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ORIGINAL ARTICLE

Biologics (mepolizumab and omalizumab) induced remission in severe asthma patients

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Abstract

Background: Asthma remission has emerged as a potential treatment goal. This study evaluated the effectiveness of two biologics (mepolizumab/omalizumab) in achieving asthma remission.

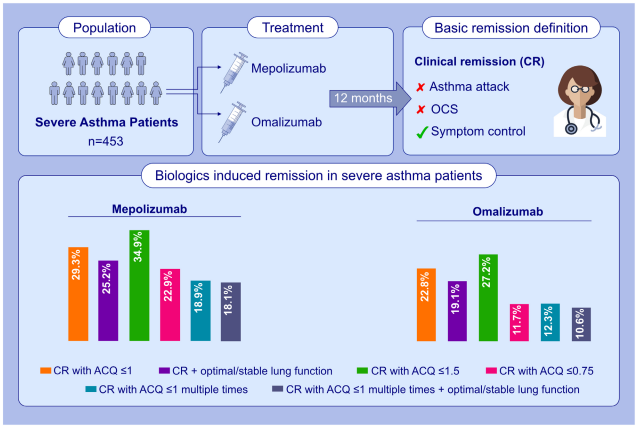
Methods: This observational study included 453 severe asthma patients (41% male; mean age ± SD 55.7 ± 14.7 years) from two real-world drug registries: the Australian Mepolizumab Registry and the Australian Xolair Registry. The composite outcome clinical remission was defined as zero exacerbations and zero oral corticosteroids during the previous 6 months assessed at 12 months and 5-item Asthma Control Questionnaire (ACQ-5) ≤1 at 12 months. We also assessed clinical remission plus optimization (post-bronchodilator FEV1 ≥80%) or stabilization (post-bronchodilator FEV1 not greater than 5% decline from baseline) of lung function at 12 months. Sensitivity analyses explored various cut-offs of ACQ-5/FEV1 scores. The predictors of clinical remission were identified.

Results: 29.3% (73/249) of AMR and 22.8% (37/162) of AXR cohort met the criteria for clinical remission. When lung function criteria were added, the remission rates were reduced to 25.2% and 19.1%, respectively. Sensitivity analyses identified that the remission rate ranged between 18.1% and 34.9% in the AMR cohort and 10.6% and 27.2% in the AXR cohort. Better lung function, lower body mass index, mild disease and absence of comorbidities such as obesity, depression and osteoporosis predicted the odds of achieving clinical remission.

Conclusion: Biologic treatment with mepolizumab or omalizumab for severe asthma-induced asthma remission in a subgroup of patients. Remission on treatment may be

an achievable treatment target and future studies should consider remission as an outcome measure.

KEYWORDS
asthma, mepolizumab, omalizumab, remission



GRAPHICAL ABSTRACT

The effectiveness of mepolizumab and omalizumab in achieving asthma remission was evaluated in an observational study. The basic definition consists of no asthma attack, no oral corticosteroids (OCS) use and ACQ5 ≤1 at 12 -months. We also evaluated various definitions and asthma control questionnaire (ACQ) cut-offs in sensitivity analyses. The observed remission rate ranged between 18.1% and 34.9% in mepolizumab and 10.6% and 27.2% in omalizumab cohorts.

1 | INTRODUCTION

Asthma is a common chronic respiratory disease affecting over 300 million people globally and leading to a substantial health and economic burden. Asthma is heterogeneous with a complex multifaceted aetiology and pathobiology. These factors need to be considered in treatment approaches. Advances in asthma medications including the introduction of inhaled corticosteroids (ICS) and long-acting beta2-agonist (LABA) in the 1990s improved asthma treatment outcomes with better symptom control and reduced frequency of asthma attacks. Consequently, asthma treatment goals seek to minimize acute exacerbations and achieve symptom control.1,2 The introduction of biologics has revolutionized asthma management during the last decade and the treatment goals have advanced to minimize treatment toxicities such as oral corticosteroid (OCS) burden and prevent accelerated loss of lung function. Although these therapeutic advances in care reduce the overall burden experienced by people with asthma and may modify the disease progression, until recently, there was less attention toward achieving a cure or even asthma remission.3,4 Open access publishing facilitated by The University of Newcastle, as part of the Wiley - The University of Newcastle agreement via the Council of Australian University Librarians.

