



Real-Life Response to Biologics in Severe Asthma with Nasal Polyposis: Insights from the Belgian Severe Asthma Registry

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Abstract

Background Nasal polyposis (NP) is a comorbidity of type 2 severe asthma (SA) which could influence response to SA biologics.

Methods We evaluated (super-) response in SA patients with (NP+) and without NP (NP-) enrolled in the Belgian Severe Asthma Registry (BSAR).

Results 914 patients, of whom 31% NP+, were included. At enrollment, NP+ patients had higher annual exacerbation rates, higher number of emergency room visits and more elevated type 2 biomarkers. In the longitudinal subanalysis of 104 patients, both groups had significant and similar asthma responses to asthma biologics, except for a greater increase in FEV₁ in the NP+ group. Super-response was achieved in 33 patients (32%), irrespective of NP status or type of biologic.

Conclusion In conclusion, both NP+ and NP- patients had positive treatment responses, with some able to achieve super-response. In SA patients with NP, a greater FEV₁ improvement as compared to SA patients without NP was observed.

Keywords Severe asthma · Nasal polyposis · Biologics · Super-response

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Introduction

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a frequent comorbidity in adults with type 2 severe asthma (SA). Still, SA with or without CRSwNP appears to manifest differently, since SA with CRSwNP is linked to a higher exacerbation rate, higher fractional exhaled nitric oxide (FeNO) and higher oral corticosteroid (OCS) burden [1]. Biologics that target this type 2 inflammation have proven to be beneficial in SA and in nasal polyposis (NP) separately. In SA on the one hand, they have shown to reduce exacerbations and OCS use, and to improve symptoms, quality of life and forced expiratory volume in one second (FEV₁) [2, 3]. In NP on the other hand, some of these anti-type 2 biologics have exhibited positive effects in terms of polyp size, symptoms and treatment needs [4, 5]. Moreover, it has been suggested that the presence of CRS [6] and of CRSwNP [7] in SA represents a biomarker predictive of positive outcomes with biologics. Another emerging concept is that of super-response, recently defined through a Delphi process [8]. Regarding its relation to nasal polyposis, a retrospective study with mepolizumab (where super-response was defined as no exacerbations and no OCS maintenance at one year) showed a significantly higher prevalence of NP in super-responders [9]. In another recent real-world study in patients with SA treated with benralizumab, super-responders were found to have a higher frequency of comorbid NP than nonresponders [10]. In the latter study, the criteria of super-response were absence of exacerbations, absence of OCS maintenance and pre-defined improvements of asthma control questionnaire (ACQ), sputum eosinophil count and FEV₁ at 24 weeks.

As an addition to these studies sourcing from real-life or registries, we used the Belgian Severe Asthma Registry (BSAR) (Central ethics committee UZ Gent B67020084584) to evaluate the response and super-response to biologics in patients with SA stratified according to the presence (NP+) or absence of NP (NP−). Also, we assessed patient and disease characteristics associated with NP in SA patients.

Methods

In this retrospective study, we included SA patients enrolled in BSAR between March 2009 and June 2021. From March 2009 onwards, demographic, clinical and social data of severe asthmatics who fulfil the European Respiratory Society/American Thoracic Society definition [11, 12] were collected in this national multicenter secured web-based registry. In the BSAR, data from 30 participating centers are updated every year for every enrolled patient.

We first compared NP+ and NP− SA patients who were not on a biologic at enrollment. The NP+ group was limited to patients with CRSwNP, while the NP− group included patients with chronic rhinosinusitis without nasal polyposis (CRSSNP) and SA patients having neither CRS nor NP. The reported NP data were based on medical records, with diagnosis either being based on ear-nose-throat examination or on computed tomography. Additionally, logistic regression was performed to identify predictors of NP. Age at enrollment, sex, body mass index, age of onset, asthma quality of life questionnaire (AQLQ), asthma control test (ACT), ACQ-7, exacerbation(s) in year preceding, FEV₁, FeNO and blood eosinophil count (BEC) were included in this model. We then studied response and super-response in the subset of patients who initiated a biologic due to uncontrolled SA during the observation period. To do this, each patient's data were evaluated at the time of enrollment in the BSAR and at the last visit recorded on a biologic. Patients with only one visit on a biologic were excluded. To initiate a biologic for the first time, a patient must have experienced at least two exacerbations in the year preceding or has to be on a maintenance therapy with oral corticosteroids according to the Belgian reimbursement criteria for omalizumab, benralizumab and mepolizumab. During the observation period, dupilumab was not yet available in Belgium.

