unlike CRS with or without NPs and NPs alone, neither comorbid AR nor AD were associated with improved effectiveness of biologic therapy for any asthma outcome assessed. *Post hoc* analyses of the EXTRA (A Study of Omalizumab (Xolair) in Subjects With Moderate to Severe Persistent Asthma), INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment), and single-arm PROSPERO (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab) omalizumab studies also reported similar lung function improvement (albeit measured in absolute FEV_1) in omalizumab-treated patients with and without AR (39). This may suggest a greater role of the eosinophil (with associated mucus hypersecretion and remodeling) rather than IgE in lung function impairment. The effectiveness of anti-IgE therapy in those with and without an AR or AD comorbidity is arguably a positive result in itself. Taken together, our results identify patient subgroups that may derive greater benefit from biologic therapies (40).

Limitations

Limitations of our study include those common to observational studies (e.g., bias, confounding, and challenges in demonstrating causality). Clinical variables were not available for all patients. Some of the missing data was due to a lack of spirometry data, especially during the coronavirus disease (COVID-19) pandemic. There was also potentially lower power to detect differences in the anti-IgE arm as a result of smaller numbers of patients and less room for improvement. Those treated with an anti-IgE agent also tended to have less severe disease, although we adjusted all estimates for baseline values. Because of an insufficient number of patients, we did not investigate the association of comorbidities with the effectiveness of anti–IL-4/13 therapy. The results may also have been influenced by variations between countries in terms of the presence of comorbidities, how comorbidities were assessed and diagnosed,

and biologic therapy access criteria (41). We hypothesize that intercountry variability in comorbidity diagnosis protocols would have biased our results toward the null rather than overestimating the associations. The extent to which improvement in asthma outcomes was associated with improvement in comorbidity outcomes is unknown because improvement in comorbidities is not part of the data collected by ISAR. The presence of comorbidities was assessed using all available visits to maximize data availability, and this could have diluted our results. A small proportion of comorbidities (<5%) were found to be first reported only after the initiation of biologic therapy. However, the comorbidities considered tend to be lifelong, and how they are reported by physicians varies over time and across countries. It should be noted that "active" disease is different from a "history of" disease, and misclassification might have further diluted our results. No statistical association was detected between AD and the effectiveness of biologic agents.

Strengths of our study are the inclusion of a large, multinational cohort with severe and heterogenous asthma. In the context of comorbidities, the sample sizes used for our analysis were generally large and allowed the detection of the associations between the presence of comorbidities and multiple asthma-related outcomes. Rigorous statistical analyses were also employed, adjusting for pre–biologic therapy values as well as for age and sex. Future work is planned to investigate the association of comorbidity on the effectiveness of other biologic therapies (e.g., anti–IL-4/13 and anti–thymic stromal lymphopoietin therapies), the association of multimorbidity on the effectiveness of biologic therapy, biomarker agent profiles by comorbidity status, and head-to-head comparisons between biologic agent classes in patients with specific comorbidity profiles.

Conclusions

In conclusion, these findings suggest that patients with SA and CRS with or without NPs or NPs alone might benefit from biologic therapy to a greater extent than patients without these comorbidities. Our results highlight the importance of systematic evaluation for comorbidities and a multidisciplinary approach to their management in patients with SA. ■

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