Cure as a treatment goal may not be achievable in the current environment since cure requires complete and sustained elimination of clinical symptoms, normalization of the underlying pathology and no requirement of ongoing treatment. It is far from clear whether currently available medications have the potential to completely reverse the underlying pathology such as airway remodelling. However, research now suggests that it is feasible to aim for remission, a step closer to cure. The improved efficacy achieved with newer add-on biologics therapies over and above standard therapy may lead to remission in otherwise persistent asthma.[3–5] Asthma remission is characterized by a high level of disease control, including the elimination of symptoms and exacerbations for a prolonged period of time, and optimization or stabilization of lung function with or without ongoing treatment. Complete remission also requires resolution of underlying pathology.[3,6]

This is an emerging area, and various definitions of remission have been proposed with varying degrees of rigour in the criteria used.[3,6] Recent reviews emphasized the potential of biologics in achieving remission.[3,5] In response, researchers are racing to publish remission data on biologics. A few recent small studies,[7–9] a secondary analysis of a clinical trial dataset[10] and two recent observational studies[11,12] have evaluated the efficacy of various biologics in achieving remission. All these studies used different definitions and various biomarker cut-off points to identify remission. It is important to compare different definitions and various biomarker cut-off points in sensitivity analyses to establish and propose a uniform definition for asthma remission. It is also necessary to identify the comparative effectiveness of different biologics in achieving remission.

In this study, we evaluated the effectiveness of two biologics, mepolizumab and omalizumab, in achieving clinical remission (no exacerbations, no OCS use and a high level of symptom control) in severe asthma patients. We also explored clinical remission with optimization or stabilization of lung function. Our sensitivity analyses explored various cut-offs of 5-item Asthma Control Questionnaire (ACQ-5)/FEV1 and evaluation of ACQ at multiple time points. In addition, we identified the predictors of clinical remission and also the impact of comorbidities on asthma remission.

2 | METHODS

This study represents a secondary analysis of two drug registries. The details of the registries are provided in Table 1.

2.1 | Outcome measures

We explored various definitions of remission proposed by our team and others.[3,6] Consistent outcome measures were used in both registries.

The primary remission definition included the following components, and is referred to as clinical remission: zero exacerbations and zero OCS use (i.e. absence of both OCS burst and maintenance OCS) during the previous 6 months when assessed at 12 months and ACQ-5 ≤1 at 12 months. We also explored clinical remission plus stabilization or optimization of lung function at 12 months.

Exacerbations were assessed using a standardized exacerbation module[13] and 'exacerbation free' was defined as no OCS burst (not even a single dose) or hospitalization or emergency department visit due to asthma during the evaluation period. Optimization of lung function was defined as post-bronchodilator forced expiratory volume in 1 s (FEV1) ≥80% predicted. Stabilization of lung function was defined as a change in post-bronchodilator FEV1 not greater than a 5% decline from the baseline. A sensitivity analysis also explored a change in post-bronchodilator FEV1 not greater than a 10% decline from the baseline.[14,15]

Additional sensitivity analyses explored various ACQ cut-offs such as 1.5 and 0.75 and evaluation of ACQ at multiple time points (i.e. ACQ ≤1 at 6 and 12 months). Another sensitivity analysis explored the most stringent clinical remission definition: zero exacerbations, zero OCS use, ACQ ≤1 at 6 and 12 months plus stabilization or optimization of lung function at 12 months.

TABLE 1 Datasets included in the analysis.