Super-responders were defined as by the Delphi process [8], presenting 3 major criteria, or 2 major criteria combined with at least 1 minor criterion for response, assessed over 12 months. Major criteria include exacerbation elimination, major improvement in asthma control (≥ 2 times the minimal clinically important difference (MCID)), and cessation of maintenance oral steroids (or weaning to the dose necessary to compensate adrenal insufficiency). Minor criteria include 75% exacerbation reduction (not combinable with the major criterion of exacerbation elimination), well-controlled asthma (ACQ < 1 or ACT > 19) and ≥ 500 ml improvement in FEV₁. Finally, we scrutinized the specific response regarding SA to anti-IL5 (mepolizumab and benralizumab) and anti-IgE biologics (omalizumab) separately.

The statistical analysis was done in MedCalc (MedCalc 17.9.7, Mariakerke, Belgium). Depending on variables being continuous or categorical, the Mann–Whitney U test and the Chi-squared test, respectively, were used to analyze patient and disease characteristics at enrollment, and a logistic regression analysis was performed to identify predictors of nasal polyposis in severe asthma. To analyze the longitudinal data within and between cohorts, a repeated measurements ANOVA test was performed with a supplementary Mann–Whitney U test for significant results. For the small super-responder group, Fisher's exact test was used. Categorical data are expressed as frequency or proportion, and continuous data as median with interquartile range (IQR) or

Table 1 Comparison of characteristics at enrolment between NP+ and NP- patients ($n=914$)

		NP + patients (<i>n</i> = 286)	NP– patients (<i>n</i> = 628)	Number of patients assessed		<i>p</i> -value
				NP +	NP–	
Demographics	Age at enrolment, years	56 [45–65]	55 [45–65]	286	628	> 0.1
	Female (%)	176 (62)	347 (55)	286	628	0.08
	Body mass index, kg/m ²	26.3 [22.9–29.8]	26.7 [23.4–30.6]	286	628	> 0.1
	Smoking history: current (%)	12 (4)	60 (10)	286	628	0.005
	Current housing: urban	194 (68)	403 (64)	284	625	> 0.1
	Age of onset: ≤40 years (%)	191 (68)	415 (67)	281	621	> 0.1
	Family history of asthma (%)	121 (42)	292 (46)	286	628	> 0.1
	Atopic status (%)	185 (65)	403 (64)	286	628	> 0.1
Asthma quality of life	AQLQ	4.4 [3.2–5.5]	4.2 [3.0–5.3]	221	470	> 0.1
Asthma control	ACT	14.0 [10.0–18.0]	14.0 [9.0–18.0]	233	489	> 0.1
	ACQ	2.3 [1.3–3.4]	2.4 [1.4–3.4]	215	445	> 0.1
	Dyspnea assessment scale, visual analogue scale	7.0 [6.0–8.0]	7.0 [5.0–8.0]	94	180	0.07
	Exacerbation(s) in year preceding (%)	230 (81)	447 (72)	283	622	0.003
	Number of exacerbations in year preceding			283	622	0.009
	0 (%)	53 (19)	175 (28)			
	1 (%)	32 (11)	89 (14)			
	2 (%)	70 (25)	137 (22)			
	3 (%)	45 (16)	82 (13)			
	> 3 (%)	83 (29)	139 (22)			
	Near fatal asthma episode(s) in year preceding (%)	33 (12)	48 (8)	286	628	0.05
	Unscheduled visit(s) in year preceding (%)	188 (66)	402 (64)	286	628	> 0.1
	Emergency visit(s) in year preceding (%)	116 (41)	197 (31)	286	628	0.007
	Hospitalisation(s) in year preceding (%)	99 (35)	190 (30)	286	628	> 0.1
Treatments	Oral corticoids methylprednisolone equivalent total dose, mg/d	5.5 [4.0–8.0]	6.4 [4.0–9.0]	286	628	> 0.1
	Oral corticoids (%)	66 (23)	118 (19)	286	628	> 0.1
	Long acting muscarinic antagonist (%)	47 (16)	144 (23)	286	628	0.003
	Macrolide (%)	5 (2)	14 (2)	286	628	> 0.1
	Antihistamine (%)	99 (45)	176 (40)	219	444	> 0.1
	Antileukotriene (%)	162 (74)	313 (70)	219	444	> 0.1
	Intranasal steroids (%)	189 (75)	184 (37)	252	492	< 0.0001
	FEV ₁ , % predicted	70 [60–86]	68 [53–84]	284	618	0.029
Lung function	FVC, % predicted	88 [79–100]	86 [84–87]	284	618	0.020
	FEV ₁ /FVC, %	66 [59–74]	65 [57–74]	284	618	> 0.1
Inflammatory markers	Fractional exhaled nitric oxide, ppb	31 [16–57]	24 [13–43]	235	487	0.0002
	Blood eosinophils, /mm ³	400 [170–720]	249 [110–500]	266	544	< 0.0001
	Blood eosinophils, /mm ³			266	544	< 0.0001
	< 150 /mm ³ (%)	54 (20)	177 (33)			
	150 – < 300 /mm ³ (%)	46 (17)	122 (22)			
	300 – < 400 /mm ³ (%)	30 (11)	66 (12)			
	≥ 400 /mm ³ (%)	136 (51)	179 (31)			
	Sputum eosinophils, %	15.5 [3.0–46.0]	5.2 [1.0–26.0]	72	131	0.012
	Sputum neutrophils, %	50.0 [25.0–71.8]	51.5 [35.0–73.0]	71	130	> 0.1
	Total serum IgE, kU/l	136 [56–331]	156 [53–416]	254	527	> 0.1

