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ORIGINAL RESEARCH ARTICLE

Safety of Biological Therapies for Severe Asthma: An Analysis of Suspected Adverse Reactions Reported in the WHO Pharmacovigilance Database

Paola Maria Cutroneo[1] · Elena Arzenton[2] · Fabiana Furci[3] · Fabio Scapini[2] · Maria Bulzomì[1] · Nicoletta Luxi[2] · Marco Caminati[4] · Gianenrico Senna[4,5] · Ugo Moretti[2] · Gianluca Trifirò[2]

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Abstract

Background The management of uncontrolled severe asthma has greatly improved since the advent of novel biologic therapies. Up to August 2022, five biologics have been approved for the type 2 asthma phenotype: anti-IgE (omalizumab), anti-IL5 (mepolizumab, reslizumab, benralizumab), and anti-IL4 (dupilumab) monoclonal antibodies. These drugs are usually well tolerated, although long-term safety information is limited, and some adverse events have not yet been fully characterized. Spontaneous reporting systems represent the cornerstone for the detection of potential signals and evaluation of the real-world safety of all marketed drugs.

Objective The aim of this study was to provide an overview of safety data of biologics for severe asthma using VigiBase, the World Health Organization global pharmacovigilance database.

Methods We selected all de-duplicated individual case safety reports (ICSRs) attributed to five approved biologics for severe asthma in VigiBase, up to 31st August 2022 (omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab). Descriptive frequency analyses of ICSRs were carried out both as a whole class and as individual products. Reporting odds ratios (ROR) with 95% confidence intervals (CIs) were used as the measure of disproportionality for suspected adverse drug reactions (ADRs) associated with the study drugs compared with either all other suspected drugs (Reference Group 1, RG1) or inhaled corticosteroids plus long-acting β-agonists (ICSs/LABAs) (Reference Group 2, RG2) or with oral corticosteroids (OCSs) (Reference Group 3, RG3).

Results Overall, 31,724,381 ICSRs were identified in VigiBase and 167,282 (0.5%) were related to study drugs; the remaining reports were considered as RG1. Stratifying all biologic-related ICSRs by therapeutic indication, around 29.4% ($n = 48,440$) concerned asthma use; omalizumab was mainly indicated as the suspected drug ($n = 20,501$), followed by dupilumab, mepolizumab, benralizumab and reslizumab. Most asthma ICSRs concerned adults (57%) and women (64.1%). Asthma biologics showed a higher frequency of serious suspected ADR reporting than RG1 (41.3% vs 32.3%). The most reported suspected ADRs included asthma, dyspnea, product use issue, drug ineffective, cough, headache, fatigue and wheezing. Asthma biologics were disproportionally associated with several unknown or less documented adverse events, such as malignancies, pulmonary embolism and deep vein thrombosis with omalizumab; alopecia and lichen planus with dupilumab; alopecia and herpes infections with mepolizumab; alopecia, herpes zoster and eosinophilic granulomatosis with polyangiitis related to benralizumab; and alopecia with reslizumab.

Conclusions The most frequently reported suspected ADRs of asthma biologics in VigiBase confirmed the presence of well-known adverse effects such as general disorders, injection-site reactions, nasopharyngitis, headache and hypersensitivity, while some others (e.g. asthma reactivation or therapeutic failure) could be ascribed to the indication of use. Moreover, the analysis of signals of disproportionate reporting suggests the presence of malignancies, effects on the cardiovascular system, alopecia and autoimmune conditions, requiring further assessment and investigation.

Extended author information available on the last page of the article

Key Points

Most reported suspected adverse reactions related to biologics in asthma patients are known side effects, while some others could derive from the underlying indication of use (asthma reactivation or therapeutic failure).

A confounding effect is exerted by corticosteroids that are often used concomitantly or immediately before starting biologic treatment.

Several potential safety signals (e.g. malignancies, rhythm disorders, pulmonary embolism, alopecia, etc.) have been identified, requiring further investigation. Autoimmune conditions may be triggered in patients that are already affected by autoimmune diseases (e.g. eosinophilic granulomatosis with polyangiitis, sarcoidosis).

1 Introduction

Biologics for severe asthma, targeting specific steps of T-helper cell 2 (Th2) immune inflammation, represent a revolutionary treatment option for asthma management. When asthma diagnosis is confirmed and comorbidities have been addressed (e.g. rhinitis, rhinosinusitis, nasal polyps, gastroesophageal reflux, obstructive sleep apnea), severe asthma is defined as "asthma which requires treatment with high dose inhaled corticosteroids (ICSs) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy." Uncontrolled asthma is associated with high rates of exacerbations and glucocorticoid dependence [1]. The evaluation of severe asthma prevalence is still debated; in literature, the estimated frequency ranges from 1.8 to 38.9% among all asthma patients [2, 3]. These values are affected by different factors [2]. One aspect to evaluate in the management of severe asthma, especially for uncontrolled asthma, is the burden of the disease due to asthma exacerbations, asthma-related emergency room admissions and hospitalizations [3].

Currently available biologics act on Th2/eosinophilic phenotype molecules, which improve the quality of life of patients with severe asthma, achieving disease control and reducing/stopping oral steroid dependence [4, 5]. Type 2 biologics for severe asthma target key points of the type 2 inflammation including immunoglobulin E (IgE) (omalizumab), interleukin 5 (IL-5) (mepolizumab, reslizumab) or its receptor (benralizumab), thymic stromal lymphopoietin (TSLP) (tezepelumab) and interleukin 4 receptor alpha subunit (IL4rα) (dupilumab), which blocks signaling cascades induced by both IL-4 and IL-13 [6, 7]. Tezepelumab is a human monoclonal antibody (mAb) to thymic stromal lymphopoietin that was approved for severe uncontrolled asthma in patients aged 12 years and older at the end of 2022 [7]. Omalizumab, mepolizumab, benralizumab, dupilumab and tezepelumab are currently approved by the US Food and Drug Administration for use in pediatric asthma. Omalizumab, mepolizumab and dupilumab are currently approved by both the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for use in children (over 6 years of age) and/or adolescents, while benralizumab is only approved by the FDA for adolescents [6, 7].

Some biologics are authorized for therapeutic indications other than asthma, including atopic dermatitis (dupilumab), chronic spontaneous urticaria (omalizumab), chronic rhinosinusitis with nasal polyps (dupilumab, omalizumab, mepolizumab), eosinophilic esophagitis (dupilumab) and eosinophilic granulomatosis with polyangiitis [EGPA], or hypereosinophilic syndrome (mepolizumab).

Despite extensive clinical experience on the use of these biologics in asthma patients, some fundamental aspects must still be defined. These include the optimal duration of therapy, for which presently there are no precise indications in literature, as well as long-term effects even after discontinuation.

The use of biologics in asthma patients is overall safe. The most commonly reported adverse events (e.g. asthma worsening, nasopharyngitis and headache) in pivotal clinical trials were mild and well tolerated, despite those studies being based on limited sample sizes and short follow-up periods (Table 1) [8–16].

In recent years, a few safety alerts on possible risks associated with asthma biologics (ABs) have been issued by regulatory agencies, such as the FDA warning and the Medicines and Healthcare products Regulatory Agency (MHRA) safety alert regarding a slightly higher risk of heart and brain adverse events with omalizumab [17, 18]. A potential safety signal concerning malignancies related to omalizumab, detected in a previous analysis of the World Health Organization (WHO) pharmacovigilance database, is still being debated in the scientific community [19]. In addition, the identified risk of anaphylaxis with omalizumab and reslizumab still needs to be further characterized for other ABs also [20].

Considering that biologics are increasingly used in clinical practice, it is extremely important to better explore the safety of these drugs in real-world settings, especially concerning long-term use and rare adverse events. The aim of this study was to evaluate the post-marketing safety profile

Table 1 Adverse events reported in pivotal clinical trials of biologic drugs for the treatment of asthma.

Study title	Intervention	Study population	Phase	Primary outcomes	Number enrolled (treatment vs placebo)	Most common adverse events potentially related to treatment			
						SAEs *n* (%)	AEs *n* (%)	Reported AEs (PT), *n* (%)	
Reslizumab for Inadequately Controlled Asthma with Elevated Blood Eosinophil Levels: A Randomized Phase 3 Study [9]	Reslizumab	Patients aged between 12 and 75 years with no controlled asthma, in treatment with at least a medium dose of ICS and with blood eosinophil count ≥400 cells/μL	III	To evaluate the efficacy and the safety of reslizumab	315 (210 vs 105)	4 (1.9)	120 (57.1)	Asthma worsening	22 (10.5)
								Headache	19 (9.0)
								Nasopharyngitis	12 (5.7)
								Upper respiratory tract infection	8 (3.8)
								Sinusitis	7 (3.3)
								Bronchitis	7 (3.3)
								Nausea and vomiting	6 (2.9)
								Dyspnea	5 (2.4)
								Allergic rhinitis	5 (2.4)
								Urinary tract infection	5 (2.4)
								Pharyngitis	4 (1.9)
								Acute sinusitis	4 (1.9)
Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Counts: Results From Two Multicentre, Parallel, Double-Blind, Randomised, Placebo-Controlled, Phase 3 Trials [10]	Reslizumab	Patients aged between 12 and 75 years with no controlled asthma, in treatment with at least a medium dose of ICS and with blood eosinophil count ≥400 cells/μL	III	To evaluate the efficacy and safety of reslizumab	925 (477 vs 475)	42 (8.8)	374 (78.4)	Asthma worsening	164 (34.4)
								Nasopharyngitis	73 (15.3)
								Headache	52 (10.9)
								Sinusitis	30 (6.3)
								Upper respiratory tract infection	47 (9.9)
								Back pain	25 (5.2)
								Influenza	24 (5.0)
								Allergic rhinitis	19 (4.0)
								Oropharyngeal pain	18 (3.8)
								Urinary tract infection	13 (2.7)
								Pharyngitis	17 (3.6)
								Respiratory tract infection	15 (3.1)
								Bronchitis	15 (3.1)
								Cough	14 (2.9)
								Nausea	14 (2.9)
								Dyspnea	12 (2.5)
								Dizziness	11 (2.3)

Table 1 (continued)