Australian Mepolizumab Registry (*AMR*): An investigator-initiated, observational database of patients with severe eosinophilic asthma undergoing mepolizumab therapy. Patients were registered consecutively between January 2017 and April 2019 at 20 specialist clinics. Eligible patients need to have met the criteria set by the Australian Government Pharmaceutical Benefits Scheme (PBS) to initiate subsidized mepolizumab therapy. The AMR was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) (ACTRN12618001497291). The detailed methodology and patient eligibility are published elsewhere[23,26]
Australian Xolair Registry (*AXR*): An investigator-initiated, observational database of patients with severe allergic asthma undergoing omalizumab therapy. Patients were registered consecutively between October 2011 and June 2014 at 21 specialist clinics. Eligible patients need to have met the criteria set by the Australian Government PBS to initiate subsidized omalizumab therapy. The detailed methodology and patient eligibility are published elsewhere[27–29]
Each registry was approved by the centres' relevant Human Research Ethics Committee, and all patients provided written informed consent prior to enrolment

2.2 | Statistical analysis

Statistical analyses were performed using Stata 14.2 (StataCorp); results are reported as mean ± SD for normally distributed data and median (quartiles 1 and 3 [Q1, Q3]) for non-normally distributed data. Proportions of participants meeting the composite outcome remission and individual remission criteria were reported descriptively.

Both datasets were combined to identify the predictors of clinical remission using a complete case analysis method. Univariate analysis (chi-squared test or Fisher's exact test for categorical data and Student's *t*-test or the Wilcoxon rank-sum test for continuous data) was used initially to explore the predictors. The variables with a $p \leq .2$ in the univariate analysis were entered into the multivariate model. A backwards selection of the variables was used, with an exclusion criterion of a $p > .2$. The removal of variables was completed one at a time. The revised model was compared with the previous level using the Likelihood ratio test, checking for an improvement in fit. The same number of participants was used in the model each time, allowing for valid comparison with the full model via the Likelihood ratio test. The goodness of fit of the final model was confirmed by the Hosmer–Lemeshow test. Further logistic regression model with the same methodology described above explored the impact of comorbidities in achieving remission with biologics. Results were considered statistically significant when $p < .05$.

3 | RESULTS

The baseline characteristics of the 453 severe asthma participants included in this analysis are presented in Table 2. The baseline asthma medications are presented in Table S1.

3.1 | AMR dataset

AMR participants ($N = 278$) had a median age of 59.4 (50.2, 68.2) years and 41.0% were male. Their median (Q1, Q3) ACQ-5 score

TABLE 2 Baseline characteristics.

	AMR (*N* = 278)	AXR (*N* = 175)
Age (years)	59.41 (50.17, 68.18)	53.15 (42.69, 61.39)
Male[a]	114 (41.0%)	70 (40.2%)
BMI (kg/m^2)	29.71 (25.77, 34.58)	28.90 (24.70, 34.10)
Smoking status[b]		
Never	170 (61.8%)	92 (68.1%)
Ex	102 (37.1%)	38 (28.1%)
Asthma duration (years)	29.51 (13.40, 46.77)	16.45 (3.79, 37.79)
OCS burst in the past year	262 (94.2%)	155 (88.6%)
Hospitalization in the past year	76 (27.3%)	62 (35.4%)
ED visit in the past year	46 (16.5%)	48 (27.4%)
Unscheduled GP visit for asthma in the past year	72 (25.9%)	61 (34.9%)
FEV1%predicted Pre BD	57.06 (17.80)	56.35 (20.07)
FVC %predicted Pre BD	78.69 (17.16)	76.60 (19.56)
FEV1/FVC Pre BD	0.57 (0.13)	0.58 (0.12)
FEV1%predicted Post-BD	62.53 (18.91)	63.36 (20.99)
FVC %predicted Post-BD	83.77 (16.39)	84.46 (19.79)
FEV1/FVC Post-BD	0.59 (0.14)	0.59 (0.12)
ACQ-5 mean	3.40 (3.00, 4.20)	3.60 (3.00, 4.20)
AQLQ mean	3.75 (2.97, 4.67)	3.38 (2.84, 4.56)
mOCS	118 (42.4%)	72 (41.1%)
mOCS dose in mOCS users (mg/day)	10.00 (5.00, 12.50)	10.00 (7.50, 15.00)
Triple Therapy (ICS/LABA/LAMA)	163 (58.6%)	56 (32.0%)

Note: Data are median (IQR), *n* (%). Missing values: [a]AXR 1; [b]AMR 3 and AXR 40.