Table 1 (continued)

		NP + patients (<i>n</i> = 286)	NP– patients (<i>n</i> = 628)	Number of patients assessed		<i>p</i> -value
				NP +	NP–	
Comorbidities	Non-steroidal anti-inflammatory drugs exacerbated respiratory disease (%)	42 (15)	18 (3)	279	618	<0.0001
	Gastroesophageal reflux disease (%)	110 (39)	261 (42)	279	618	>0.1
	Allergic bronchopulmonary aspergillosis (%)	7 (3)	25 (4)	277	618	>0.1
	Aspergillar asthma (%)	6 (4)	9 (3)	141	287	>0.1
	Bronchiectasis (%)	49 (23)	97 (20)	215	489	>0.1
	Eosinophilic granulomatosis with polyangiitis (%)	8 (3)	14 (2)	266	619	>0.1
	Occupational asthma (%)	4 (1)	18 (3)	280	620	>0.1

Data are expressed as median and [IQR] or as numbers and (percentages). Mann–Whitney U test and Chi-squared test

NP+/NP– severe asthma with/without nasal polyposis, AQLQ asthma quality of life questionnaire, ACT asthma control test, ACQ asthma control questionnaire, FEV₁ forced expiratory volume in one second, FVC forced vital capacity

as mean with standard deviation (SD). A *p*-value of < 0.05 was considered statistically significant.

Results

Out of 914 patients eligible for analysis (not on a biologic at enrollment), 286 (31%) were NP+. Compared to NP–, NP+ patients had a higher annual SA exacerbation rate, a higher annual number of emergency room visits in the context of their SA, and higher values of type 2 biomarkers (FeNO, BEC and sputum eosinophil count) at enrollment (Table 1). Among the NP– group, there was a greater proportion of LAMA-users and of active smokers. AQLQ and symptom scores were not different between both groups. Logistic regression analysis identified FeNO as the single most important independent predictor of the presence of NP (*p* = 0.0013).

In the longitudinal part of the study, comprising 104 patients that initiated a biologic during the observation period, the mean ($\pm$ SD) interval between enrollment and last recorded visit on a biologic was 3.9 ± 2.4 years. Table 2 shows significant responses to biologics, in terms of reduced exacerbation rates and improvements in asthma control, asthma quality of life and lung function in both groups. With regard to clinical outcomes to biologics, the only difference in response between NP+ and NP– patients was observed for FEV₁, with a significantly greater mean ($\pm$ SD) increase in the NP+ patients ($15 \pm 20\%$ predicted versus $6 \pm 17\%$ predicted). This greater improvement in FEV₁ was also present when considering the anti-IgE subgroup separately, but

was not seen in the anti-IL5 subgroup. In the two groups there was a similar proportion of patients that became exacerbation-free under biologic treatment (68% (25/37)) in NP+ compared to 67% (45/67) in NP– patients (*p* > 0.1), and mean changes of the ACT, the ACQ-7 and the AQLQ all exceeded their respective MCIDs [13–15]. Similar results were obtained when considering patients on anti-IL5 or anti-IgE therapy separately.