Study title	Intervention	Study population	Phase	Primary outcomes	Number enrolled (treatment vs placebo)	Most common adverse events potentially related to treatment			
						SAEs *n* (%)	AEs *n* (%)	Reported AEs (PT), *n* (%)	
Omalizumab in Severe Allergic Asthma Inadequately Controlled with Standard Therapy [11]	Omalizumab	Patients aged between 12 and 75 years with no controlled asthma, in treatment with high-dose ICS plus LABAs	III	To evaluate the efficacy and safety of omalizumab	848 (428 vs 420)	40 (9.3)	344 (80.4)	Bleeding-related adverse event	16 (3.7)
								Urticaria	9 (2.1)
								Hypersensitivity reactions	7 (1.6)
								Injection-site reaction	5 (1.2)
								Thrombocytopenia	2 (0.5)
								Anaphylaxis	1 (0.2)
								Cancer	1 (0.2)
Omalizumab, Anti-IgE Recombinant Humanized Monoclonal Antibody, for the Treatment of Severe Allergic Asthma [12]	Omalizumab	Subjects aged 12 to 75 years with severe allergic asthma requiring daily ICS	III	To evaluate the efficacy and safety of omalizumab	525 (268 vs 257)	7 (2.6)	239 (89.2)	Upper respiratory tract infection	84 (31.3)
								Viral infection	71 (36.5)
								Headache	60 (22.4)
								Sinusitis	52 (19.4)
								Pharyngitis	39 (14.6)
								Pain (back)	38 (14.2)
								Arthralgia	26 (9.7)
								Rhinitis	22 (8.2)
								Coughing	20 (7.5)
								Sprains and strains	20 (7.5)
								Myalgia	19 (7.1)
								Bronchitis	18 (6.7)
								Nausea	18 (6.7)
								Pain	18 (6.7)
								Dyspepsia	17 (6.3)
								Diarrhea	14 (5.2)
								Insomnia	11 (4.1)
								Sinus headache	4 (1.5)

Table 1 (continued)

Study title	Intervention	Study population	Phase	Primary outcomes	Number enrolled (treatment vs placebo)	Most common adverse events potentially related to treatment			
						SAEs *n* (%)	AEs *n* (%)	Reported AEs (PT), *n* (%)	
Efficacy and Tolerability of Anti-Immunoglobulin E Therapy with Omalizumab in Patients with Poorly Controlled (Moderate-to-Severe) Allergic Asthma [13]	Omalizumab	Eligible subjects were aged 12–75 years with persistent moderate-to-severe allergic asthma		To evaluate the efficacy and tolerability of omalizumab	312 (206 vs 106)	34 (16.5)	175 (85.0)	Asthma aggravated	90 (43.7)
								Nasopharyngitis	56 (27.2)
								Headache	36 (17.5)
								Lower respiratory tract infection	33 (16.0)
								Pharyngitis	19 (9.2)
								Bronchitis	18 (8.7)
								Cough	16 (7.8)
								Sinusitis	14 (6.8)
								Nausea	14 (6.8)
								Upper respiratory tract infection	13 (6.3)
								Influenza	12 (5.8)
								Dyspnea	12 (5.8)
								Chest pain	11 (5.3)
								Rhinitis	9 (4.4)
Benralizumab for Patients with Mild to Moderate, Persistent Asthma (BISE): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial [14]	Benralizumab	Patients aged 18–75 years weighing at least 40 kg and with evidence of asthma	III	To assess the safety and efficacy of benralizumab	211 (106 vs 105)	2 (1.9)	44 (41.5)	Nasopharyngitis	8 (7.5)
								Upper respiratory tract infection	5 (4.7)
								Worsening asthma	4 (3.8)
								Headache	4 (3.8)
Long-Term Efficacy and Safety of Mepolizumab in Patients with Severe Eosinophilic Asthma: A Multi-Center, Open-Label, Phase IIIb Study [15]	Mepolizumab	Patients aged ≥ 12 years with history of life-threatening or seriously debilitating asthma	IIIb	To assess the long-term safety and efficacy of subcutaneous mepolizumab	651 (414 vs 237)	64 (15.5)	360 (87.0)	Nasopharyngitis	114 (27.5)
								Upper respiratory tract infection	61 (14.7)
								Headache	60 (14.5)
								Asthma	54 (13.0)
								Bronchitis	46 (11.1)
								Sinusitis	43 (10.4)

Table 1 (continued)

Study title	Intervention	Study population	Phase	Primary outcomes	Number enrolled (treatment vs placebo)	Most common adverse events potentially related to treatment			
						SAEs *n* (%)	AEs *n* (%)	Reported AEs (PT), *n* (%)	
Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma [16]	Dupilumab	Patients aged ≥ 12 years with uncontrolled asthma	III	To assess the efficacy of dupilumab	1897 (1263 vs 634)	104 (8.2)	1023 (81.0)	Viral upper respiratory tract infection	230 (18.2)
								Injection-site reaction	212 (16.8)
								Upper respiratory tract infection	146 (11.6)
								Bronchitis	144 (11.4)
								Headache	86 (6.8)
								Influenza	74 (5.9)
								Sinusitis	62 (4.9)
								Back pain	55 (4.4)
								Rhinitis allergic	39 (3.1)
								Urinary tract infection	36 (2.9)

AE adverse event, *ICS* inhaled corticosteroid, *LABAs* long-acting β-agonists, *PT* preferred term, *SAE* serious adverse event

of biologics when used in patients with severe asthma using VigiBase, the WHO global pharmacovigilance database.

2 Methods

2.1 Data Source

VigiBase is the WHO global pharmacovigilance database of individual case safety reports (ICSRs), managed by the Uppsala Monitoring Centre (UMC) in Sweden. It holds over 30 million reports of suspected adverse events of medicines (August 2022) submitted, since 1968, by member countries of the WHO Programme for International Drug Monitoring (WHO PIDM). For data extraction, we used VigiLyze, a data warehousing system provided by UMC. We used the de-duplicated dataset automatically calculated by vigiMatch, a probabilistic record matching method [21]. Drugs are encoded with the WHODrug Global dictionary for medicinal information. Suspected adverse drug reactions (ADRs) are coded with the Medical Dictionary for Regulatory Activities (MedDRA, version 25.0) terminology.

2.2 Study Drugs and Data Analysis

Omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab were the study drugs. We selected all de-duplicated ICSRs attributed to study drugs in VigiBase, from its inception date up to 31st August 2022. As such, the new biological drug tezepelumab was not considered as it was introduced into the European market only after the extraction date. Biologic-related ICSRs were stratified based on the different therapeutic indications. Focusing on asthma use, we selected suspected ADR reports in which biologics had a specific asthma-related therapeutic indication, including the following selected PT terms: 'Asthma', 'Asthma late onset', 'Asthma prophylaxis', 'Asthmatic crisis', 'Childhood asthma', 'Status asthmaticus'.

Descriptive frequency analyses of ICSRs in which selected biologics were reported as suspected drugs were carried out for asthma-related therapeutic indications. In particular, age and sex distribution of patients affected by biologic-related adverse events, frequency of seriousness, temporal trend in reporting, different types of reporter and outcomes were all examined. Descriptive comparisons of some ICSR characteristics for asthma use versus all other indications were carried out.

A Chi-square test was performed to compare categorical variables as appropriate. A p-value <0.05 denoted the statistical significance.

Serious suspected ADRs were defined as adverse events leading to death or persistent/significant disability or incapacity, life-threatening, requiring in-patient hospitalization or prolongation of hospital stay, or congenital malformation/birth defects or other important medical events based on clinical judgment or Important Medical Event (IME) list [22, 23].

A suspected ADR, whose nature, severity, specificity or outcome is not consistent with the term or description used in the FDA labels [24] and in the European Public Assessment Reports (EPARs) and Risk Management Plans (RMPs) [25], has been defined as 'unexpected' [22].

Reporting odds ratio (ROR) was used as a measure of suspected ADR reporting disproportionality, with a statistical threshold that was defined as 95% confidence interval lower bound > 1 present in three or more reports [26–29]. These thresholds are the most frequently used, although the minimum number of cases could be modified depending on different factors, including the database and the drug/event under investigation [27].

When both these criteria were satisfied for a given drug–event combination, it was called a signal of disproportionate reporting (SDR) [30, 31]. The calculation and interpretation of disproportionality findings were performed in accordance with available regulatory guidances [31–33].

Specifically, disproportionality analysis was carried out for suspected ADRs reported in ICSRs with a specified asthma-related therapeutic indication at MedDRA PT level for each single study drug. When feasible on the basis of available information, case-by-case assessment for unexpected adverse events was carried out examining ICSR line listings related to the selected SDRs.

RORs were calculated by using ICSRs related to all other drugs collected in VigiBase, vaccines included, (Reference Group 1, RG1) as the primary comparison group. As restricting the comparator background to drugs for common therapeutic areas may be useful to mitigate potential confounders and to evaluate study finding robustness when implemented as a sensitivity analysis [34, 35], we also used as an additional comparison group (Reference Group 2, RG2) ICSRs including ICSs plus long-acting β-agonists (LABAs) (ICSs/LABAs) (Anatomical Therapeutic Chemical class: R03AK) as suspected drugs for asthma-related therapeutic indication.

Considering the large amount of COVID-19 vaccine-related reports received in the last 3 years, to explore the potential masking effect of COVID-19 vaccines on disproportionality analysis of biologics, we conducted a sensitivity analysis removing all vaccine-related reports (almost all of them were COVID-19 vaccine related).

In severe uncontrolled asthma, patients often start on oral corticosteroid (OCS) treatment; whenever needed thereafter, biologics are initiated to replace or reduce OCSs. For this reason, to better explore the adverse events attributable to biologic drugs, irrespective of the concomitant/previous

use of OCSs, we conducted an additional sensitivity analysis selecting as comparator ICSRs in which OCSs typically used in asthmatic patients (i.e. betamethasone, deflazacort, methylprednisolone and prednisone) were reported as suspected drugs for asthma-related conditions (RG3). Furthermore, a sensitivity analysis was carried out, after excluding reports in which ABs were co-reported with one of these four OCSs as suspected drugs, to evaluate confounding in RORs derived from primary disproportionality analysis.

3 Results

3.1 General Analysis

Up to 31st August 2022, 31,724,381 de-duplicated ICSRs were collected in VigiBase; among these, 167,282 (0.5%) were related to biologics under study, while the remaining reports were considered as Reference Group 1 (RG1) ($n = 31,557,099$). Dupilumab was indicated as a suspected drug in 101,297 (60.5%) reports, followed by omalizumab ($n = 44,043$; 26.3%), mepolizumab ($n = 13,909$; 8.3%), benralizumab ($n = 7853$; 4.7%) and reslizumab ($n = 475$; 0.3%). In 274 reports, two or more ABs were co-reported as suspected/interacting drugs.