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; AMR, Australian Mepolizumab Registry; AQLQ, Asthma Quality of Life Questionnaire; AXR, Australian Xolair Registry; BD, bronchodilator; BMI, body mass index; ED, Emergency Department; FEV1, Forced Expiratory Volume in 1 s; FVC, forced vital capacity; GP, general practitioner; mOCS, maintenance OCS; OCS, oral corticosteroid.

at baseline was 3.4 (3.0, 4.2) and mean ± SD FEV1% predicted post-BD was 62.5 ± 18.9 with 94.2% experienced an OCS burst in the previous year and 42.4% were on maintenance OCS at baseline.

3.2 | AXR dataset

AXR participants (*N* = 175) had a median age of 53.2 (42.7, 61.4) years and 40.2% were male. Their median ACQ-5 score at baseline was 3.6 (3.0, 4.2) and mean FEV1% predicted post-BD was 63.4 ± 21.0 with 88.6% experienced an OCS burst in the previous year and 41.1% were on maintenance OCS at baseline.

3.3 | Remission assessment

The proportions of participants achieving the predefined definitions of clinical remission with each treatment are presented in Table 3 and Figure 1.

3.3.1 | Mepolizumab (AMR)

Clinical remission was achieved by 29.3% of participants treated with mepolizumab and 25.2% achieved clinical remission plus lung function criteria. The remission rate ranged between 18.9% and 34.9% in sensitivity analyses.

3.3.2 | Omalizumab (AXR)

Clinical remission was achieved by 22.8% of participants treated with omalizumab and 19.1% achieved clinical remission plus lung function criteria. The remission rate ranged between 11.7% and 27.2% in sensitivity analyses.

3.3.3 | Predictors of achieving clinical remission

Following the univariate analysis, 10 variables (age, gender, BMI, asthma duration, post-bronchodilator % predicted FEV1, ACQ mean, AQLQ

TABLE 3 Remission analysis.

Item	Primary remission criteria	Mepolizumab		Omalizumab	
		N[a]	*N* (%)[b]	*N*[a]	*N* (%)[b]
1	ACQ-5 ≤1	249	111 (44.6)	162	58 (35.8)
2	No exacerbations	278	179 (64.4)	175	109 (62.3)
3	No maintenance OCS use	278	216 (77.7)	175	149 (85.1)
	Clinical remission	249	73 (29.3) (23.7, 35.4)[c]	162	37 (22.8) (16.6, 30.1)c
4	Optimization/stabilization of lung function (FEV1%predicted post-BD ≥80% or not greater than 5% decline from baseline)	128	109 (85.2)	49	32 (65.3)
	Clinical remission + lung function criteria	127	32 (25.2) (17.9, 33.7)[c]	47	9 (19.1) (9.1, 33.3)[c]
Sensitivity analyses					
1	Clinical remission using ACQ cut off 1.5	249	87 (34.9)	162	44 (27.2)
2	Clinical remission using ACQ cut off 0.75	249	57 (22.9)	162	19 (11.7)
3	Clinical remission evaluating ACQ at multiple timepoints (i.e. ACQ ≤1 at 6 and 12 months)	249	47 (18.9)	162	20 (12.3)
4	Clinical remission with ACQ ≤1 at multiple time points (6 and 12 months) plus lung function criteria	127	23 (18.1)	47	5 (10.6)
5	Clinical remission + lung function criteria (FEV1%predicted post-BD ≥80% or not greater than 10% decline from baseline)	127	35 (27.6)	47	11 (23.4)

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; *N*, number of participants; OCS, oral corticosteroid.