Thirty-three out of 104 patients included in the longitudinal subanalysis (32%) exhibited super-response, irrespective of NP status (*p* = 1.0) or type of biologic (*p* = 0.3) (Fig. 1).

Discussion

In this large Belgian SA registry cohort, 31% of SA patients had comorbid NP. In two other large SA registries a similar CRSwNP prevalence of 36.2% and 40.6% has been described [1, 6]. At enrollment, we observed higher annual exacerbation rates in the NP+ group, likely due to uncontrolled type 2 inflammation in these patients. Accordingly, we also found higher values of type 2 biomarkers in the NP+ group, which matches with NP being a type 2 asthma comorbidity [1]. In the NP– group, the significantly greater proportion of LAMA-users could be explained by the more prevalent non-T2-phenotype in this group. Furthermore, we identified FeNO as an independent predictor of NP in this SA population. This is consistent with the IL4/IL13 pathway being a driver pathway linking nitric oxide synthesis and NP pathogenesis [2, 16].

Table 2 Longitudinal subanalysis of NP+ and NP− initiated on any biologic (n = 104)

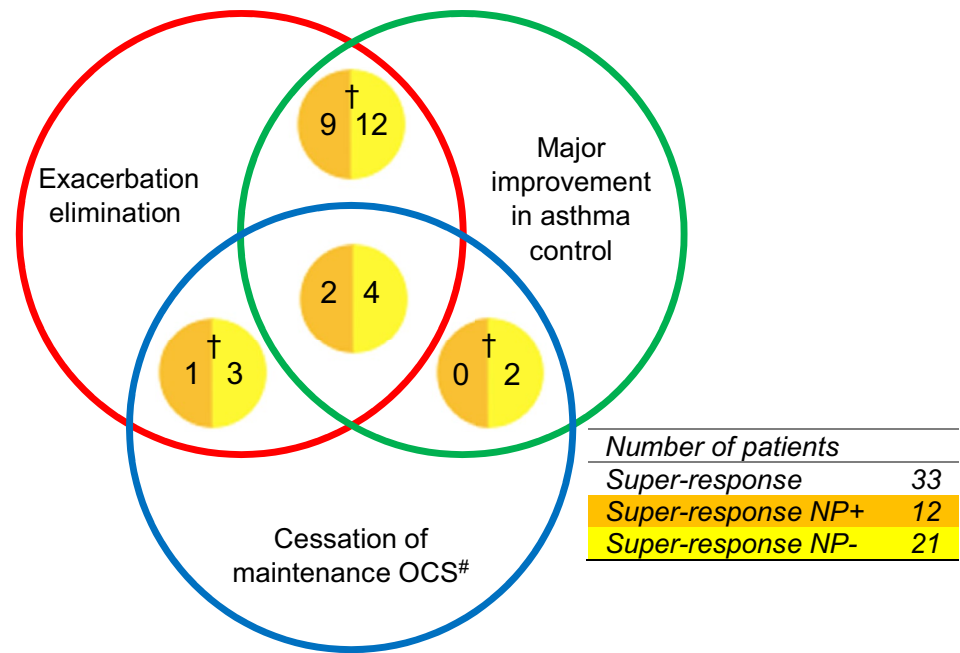
	NP+ and NP− initiated on any biologic				
	NP+ patients (n = 37)		NP− patients (n = 67)		Number of patients assessed
	Enrollment	Last visit on biologic	Change	Change	
AQLQ	3.87 ± 1.48	5.14 ± 1.67	1.27 ± 1.67	3.76 ± 1.35	21
ACT	11.4 ± 5.0	18.4 ± 6.0	7.0 ± 5.5	12.1 ± 5.2	23
ACQ	3.11 ± 1.21	1.68 ± 1.59	− 1.43 ± 1.74	2.93 ± 1.35	25
Exacerbations in year preceding	2.4 ± 1.3	0.5 ± 0.8	− 1.9 ± 1.6	2.7 ± 1.1	36
FEV ₁ , %predicted	63 ± 18	78 ± 22	15 ± 20	59 ± 24	35
FeNO, ppb	59.1 ± 42.9	41.6 ± 42.1	− 17.5 ± 44.1	38.9 ± 28.4	23
BEC, /mm3	576 ± 501	92 ± 147	− 484 ± 496	527 ± 400	14
NP+ and NP− initiated on an anti-IL5 biologic (n = 70) (mepolizumab 61%, benralizumab 39%)					
	NP+ patients (n = 30)		NP− patients (n = 40)		
AQLQ	3.74 ± 1.44	5.22 ± 1.56 ±	1.48 ± 1.48	3.86 ± 1.33	16
ACT	11.1 ± 5.2	18.2 ± 6.1	7.2 ± 5.7	11.3 ± 5.0	18
ACQ	3.10 ± 1.33	1.71 ± 0.90	− 1.39 ± 1.64	3.09 ± 1.20	21
Exacerbations in year preceding	2.4 ± 1.3	0.5 ± 0.9	− 1.8 ± 1.6	2.7 ± 1.2	30
FEV ₁ , %predicted	62 ± 17	76 ± 19	14 ± 18	58 ± 25	29
FeNO, ppb	59.3 ± 43.1	46.9 ± 46.3	− 12.4 ± 42.7	44.2 ± 31.2	18
BEC, /mm3	684 ± 517	85 ± 165	− 599 ± 500	573 ± 419	11
NP+ and NP− initiated on an anti-IgE biologic (n = 34) (omalizumab)					
	NP+ patients (n = 7)		NP− patients (n = 27)		
AQLQ	4.30 ± 1.69	4.89 ± 2.15	0.59 ± 1.73	3.58 ± 1.40	5
ACT	12.8 ± 4.3	19.0 ± 6.4	6.2 ± 5.2	13.4 ± 5.3	5
ACQ	3.14 ± 1.344	1.54 ± 2.42	− 1.61 ± 2.06	2.61 ± 1.14	4
Exacerbations in year preceding	2.5 ± 1.4	0.2 ± 0.4	− 2.3 ± 1.2	2.8 ± 0.9	6
FEV ₁ , %predicted	65 ± 25	86 ± 34	21 ± 27	61 ± 23	6
FeNO, ppb	58.4 ± 47.2	22.6 ± 9.3	− 35.8 ± 49.0	32.9 ± 24.7	5
BEC, /mm3	181 ± 17	120 ± 44	− 61 ± 55	270 ± 61	3