Stratifying all biologic-related ICSRs ($n = 167,282$) by therapeutic indication, around 34% of reports concerned use in atopic dermatitis ($n = 56,682$), 29.4% ($n = 48,440$) in asthma, 7% in urticaria ($n = 11,495$) and 3% in chronic rhinosinusitis with nasal polyps (ChRNP) ($n = 4,673$). The remaining reports concerned various other indications ($n = 7023$; 4.2%) or non-specified indications ($n = 38,969$; 23.3%). An ICSR could have multiple indications reported, but for disproportionality analysis the reports were counted only once (either in the asthma group or in the reference group).

Focusing specifically on asthma-related ICSRs ($n = 48,440$), omalizumab was mainly reported as the suspected drug ($n = 20,501$; 42.3%), followed by dupilumab ($n = 13,677$; 28.2%), mepolizumab ($n = 8731$; 18.0%), benralizumab ($n = 5512$; 11.4%) and reslizumab ($n = 219$; 0.5%) (see flow chart in Fig. 1). Two or more ABs were co-reported as suspected or interacting drugs in 183 reports.

Table 2 shows the main characteristics of biologic-related ICSRs in asthma patients as compared with those related to the same drugs for other therapeutic indications, as well as versus all other drugs in VigiBase (RG1). The female/male ratio of biologic-related asthma ICSRs was higher than that related to other therapeutic uses (2.3 vs 1.7) or all other drugs in the database (1.6).

The percentage of serious suspected ADRs with biologic drugs was much higher in asthma use (41.3%) as compared with other indications (15.7%) as well as versus RG1 (32.3%) ($p < 0.001$).

Table 3 describes the characteristics of biologic-related ICSRs in asthma use by a single biologic agent. Female/male ratio was comparable across all asthma biologics. The age distribution of reports concerning all biologics exhibits slight variations; dupilumab and omalizumab were associated with higher rates of ICSRs in adolescents (aged 12–17 years). Higher frequencies of serious suspected ADRs were documented for omalizumab (57.5%), mepolizumab (47.3%) and reslizumab (44.3%).

The most reported suspected ADRs for all five biologics specifically used in asthma are shown in Table 4. Asthma, dyspnea, product use issue, drug ineffective, cough, headache, fatigue and wheezing were the most frequent suspected adverse reactions included in ICSRs.

In Fig. 2, RORs of biologic-related ICSRs in asthma patients versus other indications of use (Part A) and versus all other drugs in the database (Part B) by System Organ Class (SOC) level are reported. Considering Part A, biologic-related ICSRs in asthma patients were mainly involved in the following SOCs: 'respiratory disorders' (Resp), 'social circumstances' (SocCi) and 'cardiac disorders' (Card). Instead, considering Part B, the SOCs mainly involved in reports of asthma study drugs were 'respiratory disorders' (Resp), 'infection and infestations' (Infec) and 'immune system disorders' (Immun).

Analyzing the proportion of reports by SOC for each single biologic in asthmatic patients (Fig. 3), dupilumab was mainly related to 'social circumstances', 'injury, poisoning and procedural complications' and 'eye disorders'; omalizumab resulted in higher proportions of 'pregnancy, puerperium and perinatal conditions', 'neoplasms benign, malignant and unspecified (incl cysts and polyps)' and 'immune disorders'; mepolizumab was mainly associated to 'product issues', 'infections and infestations' and 'surgical and medical procedures'; benralizumab with 'nervous system disorders', 'respiratory, thoracic and mediastinal disorders' and 'general disorders and administration site conditions'; reslizumab with 'endocrine disorders', 'pregnancy, puerperium and perinatal conditions' and 'musculoskeletal and connective tissue disorders'.

3.2 Disproportionality Analysis

Disproportionality analysis was carried out on ICSRs related to biologics with a specified asthma indication by using all other drugs in the databases (RG1) as the primary comparator and, in order to limit confounding by indication, ICS/LABA-related ICSRs as the second reference group (RG2). Many SDRs, significant in both comparator groups (vs RG1 and RG2), concerned already known side effects (reported in package inserts of asthma

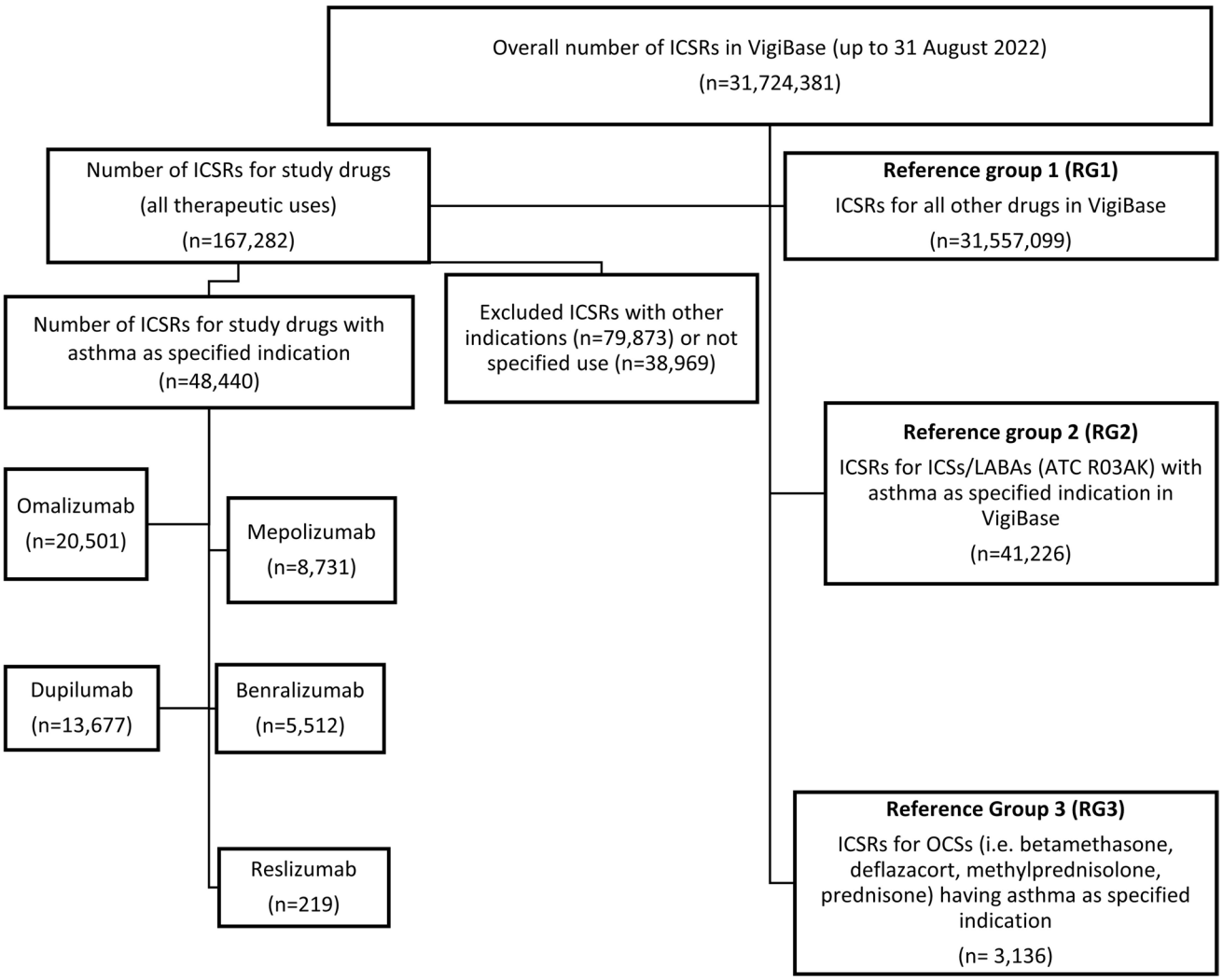

Fig. 1 Flow chart for individual case safety report selection process in VigiBase. The sum of the reports by single asthma drug is higher than the total number of reports, since a single report could contain two or more biologic drugs as suspected. *ICSRs* individual case safety reports, *ICSs/LABAs* inhaled corticosteroids plus long-acting β-agonists, *OCSs* oral corticosteroids

biologics), such as hypersensitivity conditions including anaphylaxis, headache, fatigue and injection-site reactions (see Table 4). Specifically, anaphylactic reactions were observed for omalizumab ($N = 808$, 3.9%) as well as for mepolizumab ($N = 82$, 0.9%), benralizumab ($N = 79$, 1.4%) and reslizumab ($N = 6$, 2.7%), resulting in SDRs (data not shown).

Several suspected ADRs resulting in positive SDRs (vs RG1), likely related to an underlying therapeutic indication (e.g. dyspnea, cough, etc.), did not reach statistically significance anymore when using other anti-asthma agents as comparator (RG2) (see Table 4).

We also observed several positive SDRs concerning adverse events commonly linked to corticosteroids (e.g. adrenal insufficiency, Cushing's syndrome, diabetes mellitus, hyperglycemia, overweight, etc.). In order to mitigate the possible impact of corticosteroid use as an important confounding factor and to increase the specificity of results, an additional disproportionality analysis by each single agent was carried out using some selected OCSs (RG3) as comparator group. As a result, comparing the ROR values resulting from RG1 and RG3, the above cited adverse events lose their significance (see Table 5).