[a]Total observations available.

[b]The proportions are based on the available observations.

[c]CI of proportions.

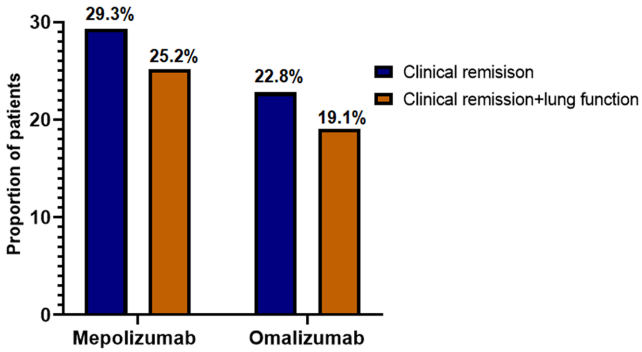


FIGURE 1 The proportion of participants who achieved clinical remission criteria and clinical remission with lung function criteria in each dataset.

mean, OCS burst, hospitalization in the previous year and maintenance OCS use status at baseline) were entered into the multivariable model (Table S2). Of those, six variables (gender, BMI, post-bronchodilator % predicted FEV1, mean ACQ, maintenance OCS use status at baseline and hospitalization in the previous year) were retained in the model (Table 4). The odds of achieving clinical remission increased by 2% for each unit increase in post-bronchodilator % predicted FEV1. It reduced by 9% for each unit increase in BMI, 42% for each unit increase in ACQ, 65% for those who were on maintenance OCS at baseline and 68% for those who were hospitalized for asthma exacerbation in the previous year. The Hosmer–Lemeshow test indicated a good model fit and there was no collinearity in the final model. The model correctly classified 73.8% of remission cases.

3.3.4 | Impact of comorbidities in achieving remission

Following univariate analyses, eight comorbidities (anxiety, chronic obstructive pulmonary disease, depression, obesity, obstructive sleep apnoea, vocal cord dysfunction, osteoporosis and other psychiatric illness) were entered into the multivariable model (Table S3). Of those, three variables (depression, obesity and osteoporosis) were retained in the model (Table 4). The odds of achieving clinical remission decreased by 60%, 59% and 65% for those with depression, obesity and osteoporosis, respectively. The Hosmer–Lemeshow test indicated a good model fit and there was no collinearity in the final model. The model correctly classified 73.2% of remission cases.

4 | DISCUSSION

This study evaluated the possibility of achieving treatment-induced remission in severe asthma patients using two biological agents, mepolizumab and omalizumab. Using predefined multicomponent definitions of clinical remission aligned with the literature, we found that after 12 months of treatment with mepolizumab or omalizumab, a

TABLE 4 Predictors of clinical remission.

Variables	Odds ratio	*p*-value	95%CI
Gender (Male)	0.48	.071	0.21–1.06
BMI	0.91	.002	0.85–0.96
FEV1%predicted Post BD	1.02	.032	1.002–1.05
ACQ mean	0.58	.018	0.37–0.91
mOCS at baseline	0.35	.010	0.16–0.78
Hospitalization	0.32	.032	0.11–0.90
Comorbidities affecting remission			
Depression	0.40	.012	0.19–0.82
Obesity	0.41	.009	0.21–0.80
Osteoporosis	0.35	.004	0.17–0.72

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; BD, bronchodilator; BMI, body mass index; CI, confidence interval; FEV1, forced expiratory volume in 1 s; mOCS, maintenance oral corticosteroid.

subset of patients (29% and 23%, respectively) achieved clinical remission. In order to improve the precision of the remission definition, we used sensitivity analyses to explore various categories and cut-offs that are reported in the literature. These results demonstrate that on-treatment asthma remission is a realistic target for severe asthma patients for those treated with biological agents.