Data are expressed as mean ± SD. Repeated measurements ANOVA test

Abbreviations: see Table 1, fractional exhaled nitric oxide (FeNO), blood eosinophil count (BEC)

P-values; P^a: treatment effect; P^b: interaction of treatment and group effect

Fig. 1 Classification of super-responders by criteria (assessed over 12 months). Abbreviations: see Table 1, oral corticosteroids (OCS)



† 2 major criteria and at least 1 minor criterion

Minor criterion 1: 75% exacerbation reduction

Minor criterion 2: well controlled asthma

Minor criterion 3: FEV₁ improvement 500 ml

OCS-dependent at enrolment

Even though we found a higher exacerbation rate at enrollment in the NP + group, NP– patients with type 2 severe asthma were also able to achieve a significant exacerbation rate reduction under treatment with asthma biologics. Moreover, relevant improvements in asthma control, asthma quality of life and super-response, were observed in NP– as well as in NP+ patients. These results stress that all patients with severe asthma should be assessed for eligibility for biologics treatment, regardless of their NP status. There was however a difference in FEV₁ response in the overall group and in the anti-IgE subgroup. This particular difference in response was also observed in a previous study with mepolizumab [17]. Here, it was not seen in the anti-IL5 subgroup, maybe due to the small sample size. Recently, in the International Severe Asthma Registry, an association between the presence of CRS and improvement in FEV₁ was observed in patients on biologics. In contrast, the presence of NP was not associated with better FEV₁ response to biologics [6]. These discrepancies between studies could be explained by differences in population grouping.