Reporting of asthma biologics was also disproportionally associated with several unexpected (on the basis of the Summaries of Product Characteristics) or less documented adverse events, including malignancies, pulmonary embolism and deep vein thrombosis, sarcoidosis, blood pressure increased, herpes zoster and erythema nodosum with omalizumab; alopecia and lichen planus with dupilumab; alopecia, polymyalgia rheumatica and herpes infections with mepolizumab; alopecia, herpes zoster and EGPA related to

Table 2 Characteristics of biologic-related suspected ADR reports for asthma use and for all other therapeutic indications, as compared with all other drugs in VigiBase (ICSRs total n. 31,724,381)

	Study drugs (asthma use)	Study drugs (other uses)	RG1: all other drugs	*p* value (asthma use vs all other drugs)	*p* value (other uses vs all other drugs)
Total reports	48,440	118,842	31,557,099		
Sex, *n* (%)					
Female	31,030 (64.1)	62,155 (52.3)	18,091,628 (57.3)	< 0.001	< 0.001
Male	13,646 (28.2)	36,363 (30.6)	11,617,376 (36.8)		
F/M ratio	2.3	1.7	1.6	< 0.001	< 0.001
Unknown	3764 (7.8)	20,324 (17.1)	1,848,095 (5.9)		
Age groups (years), *n* (%)					
< 2	59 (0.1)	113 (0.1)	693,180 (2.2)	< 0.001	< 0.001
2–11	501 (1.0)	2374 (2.0)	888,228 (2.8)	< 0.001	< 0.001
12–17	1319 (2.7)	4613 (3.9)	678,705 (2.2)	< 0.001	< 0.001
18–44	7273 (15.0)	23,411 (19.7)	6,700,875 (21.2)	< 0.001	< 0.001
45–64	13,639 (28.2)	22,440 (18.9)	7,758,082 (24.6)	< 0.001	< 0.001
65–74	4680 (9.7)	6556 (5.5)	3,619,807 (11.5)	< 0.001	< 0.001
≥ 75	1970 (4.1)	3807 (3.2)	2,799,043 (8.9)	< 0.001	< 0.001
Unknown	18,999 (39.2)	55,528 (46.7)	8,419,179 (26.7)		
Continents, *n* (%)					
Africa	60 (0.1)	132 (0.1)	439,079 (1.4)	< 0.001	< 0.001
Americas	38,275 (79)	101,338 (85.3)	15,435,902 (48.9)	< 0.001	< 0.001
Asia	1050 (2.2)	1699 (1.4)	6,584,217 (20.9)	< 0.001	< 0.001
Europe	8435 (17.4)	15,139 (12.7)	8,372,803 (26.5)	< 0.001	< 0.001
Oceania	620 (1.3)	534 (0.4)	725,098 (2.3)	< 0.001	< 0.001
Reporter qualification[a], *n* (%)					
Physician[b]	18,095 (37.4)	38,899 (32.7)	8,475,297 (26.9)	< 0.001	< 0.001
Pharmacist	1172 (2.4)	3297 (2.8)	2,435,322 (7.7)	< 0.001	< 0.001
Other healthcare professional[c]	8061 (16.6)	13,214 (11.1)	4,065,066 (12.9)	< 0.001	< 0.001
Lawyer	7 (0.0)	12 (0.0)	503,007 (1.6)	< 0.001	< 0.001
Consumer[d]	22,616 (46.7)	66,572 (56.0)	10,030,508 (31.8)	< 0.001	< 0.001
Unknown	0 (0.0)	1521 (1.3)	7,329,814 (23.2)		
Serious, *n* (%)					
No	28,284 (58.4)	99,563 (83.8)	16,897,742 (53.5)	< 0.001	< 0.001
Yes	19,985 (41.3)	18,700 (15.7)	10,185,053 (32.3)		
Unknown	171 (0.4)	579 (0.5)	4,474,304 (14.2)		
Seriousness criteria[e], *n* (%)					
Caused/prolonged hospitalization	8100 (16.7)	6042 (5.1)	3,611,957 (11.4)	< 0.001	< 0.001
Congenital anomaly/birth defect	33 (0.1)	54 (0.0)	37,975 (0.1)	0.001	< 0.001
Death	1470 (3)	1184 (1.0)	1,129,474 (3.6)	< 0.001	< 0.001
Disabling/incapacitating	595 (1.2)	533 (0.4)	446,034 (1.4)	< 0.001	< 0.001
Life threatening	808 (1.7)	549 (0.5)	494,595 (1.6)	0.027	< 0.001
Other medically important condition	13,051 (26.9)	13,633 (11.5)	5,340,763 (16.9)	< 0.001	< 0.001

[a]Not all report formats include this information and the same report can also be reported with more than one reporter

[b]Hospital doctors, general practitioners, family pediatricians, specialists

[c]Nurses, dentists, poison centers, etc.

[d]Non-healthcare professional, pharmaceutical companies, etc.

[e]Not all report formats include this information and the same report can also be reported with more than one seriousness criteria

ADR adverse drug reaction, *ICSR* individual case safety report, *RG1* Reference Group 1

Table 3 Characteristics of biologic-related ICSRs for asthma use by single active ingredient

	Benralizumab	Dupilumab	Mepolizumab	Omalizumab	Reslizumab	*p* value
Total reports	5512	13,677	8731	20,501	219	
Sex, *n* (%)						
Female	3742 (67.9)	7991 (58.4)	5649 (64.7)	13,620 (66.4)	141 (64.4)	0.039
Male	1560 (28.3)	3480 (25.4)	2406 (27.6)	6189 (30.2)	68 (31.1)	
F/M ratio	2.4	2.3	2.3	2.2	2.1	0.039
Unknown	210 (3.8)	2206 (16.1)	676 (7.7)	692 (3.4)	10 (4.6)	
Age groups (years), *n* (%)						
< 2	1 (0)	3 (0)	34 (0.4)	21 (0.1)	0 (0)	< 0.001
2–11	6 (0.1)	113 (0.8)	24 (0.3)	359 (1.8)	0 (0)	< 0.001
12–17	55 (1)	429 (3.1)	73 (0.8)	764 (3.7)	0 (0)	< 0.001
18–44	759 (13.8)	2082 (15.2)	992 (11.4)	3424 (16.7)	38 (17.4)	< 0.001
45–64	1812 (32.9)	4002 (29.3)	2661 (30.5)	5128 (25)	80 (36.5)	< 0.001
65–74	719 (13)	1176 (8.6)	1157 (13.3)	1620 (7.9)	35 (16)	< 0.001
≥ 75	335 (6.1)	445 (3.3)	525 (6)	658 (3.2)	12 (5.5)	< 0.001
Unknown	1825 (33.1)	5427 (39.7)	3265 (37.4)	8527 (41.6)	54 (24.7)	
Continents, *n* (%)						
Africa	0 (0)	6 (0)	0 (0)	54 (0.3)	0 (0)	< 0.001
Americas	2962 (53.7)	12,800 (93.6)	5939 (68)	16,594 (80.9)	124 (56.6)	< 0.001
Asia	114 (2.1)	42 (0.3)	163 (1.9)	726 (3.5)	10 (4.6)	< 0.001
Europe	2330 (42.3)	813 (5.9)	2169 (24.8)	3087 (15.1)	85 (38.8)	< 0.001
Oceania	106 (1.9)	16 (0.1)	460 (5.3)	40 (0.2)	0 (0)	< 0.001
Reporter qualification[a], *n* (%)						
Physician[b]	2364 (42.9)	4960 (36.3)	1835 (21)	8943 (43.6)	76 (34.7)	< 0.001
Pharmacist	103 (1.9)	162 (1.2)	264 (3)	631 (3.1)	16 (7.3)	< 0.001
Other healthcare professional[c]	944 (17.1)	968 (7.1)	1729 (19.8)	4406 (21.5)	49 (22.4)	< 0.001
Lawyer	0 (0)	0 (0)	1 (0)	6 (0)	0 (0)	0.073
Consumer[d]	1928 (35)	7752 (56.7)	5911 (67.7)	7043 (34.4)	80 (36.5)	< 0.001
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Serious, *n* (%)						
No	3883 (70.4)	11,228 (82.1)	4590 (52.6)	8558 (41.7)	122 (55.7)	< 0.001
Yes	1626 (29.5)	2447 (17.9)	4134 (47.3)	11,784 (57.5)	97 (44.3)	
Unknown	3 (0.1)	2 (0)	7 (0.1)	159 (0.8)	0 (0)	
Seriousness criteria [e], *n* (%)						
Caused/prolonged hospitalization	656 (11.9)	1296 (9.5)	1819 (20.8)	4335 (21.1)	37 (16.9)	< 0.001
Congenital anomaly/birth defect	4 (0.1)	3 (0)	2 (0)	24 (0.1)	0 (0)	0.009
Death	175 (3.2)	94 (0.7)	281 (3.2)	919 (4.5)	3 (1.4)	< 0.001
Disabling/incapacitating	56 (1)	140 (1)	70 (0.8)	329 (1.6)	4 (1.8)	< 0.001
Life-threatening	74 (1.3)	39 (0.3)	77 (0.9)	614 (3)	6 (2.7)	< 0.001
Other medically important condition	935 (17)	1504 (11)	3086 (35.3)	7535 (36.8)	66 (30.1)	< 0.001
Fatal, *n* (%)						
No	5337 (96.8)	13,582 (99.3)	8449 (96.8)	19,567 (95.4)	216 (98.6)	< 0.001
Yes	175 (3.2)	95 (0.7)	282 (3.2)	934 (4.6)	3 (1.4)	
Outcomes[f], *n* (%)						
Died	173 (3.1)	87 (0.6)	250 (2.9)	797 (3.9)	2 (0.9)	< 0.001
Not recovered	1282 (23.3)	2906 (21.2)	1943 (22.3)	3814 (18.6)	56 (25.6)	0.017
Recovered	1635 (29.7)	1547 (11.3)	2261 (25.9)	5414 (26.4)	78 (35.6)	< 0.001
Recovered with sequelae	30 (0.5)	5 (0)	34 (0.4)	176 (0.9)	2 (0.9)	< 0.001
Recovering	521 (9.5)	796 (5.8)	1130 (12.9)	2670 (13)	34 (15.5)	< 0.001
Unknown/not reported	3281 (59.5)	11,774 (86.1)	6096 (69.8)	15,386 (75)	116 (53)	< 0.001

Table 3 (continued)

[a]Not all report formats include this information and the same report can also be reported with more than one reporter

[b]Hospital doctors, general practitioners, family pediatricians, specialists

[c]Nurses, dentists, poison centers, etc.

[d]Non-healthcare professional, pharmaceutical companies, etc.

[e]Not all report formats include this information and the same report can also be reported with more than one seriousness criteria

[f]Not all report formats include this information and the same report can also be reported with more than one outcome

ICSR individual case safety report

Table 4 Most frequently* reported suspected ADRs for all five biologics used in asthma-related conditions and corresponding ROR values (vs RG1 and RG2)

Suspected ADR_PT level	ICSRs ($N=48,440$)	ROR (vs RG1)	95% CIs	ROR (vs RG2)	95% CIs
Asthma	7398	82.37	80.27–84.52	1.10	1.06–1.14
Dyspnea[# ABs]	5560	4.16	4.05–4.28	0.64	0.62–0.67
Product use issue	4598	28.70	27.82–29.60	5.61	5.19–6.06
Drug ineffective	3761	2.29	2.21–2.36	0.53	0.51–0.55
Cough[# O]	3740	5.69	5.50–5.88	0.87	0.83–0.91
Headache[# B,M,O]	3406	1.17	1.13–1.21	2.25	2.11–2.40
Fatigue[# M,O,R]	2866	1.34	1.29–1.39	2.89	2.67–3.12
Wheezing	2706	39.22	37.69–40.81	1.38	1.30–1.47
Product dose omission issue	2300	4.89	4.69–5.10	0.58	0.55–0.61
Arthralgia[# D,M,O]	2219	2.02	1.94–2.11	4.70	4.23–5.23
Malaise[# O]	2146	1.85	1.77–1.93	1.29	1.21–1.38
Pneumonia	2105	5.78	5.54–6.04	1.32	1.23–1.41
Rash[# Abs]	2070	0.92	0.88–0.96	2.79	2.55–3.05
Pruritus[# Abs]	2064	1.01	0.97–1.06	2.94	2.68–3.22
Nasopharyngitis[# B,D,M,O]	1809	7.02	6.69–7.36	2.12	1.94–2.31
Chest discomfort[# R]	1703	6.05	5.76–6.35	0.98	0.91–1.05
Pyrexia[# B,M,O]	1661	0.66	0.63–0.69	4.42	3.92–4.98
Injection site pain[# ABs]	1602	1.48	1.41–1.56	100.55	59.41–170.20
Dizziness[# D,M,O]	1533	0.77	0.74–0.81	1.26	1.16–1.36
Urticaria[# ABs]	1453	1.24	1.18–1.31	2.92	2.62–3.26
Hypersensitivity[# ABs]	1437	3.37	3.20–3.55	2.41	2.18–2.67
Pain[# D,O]	1432	1.07	1.02–1.13	2.43	2.20–2.70
Nausea[# M,O,R]	1345	0.44	0.42–0.47	1.58	1.44–1.73
Productive cough	1287	26.5	25.04–28.03	1.97	1.78–2.18
Pain in extremity[# O,R]	1123	1.26	1.19–1.34	3.16	2.78–3.59
Condition aggravated	1097	3.08	2.90–3.28	1.35	1.22–1.48
Sinusitis[# D,O]	1084	9.56	9.0–10.15	2.38	2.12–2.67
Blood pressure increased	1076	3.86	3.63–4.10	2.40	2.14–2.70
Influenza[# M,O]	1036	5.37	5.04–5.71	3.21	2.81–3.67
Anaphylactic reaction[# ABs]	1007	4.31	4.06–4.60	12.29	9.66–15.64

*The table shows only PTs for which at least 1000 reports were reported

[#]Expected suspected ADR based on FDA labels [51] or EMA Summaries of Product Characteristics [20] of each single agent

ABs all asthma biologics, *ADR* adverse drug reaction, *B* benralizumab, *CI* confidence interval, *D* dupilumab, *ICSR* individual case safety report, *M* mepolizumab, *O* omalizumab, *PT* preferred term, *R* reslizumab, *RG1* Reference Group 1, *RG2* Reference Group 2, *ROR* reporting odds ratio

benralizumab; and alopecia with reslizumab (see Table 6). Most cases of biologic-induced alopecia involved females and adult patients.

In the sensitivity analysis in which all vaccine-related reports were removed, all these potential signals were confirmed, except for basal cell carcinoma with mepolizumab

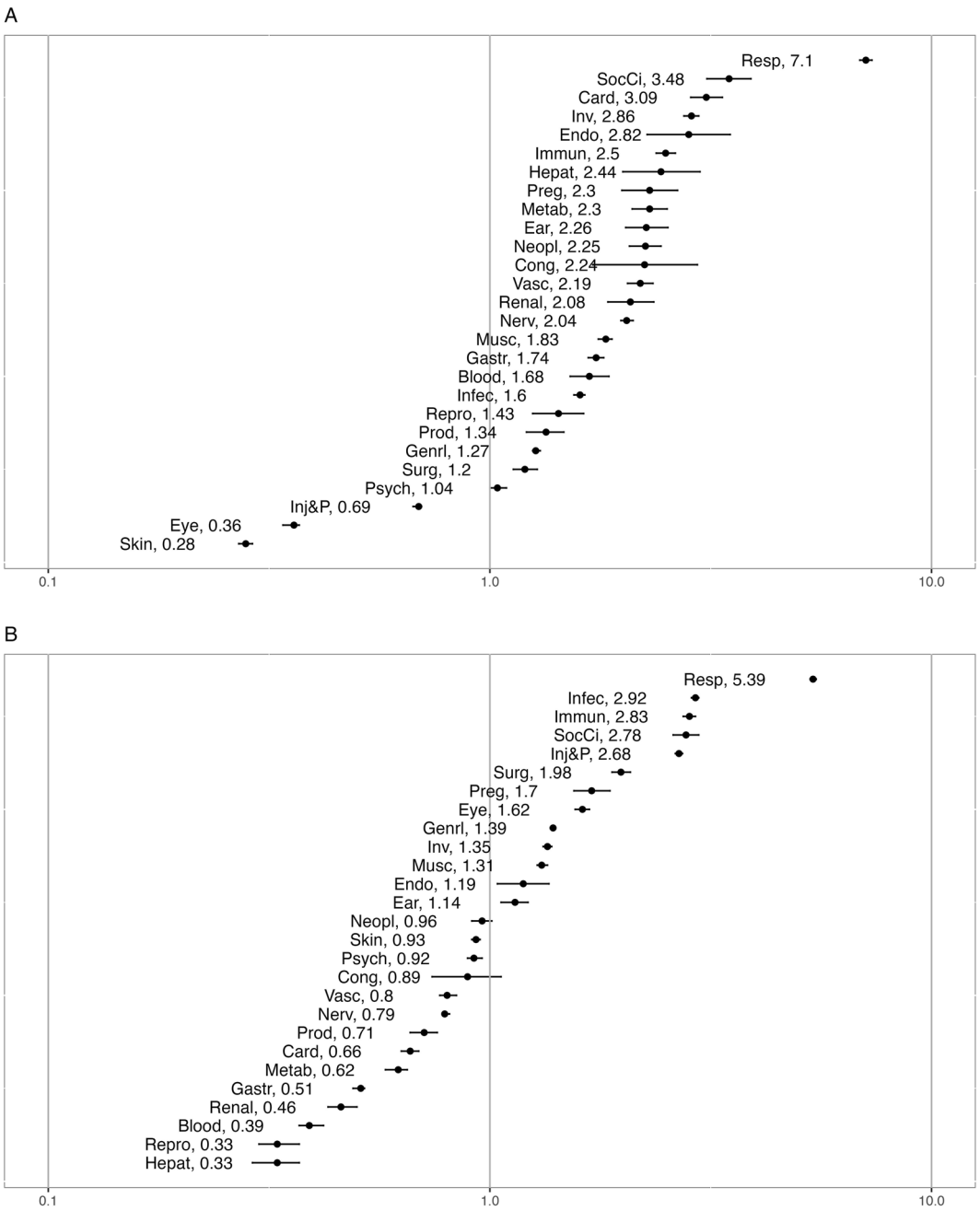

Fig. 2 RORs of System Organ Classes comparing biologics used in asthma with biologics in all other indications (Part A) and with all other drugs in VigiBase (Part B). *Blood* blood and lymphatic system disorders, *Card* cardiac disorders, *Cong* congenital, familial and genetic disorders, *Ear* ear and labyrinth disorders, *Endo* endocrine disorders, *Eye* eye disorders, *Gastr* gastrointestinal disorders, *Genrl* general disorders and administration-site conditions, *Hepat* hepatobiliary disorders, *Immun* immune system disorders, *Infec* infections and infestations, *Inj&P* injury, poisoning and procedural complications, *Inv* investigations, *Metab* metabolism and nutrition disorders, *Musc* musculoskeletal and connective tissue disorders, *Neopl* neoplasms benign, malignant and unspecified (incl cysts and polyps), *Nerv* nervous system disorders, *Preg* pregnancy, puerperium and perinatal conditions, *Prod* product issues, *Psych* psychiatric disorders, *Renal* renal and urinary disorders, *RG1* Reference Group 1, *Repro* reproductive system and breast disorders, *Resp* respiratory, thoracic and mediastinal disorders, *RORs* reporting odds ratios, *Skin* skin and subcutaneous tissue disorders, *SocCi* social circumstances, *Surg* surgical and medical procedures, *Vasc* vascular disorders

(OR 1.81, 95% CI 0.81–4.03), alopecia with dupilumab (OR 1.04, 95% CI 0.87–1.25) and alopecia with benralizumab (OR 1.11, 95% CI 0.84–1.46).

To examine possible differences by therapeutic indication, RORs for the most relevant adverse events related to ABs by therapeutic indication (asthma use vs all other

uses) are reported in Fig. 4. Cardiac arrhythmias, solid neoplasms, anaphylactic reaction, cardio-cerebral ischemic disease, arthritis and musculoskeletal disorders were more commonly reported in ICSRs specific for asthma use, while skin and ocular disorders were more likely occur for other therapeutic uses.

In the sensitivity analysis, RORs were calculated using all other reports in VigiBase (RG1) as a comparison group, after excluding reports in which ABs were co-reported with one of the four OCSs included as suspected drugs in RG3 ($n = 453$). No substantial variation was observed in ROR values derived from primary analysis (data not shown).

4 Discussion

To our knowledge, this is the first extensive study that explored the safety profiles of biologics approved for severe asthma treatment using the WHO global pharmacovigilance database. Previously published ICSR analyses from VigiBase were restricted only to single compounds or to specific safety issues [19, 36–40].

In our analysis, ICSRs mainly involved females and adult patients, especially in asthmatic patients. This finding is expected considering the higher prevalence of female adult patients with asthma disease [41]. Among biologic-related ICSRs in asthma patients, about 40% included omalizumab as suspected drug, differently from ICSRs related to other therapeutic uses in which dupilumab was the most implicated drug.

Our findings corroborated well-known safety issues related to ABs, already described in pivotal clinical trials as well as observational studies, including general disorders (e.g. malaise, fatigue), injection-site reactions, nasopharyngitis, headache and hypersensitivity.

In our study, the majority of cases concerned adverse events that most likely result from the underlying condition (e.g. asthma re-exacerbation or therapeutic failure, cough, dyspnea, etc.). In line with this hypothesis, when using ICSs/LABAs as reference group, most of these disproportionate signals no longer reached statistical significance.

Biologics, considered as OCS-sparing agents, are used for severe asthma to control asthma exacerbations [42, 43]. In this context, it is also important to understand the relevance of phenotyping severe asthma patients through biomarkers and/or clinical features, such as comorbidities, in clinical practice [44–48]. Unfortunately, some severe asthma patients do not respond to biologic therapy, thus presenting asthma exacerbations or deterioration. The differences in treatment response may be multifactorial, and related to various drug and/or patient-related factors, such as the mechanisms of action, the target, dose and interval of the biological drug or the heterogeneity of asthma phenotypes and underlying endotypes [49, 50]. Persistent suboptimal responders require a re-evaluation of asthma phenotype biomarkers, and the suspected immunological pathways involved in the asthma inflammation [51].