Our study has limitations. Firstly, in the BSAR, the severity of NP and the presence of CRS are not reported. Secondly, based on the analysis performed in our study, we cannot determine whether NP and type 2 inflammatory

biomarkers are independent contributors to response. Lastly, since the BSAR has a pragmatic and purely observational design, there is no standardized time window between visits. Still, we believe the comparisons of disease characteristics at enrolment and at the last recorded visits on biologics are valid, because the data collected during the visits always refer to the preceding year. Also, the mean time interval between analysis at enrolment and the last registered visit exceeded the mean time interval between the initiation of the biologic and the last recorded visit (analysis of response) by less than 2 years (3.9 ± 2.4 and 2.0 ± 1.5 years, respectively). However, we cannot exclude the possibility that exacerbation rate and asthma characteristics might have changed between time of enrolment and initiation of biologic.

Conclusion

In conclusion, in this real-life study, SA patients with and without nasal polyposis both had significant reductions in exacerbation rate, had significant improvements of asthma control, and some were able to achieve super-response under treatment with anti-IgE and anti-IL5 biologics. However, in comparison with patients without nasal polyposis, patients

with nasal polyposis demonstrated a greater improvement in FEV₁ upon treatment with a biologic.

Author Contributions FD and SH are accountable for study concept and design, FD for data collection, FD for data analysis, and FD, SV and SH for the interpretation of data. FD drafted the manuscript. EV, SV, FS, RL, GB, CS, AM, RP, CP and SH performed critical revision of the manuscript for important intellectual content. SH supervised, initiated, and guided the entire project. All authors gave final approval of the version to be published.

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Data Availability Study data are available from the corresponding author upon reasonable request, after approval from the BSAR steering committee.

Declarations

Competing interests The authors declare no competing interests.

Conflict of interest No conflict of interest reported by FD, EV, SV and CS. FS has received grants or contracts from AstraZeneca, GlaxoSmithKline, Chiesi, Novartis, TEVA, Sanofi and ALK; has received consulting fees from AstraZeneca, Chiesi and GlaxoSmithKline; has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, GlaxoSmithKline, Chiesi, ALK, Novartis and TEVA and has received support for attending meetings and/or travel from AstraZeneca, Chiesi and Sanofi. RL has received grants or contracts from Sanofi, AstraZeneca and GlaxoSmithKline and has received lecture or consultancy fees from Sanofi, GlaxoSmithKline, AstraZeneca, Novartis and Chiesi. GB has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, Sanofi Regeneron, Boehringer Ingelheim, Chiesi, Novartis and MSD and he is the current president of the Belgian Respiratory Society. AM has received support for research from AstraZeneca, GlaxoSmithKline and Chiesi; has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events for AstraZeneca, GlaxoSmithKline and Chiesi; has received support for attending meetings and/or travel from AstraZeneca (ATS 2022), Chiesi (ATS 2023 and CHEST 2023) and Sanofi (ERS 2022 and ERS 2023) and has participated on an Advisory Board for AstraZeneca and GlaxoSmithKline. RP has received consulting fees from AstraZeneca, Chiesi, GlaxoSmithKline, MSD and Sanofi and has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, Chiesi and GlaxoSmithKline. CP has received grants or contracts from AstraZeneca, Chiesi and GlaxoSmithKline; has received consulting fees from ALK-Abello, AstraZeneca, Chiesi, GlaxoSmithKline, Sanofi and Stallergènes and has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from ALK-Abello, AstraZeneca, Chiesi, GlaxoSmithKline, Sanofi and Stallergènes. SH has received consulting fees from AstraZeneca, GlaxoSmithKline, MSD and Sanofi; has received scientific grants from Chiesi; has received support for attending meetings from AstraZeneca, GlaxoSmithKline and Sanofi and is the current president of the working group Asthma of the Belgian Respiratory Society.

Ethical Approval This retrospective study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964

Helsinki Declaration and its later amendments or comparable ethical standards. The Ethical Committee (IRB) of UZ Brussel approved this study. Ethical approval for the BSAR database was obtained through the Ethical Committee of UZ Gent (Central ethics committee UZ Gent B67020084584).

Consent to Participate Informed consent was obtained from all individual study participants at the time of first enrollment in the BSAR (Central ethics committee UZ Gent B67020084584).

Consent to publish Patients gave informed consent for publication at the time of first enrollment in the BSAR (Central ethics committee UZ Gent B67020084584).

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