As expected, a significant number of spontaneous reports including anaphylactic reactions was reported with greater frequencies for omalizumab and reslizumab in relation to reports of each biologic agent. In line with a recently published FAERS analysis [39], all biologic drugs showed positive signals of disproportionate reporting for anaphylactic reactions, except for dupilumab, which is the only fully human monoclonal antibody among the five biologic agents. The risk of hypersensitivity/allergic reactions and anaphylaxis could be related to the immunogenic properties of the protein component of monoclonal antibodies (mAbs). The role of excipients, such as polysorbates, has also been investigated in literature [20]. Although the incidence of anaphylaxis related to mAbs for severe asthma is low, asthma patients in general appear to have a higher risk of severe allergic reactions, including anaphylaxis, compared with patients that use mAbs for other indications, such as chronic urticaria [39]. In addition, the FDA included a black box warning on both omalizumab and reslizumab labels for the risk of anaphylaxis [24].

Potential differences among single biologic safety profiles also emerged from our findings as reported in the results section. Most of these findings were in line with available evidence for each biologic agent, including the corresponding FDA labels [24] and the EPARs and RMPs [25].

Due to the potential interference with the immune system, one of the major concerns with ABs was the risk of provoking or unmasking malignancies, although none of the investigated drugs exerts an immunosuppressive effect under a mechanistic perspective. Analogously to a previous disproportionality analysis of VigiBase [19], our study reported signals of disproportionate reporting for omalizumab and leukemia, melanoma, breast, lung, prostate, colon and thyroid cancers. Omalizumab is an anti Ig-E drug and a possible relationship between absent or very low serum Immunoglobulin E levels and cancer risk has been already suggested in literature [52]. A numeric imbalance in malignancy rates in patients with allergic asthma was observed in pivotal trials, leading the US FDA to require a post-marketing 5-year safety study (EXCELS) to assess the long-term safety of omalizumab in an observational setting, primarily the risk of malignancy [53]. In line with a pooled analysis of clinical trials, the results of the EXCELS study did not confirm a

significant association between omalizumab use and risk of cancer [54–57], despite the limitation of this observational study preventing a definitive conclusion to be drawn regarding this risk [58]. Although the number of cases reported in the post-marketing setting has increased during the last few years, the difficulty of establishing a causal association in spontaneous cancer-related ICSRs prevents us from assessing this risk. A few cases of malignancy, including basal cell carcinoma and melanoma, were also reported for mepolizumab, but there is no supporting evidence from literature.

Based on the findings of the above-mentioned EXCELS study [53], an FDA safety alert regarding a potential association of omalizumab and arterial thrombotic events (ATEs) was issued in 2014 [17] and information about ATEs has been added to the drug label. In addition, results from EXCELS showed a rate of pulmonary embolism or venous thrombosis corresponding to 3.2 per 1000 patient-years with omalizumab ($N = 5007$) versus 1.5 per 1000 patient-years with non-omalizumab treatment ($N = 2829$) [59]. Accordingly, in our analysis several spontaneous cases of ATEs (i.e. myocardial infarction, transient ischemic attack and stroke) were reported with omalizumab. We also observed cases of venous thromboembolic disorders, such as pulmonary embolism and deep vein thrombosis. Some case reports describing the association of omalizumab with pulmonary vein thrombosis were also published [60, 61]. However, the effects of omalizumab and other ABs on the cardiovascular system remain controversial.

Statistically significant signals of disproportionate reporting of alopecia were identified for all ABs under study. Hair loss is listed among the side effects in the omalizumab package insert, but unlisted for the other study drugs. Several published case reports and a previous analysis based on VigiBase considered the potential correlation between the onset of hair disorders and dupilumab therapy [62–64]. Nevertheless, a paradoxical effect of dupilumab as a beneficial treatment for alopecia areata has been reported [65]. In addition, a case report of mepolizumab-associated alopecia has been published [66]. In this case, the authors suggested that autoimmune mechanisms could be unmasked by the suppression of eosinophils following treatment with mepolizumab.

Several AB-related ICSRs, describing adverse events in which autoimmunity could play a role (e.g. sarcoidosis, lichen planus, myasthenia gravis, polymyalgia rheumatica, EGPA), have been detected in VigiBase. Most cases of autoimmune conditions attributed to ABs were also described in literature [36, 67–74]. It is not clear if the biologic agent could act as a trigger in patients with genetic predispositions or if it causes directly similar, but not true, autoimmune conditions. Furthermore, some reported cases could reflect a delay in the diagnosis of the autoimmune disease, more than a true side effect. In the case of EGPA, the natural history of the disease, almost invariantly characterized by severe asthma as a prodromal stage, might account for its onset in patients undergoing anti Th2 mAbs for severe asthma. In that light, EGPA occurrence could be related to the inability of the biologic therapy to prevent the disease evolution more then to a side effect triggered by the drug.

In our study, a significant disproportionality related to spontaneous abortion following omalizumab use was highlighted, but this finding could be confounded by the underlying disease. Actually, numerous studies showed a link between uncontrolled asthma during pregnancy and the increased risk of perinatal mortality, congenital anomalies, prematurity, low birth weight and adverse maternal outcomes [75–77].

Some studies have investigated the potential link between asthma and the development of herpes zoster infection caused by the re-activation of latent varicella zoster virus [78–80]. Many risk factors could play a role in this re-activation, such as stress, immunosuppression condition, age or some debilitating diseases that compromise the immune system, like asthma [79]. For this reason, the herpes zoster immunization is primarily suggested for asthmatic adults aged 50 years or more [78, 80]. Nevertheless, a recent review focusing on the risks of asthma biologic therapy underlined that a small percentage of patients receiving dupilumab, mepolizumab and benralizumab developed a herpes zoster infection and this risk is already labelled for mepolizumab [81].

A significant confounder in our analysis is represented by concomitant or recent use of OCSs that are typically administered to patients with severe asthma, according to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines [1]. In general, after starting biologics, OCS sparing up to withdrawal may be considered a primary outcome in the management of severe asthma patients to minimize side effects [82].

Frequent or continuous use of corticosteroids (OCSs or long-term high-dose ICSs) could be associated with an array of potential adverse events, such as fluid retention, bone damage, elevated blood sugars and psychiatric problems, which could be clinically relevant, especially when high doses are required for a prolonged period of time. Furthermore, the reduction or suppression of OCSs during therapy with biologics for asthma may unmask some comorbidity symptoms or patients' underlying diseases (e.g. psoriasis, multiple inflammatory diseases, etc.), known as glucocorticoid deprivation syndrome. For instance, the potential signals identified in our study of EGPA related to benralizumab or sarcoidosis with omalizumab offer a possible alternative explanation in the unmasking effect of biologics after interruption of OCS therapy, as already discussed in some published case reports [73, 83, 84]. Furthermore, several OCS-related long-term effects may emerge during therapy with biologics and be erroneously attributed to

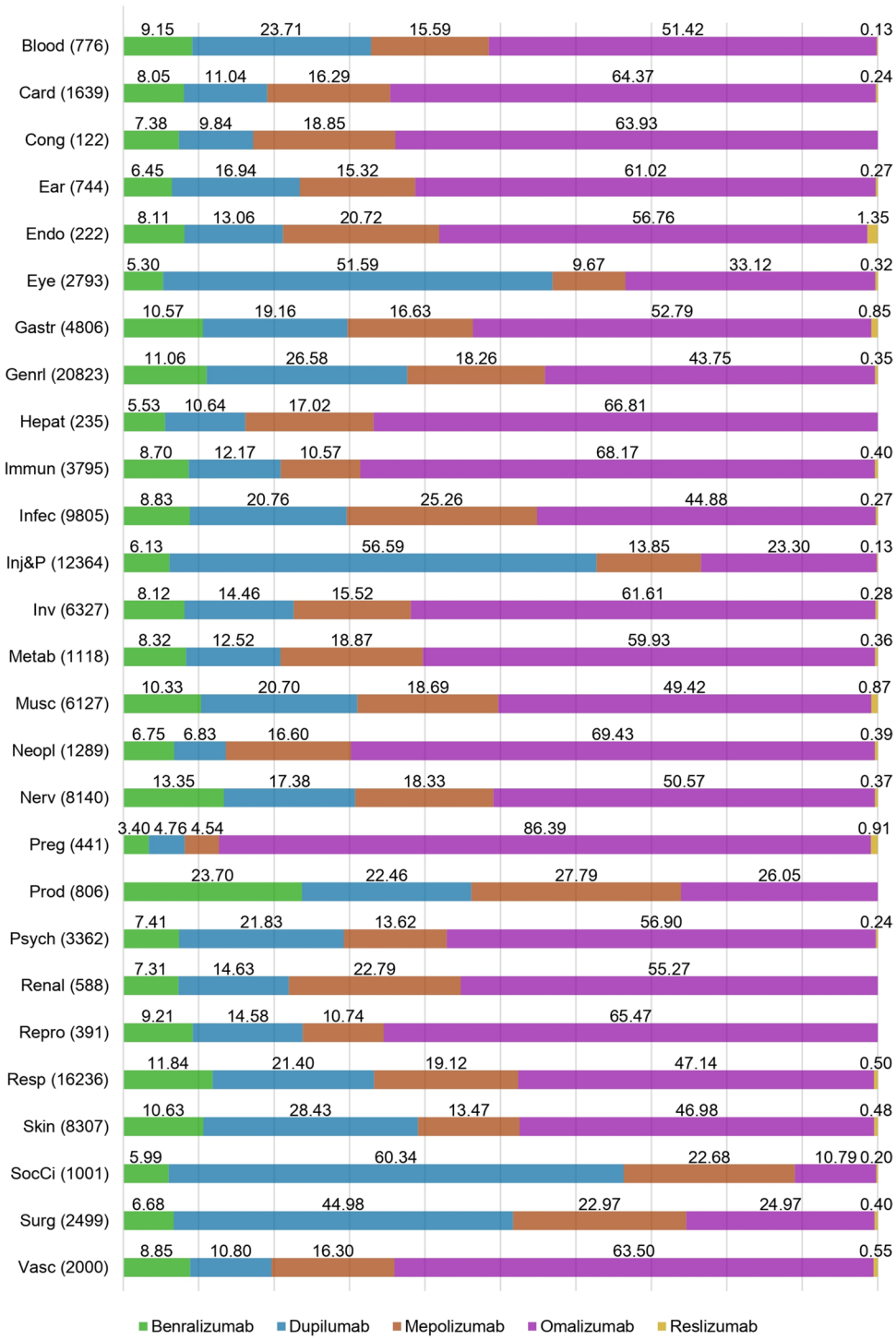

Fig. 3 Reports related to each single biologic used in asthma stratified by System Organ Classes (%). *Blood* blood and lymphatic system disorders, *Card* cardiac disorders, *Cong* congenital, familial and genetic disorders, *Ear* ear and labyrinth disorders, *Endo* endocrine disorders, *Eye* eye disorders, *Gastr* gastrointestinal disorders, *Genrl* general disorders and administration-site conditions, *Hepat* hepatobiliary disorders, *Immun* immune system disorders, *Infec* infections and infestations, *Inj&P* injury, poisoning and procedural complications, *Inv* investigations, *Metab* metabolism and nutrition disorders, *Musc* musculoskeletal and connective tissue disorders, *Neopl* neoplasms benign, malignant and unspecified (incl cysts and polyps), *Nerv* nervous system disorders, *Preg* pregnancy, puerperium and perinatal conditions, *Prod* product issues, *Psych* psychiatric disorders, *Renal* renal and urinary disorders, *Repro* reproductive system and breast disorders, *Resp* respiratory, thoracic and mediastinal disorders, *Skin* skin and subcutaneous tissue disorders, *SocCi* social circumstances, *Surg* surgical and medical procedures, *Vasc* vascular disorders

them. In our analysis, numerous ICSRs related to adrenal insufficiency, hyperglycemia, fractures, Cushing's syndrome, weight increase and other typical steroid adverse events were reported in association with asthma biologics. However, when using OCS as comparator, most of those signals no longer reached statistical significance, thus supporting our hypothesis.

Some variations in reporting trends by therapeutic use were also detected. In detail, we observed that several types of malignancies, cardiovascular adverse events, pneumonia and musculoskeletal events are more likely to be reported for asthma treatment than other therapeutic uses, whereas cutaneous and ocular events are more often reported for other indications (e.g. atopic dermatitis). These results need to be interpreted, in view of the different reporting trends

Table 5 Sensitivity analysis for suspected ADRs including several typical corticosteroid-induced effects, compared with selected oral corticosteroids (RG3)

Biologic	Suspected ADR	N. reports	RG1			RG3		
			Lower	ROR	Upper	Lower	ROR	Upper
Omalizumab	Weight increased	695	4.92	5.30	5.72	0.80	0.99	1.21
Omalizumab	Hypertension	304	1.75	1.96	2.19	0.58	0.77	1.01
Dupilumab	Weight increased	154	1.46	1.72	2.01	0.25	0.32	0.41
Omalizumab	Diabetes mellitus	117	2.48	2.98	3.57	0.22	0.30	0.41
Mepolizumab	Hypertension	104	1.29	1.57	1.90	0.45	0.62	0.85
Mepolizumab	Weight increased	86	1.21	1.50	1.85	0.21	0.28	0.37
Omalizumab	Cataract	71	2.29	2.89	3.65	0.15	0.21	0.30
Omalizumab	Osteoporosis	56	2.25	2.92	3.80	0.08	0.12	0.17
Benralizumab	Weight increased	53	1.12	1.46	1.92	0.20	0.27	0.38
Mepolizumab	Diabetes mellitus	47	2.11	2.81	3.74	0.19	0.28	0.41
Dupilumab	Cataract	42	1.89	2.56	3.47	0.13	0.19	0.28
Omalizumab	Obesity	41	4.63	6.30	8.56	0.30	0.59	1.14
Mepolizumab	Cataract	39	2.72	3.73	5.11	0.18	0.27	0.42
Omalizumab	Adrenal insufficiency	32	5.45	7.72	10.92	0.07	0.11	0.17
Omalizumab	Type 2 diabetes mellitus	31	1.36	1.93	2.75	0.17	0.30	0.56
Omalizumab	Fracture	30	2.53	3.62	5.18	0.33	0.79	1.89
Omalizumab	Ankle fracture	28	2.90	4.21	6.10	0.53	2.21	9.27
Omalizumab	Oral candidiasis	26	2.50	3.68	5.41	0.17	0.34	0.68
Omalizumab	Glaucoma	21	1.44	2.21	3.39	0.14	0.27	0.56
Mepolizumab	Type 2 diabetes mellitus	18	1.66	2.64	4.19	0.21	0.41	0.81
Omalizumab	Overweight	16	4.12	6.74	11.01	0.33	2.52	19.01
Omalizumab	Glucose tolerance impaired	15	2.74	4.56	7.56	0.15	0.39	1.01
Mepolizumab	Osteoporosis	15	1.11	1.84	3.05	0.04	0.07	0.13
Dupilumab	Ankle fracture	14	1.86	3.15	5.32	0.38	1.65	7.28
Mepolizumab	Glaucoma	14	2.05	3.46	5.84	0.20	0.43	0.93
Mepolizumab	Adrenal insufficiency	12	3.84	6.77	11.94	0.05	0.10	0.18
Benralizumab	Osteoporosis	12	1.32	2.33	4.10	0.05	0.09	0.17
Mepolizumab	Obesity	9	1.68	3.23	6.22	0.12	0.30	0.73
Omalizumab	Addison's disease	7	6.56	13.81	29.07	0.11	0.55	2.65
Mepolizumab	Oral candidiasis	7	1.11	2.32	4.87	0.08	0.22	0.55
Mepolizumab	Blood pressure systolic increased	7	1.27	2.68	5.61	0.19	0.65	2.21
Dupilumab	Adrenal insufficiency	6	0.97	2.16	4.81	0.01	0.03	0.07
Omalizumab	Cushingoid	6	1.89	4.21	9.39	0.01	0.03	0.08
Benralizumab	Oral candidiasis	6	1.42	3.15	7.02	0.11	0.29	0.78
Omalizumab	Humerus fracture	6	1.51	3.37	7.51	0.11	0.94	7.85
Mepolizumab	Overweight	6	2.66	5.92	13.19	0.27	2.22	18.44
Omalizumab	Cushing's syndrome	5	1.09	2.63	6.32	0.01	0.02	0.05
Mepolizumab	Ankle fracture	5	0.73	1.76	4.23	0.18	0.92	4.77
Benralizumab	Overweight	5	3.25	7.81	18.79	0.34	2.93	25.09
Benralizumab	Adrenal insufficiency	4	1.34	3.57	9.52	0.02	0.05	0.14
Mepolizumab	Cushing's syndrome	4	1.85	4.94	13.18	0.01	0.04	0.10
Mepolizumab	Cushingoid	4	2.47	6.59	17.58	0.02	0.05	0.14
Mepolizumab	Glucose tolerance impaired	4	1.07	2.85	7.59	0.07	0.25	0.87
Dupilumab	Overweight	3	0.61	1.89	5.85	0.07	0.71	6.81

ADR adverse drug reaction, *RG1* Reference Group 1, *RG2* Reference Group 2, *ROR* reporting odds ratio

Table 6 Some unexpected adverse events resulting in signals of disproportionate reporting from primary (vs RG1) and sensitivity (vs RG2) analyses

Drug (S/I)	Reaction (PT)	Asthma use	RORs (vs RG1)		RORs (vs RG2)	
		N. ICSRs	ROR	95% CIs	ROR	95% CIs
Benralizumab	Alopecia	51	1.32	1.00–1.74	2.28	1.66–3.12
	Herpes zoster	41	2.14	1.57–2.90	4.05	2.77–5.93
	EGPA	19	84.20	53.49–132.54	4.74	2.67–8.43
Dupilumab	Alopecia	119	1.24	1.04–1.49	2.14	1.69–2.71
	Lichen planus	5	3.82	1.59–9.18	15.06	1.76–128.90
Mepolizumab	Alopecia	71	1.16	0.92–1.46	2	1.51–2.64
	Cellulitis	41	2.49	1.83–3.39	7.47	4.57–12.21
	Bone pain	34	1.77	1.26–2.48	2.01	1.34–3.00
	Diverticulitis	25	4.86	3.28–7.20	2.88	1.75–4.74
	Immunodeficiency	9	4.61	2.40–8.87	3.03	1.31–7.01
	Malignant melanoma	8	3.04	1.52–6.09	2.90	1.20–7.01
	Polymyalgia rheumatica	7	4.58	2.18–9.61	11.01	2.85–42.59
	Basal cell carcinoma	6	2.24	1.01–4.99	7.08	2.00–25.09
Omalizumab	Heart rate increased	657	8.75	8.09–9.45	2.64	2.35–2.97
	Hypertension	304	1.96	1.75–2.19	1.29	1.12–1.49
	Breast cancer	137	2.69	2.27–3.18	3.33	2.53–4.38
	Herpes zoster	127	1.78	1.49–2.12	3.37	2.54–4.48
	Pulmonary embolism	111	1.57	1.31–1.90	4.57	3.26–6.40
	Abortion spontaneous	103	5.11	4.21–6.21	7.7	5.04–11.76
	Heart rate decreased	99	5.93	4.87–7.23	7.99	5.15–12.39
	Deep vein thrombosis	75	1.43	1.14–1.80	15.11	7.81–29.24
	Lymphoma	29	4.33	3.01–4.51	11.66	4.51–30.14
	Colon cancer	27	4.38	3.00–6.40	2.47	1.40–4.33
	Malignant melanoma	25	4.06	2.74–6.01	3.87	1.98–7.56
	Cardiomyopathy	22	2.44	1.61–3.71	4.02	1.95–8.29
	Basal cell carcinoma	19	3.02	1.93–4.74	2.99	0.40–22.37
	Sarcoidosis	18	7.36	4.63–11.70	3.62	1.67–7.84
	Thyroid cancer	14	2.49	1.47–4.20	3.13	1.35–7.22
	Erythema nodosum	13	2.95	1.71–5.08	26.12	3.42–199.72
	Myasthenia gravis	13	5.67	3.29–9.78	6.53	2.13–20.03
	Hypogammaglobulinemia	10	6.13	3.29–11.41	10.05	2.20–45.86
	Polymyalgia rheumatica	9	2.51	1.30–4.82	6.03	1.63–22.27
	B-cell lymphoma	7	5.41	2.58–11.37	14.06	1.73–114.31
	Lichen planus	6	3.06	1.37–6.81	12.05	1.45–100.13
Reslizumab	Alopecia	6	3.98	1.77–8.96	6.88	3.01–15.69

ADR adverse drug reaction, *CI* confidence interval, *EGPA* eosinophilic granulomatosis with polyangiitis, *ICSR* individual case safety report, *I* interacting, *PT* preferred term, *RG1* Reference Group 1, *RG2* Reference Group 2, *ROR* reporting odds ratio, *S* suspected

of single biologic agents by therapeutic indication. While omalizumab is the most represented drug in asthma-specific reports, for other therapeutic uses, mainly atopic dermatitis, a higher frequency of reports is observed for dupilumab that is commonly related to ocular and cutaneous adverse events, especially in patients with atopic dermatitis, as already shown in previous WHO pharmacovigilance analyses [37, 40]. Another FAERS study [85] found that patients in treatment with dupilumab for atopic dermatitis have more ocular complications than asthmatic patients, suggesting that a potential drug–disease interaction could enhance the risk of ocular complications following dupilumab administration. Furthermore, the safety profiles of biologics used in such different populations, who have different background rates of adverse events, are sometimes reflections of the characteristics of the patients being treated rather than effects of the drug under study.

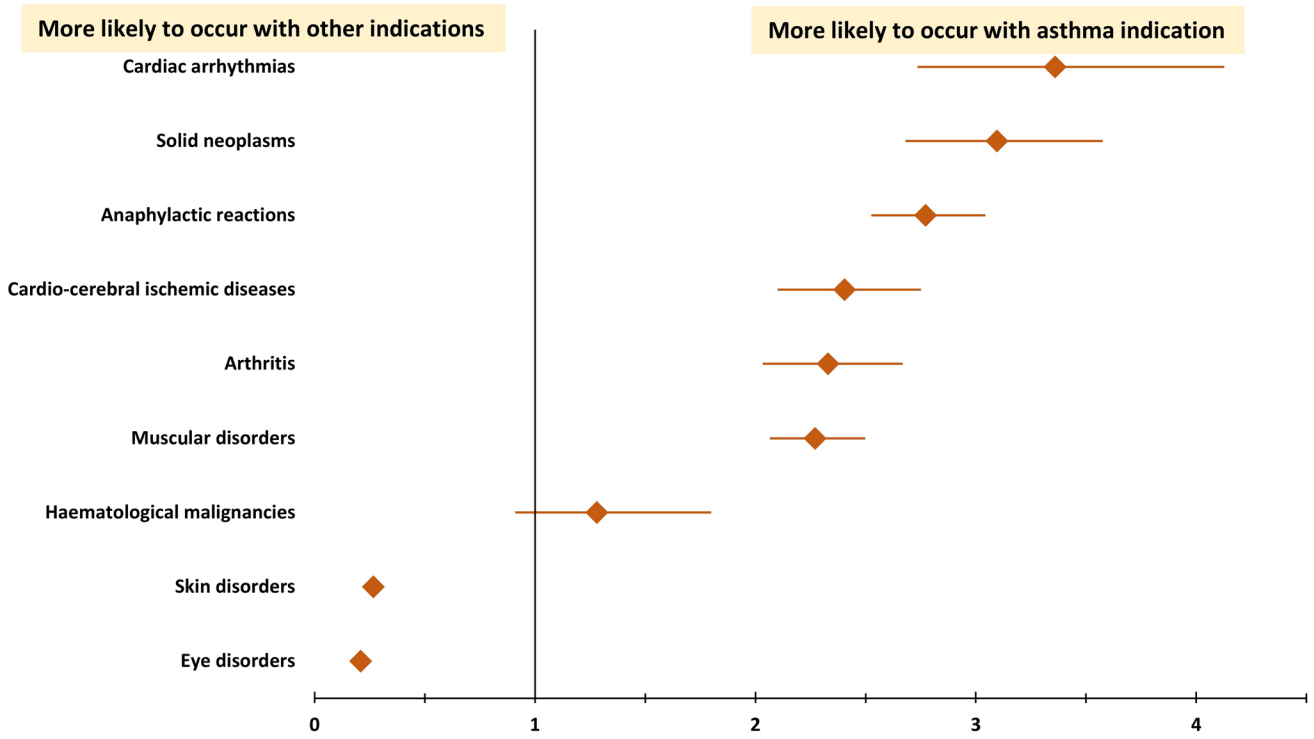

Fig. 4 RORs of some selected suspected ADRs comparing biologics used for asthma versus all other indications. Each category of adverse events was evaluated aggregating different PT terms, as follows: 'Anaphylactic reactions': Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction. 'Arthritis': Arthritis; Arthritis infective; Osteoarthritis; Periarthritis; Polyarthritis; Rheumatoid arthritis; Spinal osteoarthritis. 'Cardiac arrhythmias': Arrhythmia; Arrhythmia supraventricular; Atrial fibrillation; Atrial tachycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia; Atrioventricular block; Atrioventricular block complete. 'Cardio-cerebral ischemic diseases': Acute myocardial infarction; Cerebral infarction; Cerebral ischemia; Cerebral thrombosis; Cerebrovascular accident; Cerebrovascular disorder; Infarction; Ischemic stroke; Myocardial infarction; Myocardial ischemia; Thrombotic stroke. 'Eye disorders': Conjunctivitis; Keratitis; Ulcerative keratitis; Blepharitis; Eye pruritus; Dry eye; Eye swelling; Eye pain; Eye irritation; Eye disorder. 'Hematological malignancies': B-cell lymphoma; Cutaneous T-cell lymphoma; Lymphoma; Non-Hodgkin's lymphoma. 'Muscular disorders': Myalgia; Myopathy; Rhabdomyolysis. 'Solid neoplasms': Bladder cancer; Bone cancer; Brain neoplasm; Breast cancer; Colon cancer; Gastric cancer; Hepatic cancer; Lung neoplasm malignant; Malignant melanoma; Ocular neoplasm; Pancreatic carcinoma; Prostate cancer; Renal cancer; Skin cancer; Thyroid cancer; Uterine cancer. 'Skin disorders': Eczema; Pain of skin; Skin disorder; Skin discoloration; Skin hemorrhage; Skin plaque. *ADR* adverse drug reaction, *PT* preferred term, *ROR* reporting odds ratio, *S* suspected

4.1 Strengths and Limitations

Our data were extracted from VigiBase and the major strength is the fact that VigiBase is a global spontaneous reporting database with more than 30 million reports coming from different countries. Analysis of this worldwide spontaneous reporting system enables better identification of rare and long-term adverse events and broader generalization of study results.

Our analysis aimed to assess the overall safety profiles of all the biologics approved for asthma treatment stratifying by therapeutic indication. Even if the safety profile of reports with a missing indication was similar to our study reports, we preferred to exclude these reports from our disproportionality analyses in order to precisely explore safety data of biologics by therapeutic use. We provided additional evidence concerning several safety issues, some of which have been previously discussed in scientific literature or by regulatory agencies. Case-by-case assessment related to unexpected suspected ADRs was carried out and referred to available data contained in line listings.

However, there are some limitations to acknowledge. In general, spontaneous reporting data are subject to several biases, including under-reporting, selective reporting and the lack of a denominator (total number of drug users), all of which prevent measuring absolute risk of suspected ADRs [86]. Disproportionality findings require cautious interpretation, evaluation of the risk of bias and consideration for alternative explanations other than causal association between the drug and the adverse event. Furthermore, potential limitations in sensitivity and precision of these methods should be taken into account [27, 28]. Indeed, clinical assessment (qualitative analysis) remains essential before drawing any causal inference from disproportionality

measures. Therefore, we cannot exclude that some signals of disproportionate reporting could be confounded by the underlying conditions, baseline risk and comorbidities in asthmatic patients who are treated with biologics, even if we conducted sensitivity analyses. Moreover, ROR values may also be influenced by several biases due to specific reporting trends in the spontaneous reporting system and to different marketing authorization dates of studied biologics.

As known, few ICSRs in VigiBase provide the desired quality level of information [87]. In our study, we excluded reports with missing indication even if they could be related to patients with asthma. Reports of suspected ADRs were often incomplete for causality assessment due to unavailability of clinical details in line listings and incomplete reporting of age, drug dosing, time to onset, comorbid conditions and concomitant drugs, thus limiting case-by-case assessment.

5 Conclusions

Overall, this study found good safety profiles of biologic drugs used in patients with severe asthma. Our findings confirmed well-known side effects related to asthma biologics already described such as general disorders, injection-site reactions, nasopharyngitis, headache and hypersensitivity, while some others (e.g. asthma reactivation or therapeutic failure) could be ascribed to the indication of use. Regarding anaphylactic reactions, all study biologics, except dupilumab, showed positive signals of disproportionate reporting; this risk is probably related to the immunogenic properties of the protein component of mAbs. Confounding effect by previous or concomitant use of corticosteroids that are used often concomitantly or immediately before starting biologic treatment has also been managed by performing an additional sensitivity analysis. Several potential safety signals (e.g. malignancies, rhythm disorders, pulmonary embolism, alopecia, etc.) have been identified. Further additional studies are required to assess and validate these potential safety signals.

Declarations

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Conflict of interest Gianluca Trifirò has served on advisory boards/seminars funded by SANOFI, Eli Lilly, AstraZeneca, Abbvie, Servier, Mylan, Gilead and Amgen in the past three years; he was the scientific director of a Master's program on pharmacovigilance, pharmacoepidemiology and real-world evidence which has received non-conditional grants from various pharmaceutical companies; he coordinated a pharmacoepidemiology team at the University of Messina until October 2020, which has received funding for conducting observational studies from various pharmaceutical companies (Boehringer Ingelheim, Daichii Sankyo, PTC Pharmaceuticals). He is also scientific coordinator of the academic spin-off 'INSPIRE srl' which has received funding for conducting observational studies from contract research organizations (RTI Health Solutions, Pharmo Institute N.V.). None of the above-mentioned activities are related to the topic of the manuscript. The other authors have no conflict of interest to disclose.

UMC statement VigiBase, the WHO global database of ICSRs, is the source of our information. The information comes from a variety of sources, and the probability that the suspected adverse event is drug-related is not the same in all cases; the information does not represent the opinion of the UMC or WHO.

Data availability The datasets generated and/or analyzed in the current study are available in the VigiBase repository. The data presented in this study are obtainable on request from the corresponding author.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Author contributions All authors contributed equally to this work. All authors read and approved the final manuscript.

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Authors and Affiliations

Paola Maria Cutroneo[1] · Elena Arzenton[2] · Fabiana Furci[3] · Fabio Scapini[2] · Maria Bulzomì[1] · Nicoletta Luxi[2] · Marco Caminati[4] · Gianenrico Senna[4,5] · Ugo Moretti[2] · Gianluca Trifirò[2]

✉ Gianluca Trifirò
gianluca.trifiro@univr.it

1 Unit of Clinical Pharmacology, Sicily Pharmacovigilance Regional Centre, University Hospital of Messina, Messina, Italy

2 Section of Pharmacology, Department of Diagnostics and Public Health, University of Verona, Verona, Italy

3 Provincial Healthcare Unit, Section of Allergy, Vibo Valentia, Italy

4 Department of Medicine, University of Verona, Verona, Italy

5 Asthma Centre and Allergy Unit, University of Verona and Verona University Hospital, Verona, Italy