The observed effect may not be the complete effect of these agents and a longer duration of treatment might further improve the proportion of patients achieving remission. Previous spontaneous remission analyses identified mild asthma as a predictor of asthma remission.[3] It is important that the current study included the most difficult-to-treat asthma population and observed that remission was an achievable outcome. Hence, these treatments might provide an even larger effect in patients with milder disease, as has been observed with other inflammatory diseases such as rheumatoid arthritis.

A handful of recent studies ($N = 7$) have explored the remission rate induced by various biologics.[8–12,16] These studies evaluated several biologics concurrently ($N = 4$),[7,9,12,16] or a single agent such as mepolizumab-induced remission[11] and benralizumab-induced remission.[8] A post hoc analysis evaluated the efficacy of benralizumab in achieving clinical remission using data from three phase-III clinical trial datasets[10] (SIROCCO,[17] CALIMA,[17] ZONDA[18]). Three of the seven studies that report on biologic-induced asthma remission were small, including less than 55 participants.[7–9] The studies used a wide range of definitions including various exacerbation/symptom/OCS criteria, biomarkers and cut-offs. The exacerbation definition (e.g. severe or all exacerbations), evaluation period or OCS criteria (e.g. point estimate at final follow-up, not allowing any OCS use for a certain period etc.) reported in many of these studies are not identical, making comparison between agents difficult. The reported remission rate ranged between 15% and 38% in these studies. In addition, a small outlier study reported a remission rate of 69%.[7] The observed remission rate in our study falls within this range. The previous mepolizumab study reported a remission rate of 37%, slightly more than the remission rate observed in the current mepolizumab cohort, but the former used more lenient criteria which allowed mild exacerbations (OCS use for less than 3 days) during the remission period and evaluated OCS free as a point estimate at 12 months. Consequently, the clinical remission rate may not be comparable between these studies as they differ substantially in remission criteria and included a heterogenous patient population. This highlights the importance of having a uniform definition of asthma remission when assessing the efficacy of various biologics in achieving remission.

It is important to define the remission concept in severe asthma carefully. The suggested components in the literature include no OCS use for asthma management, no exacerbations, well-controlled symptoms and stabilization/optimization of lung function for a prolonged period.[3,6] All previous remission studies categorize people experiencing severe exacerbations as not under remission, but experiencing mild/moderate exacerbations (e.g. exacerbations leading to 1–2 days of OCS treatment) or requiring maintenance OCS to prevent exacerbations (suggesting active inflammation) are under debate and these factors indicate some levels of disease activity. In the chronic inflammatory disease of rheumatoid arthritis, clinicians have found it useful to consider low disease activity and remission as two different concepts.[19,20] In this study, we considered remission and control as different concepts and applied a stringent definition of asthma remission. We categorized people who used at least one dose of OCS or experienced even a mild exacerbation (e.g. single dose of OCS) during the evaluation period as not under remission, as remission requires complete suppression of disease activity.[3,6] We also evaluated several cut-points for symptom suppression using the ACQ and found that this influences the prevalence of asthma remission (Table 3). These data can be constructively used to reach a consensus definition of asthma remission. Likewise, clinical remission also requires optimization or stabilization of lung function in addition to eliminating symptoms and exacerbations.[3,6] However, many factors need to be considered when considering lung function in the remission definition. For example, the natural decline of lung function and the effect of gender on this decline, the daily variability of lung function, the variability of lung function based on bronchodilator use and the influence of factors such as age, smoking status, BMI, ethnicity and menopausal status.[15,21,22] A further issue is the effect of many years of active disease in causing incompletely reversible airflow obstruction, which may not be modified by therapy. Some data suggest that biologics may improve lung function,[23,24] but it is far from clear whether this improvement produces an effect over and above the factors described above, and how long it will take to produce an effect. Also, it is important to note that the patients in this study had significantly lower lung function at baseline (FEV1%predicted post-BD ~63%). To address these issues, we used a composite criterion for lung function, which allows both optimization (including all those who achieved a normal lung function) and stabilization of lung function. To establish stabilization, we used two cut-offs of FEV1%predicted post-BD, that is, no more than 5% decline from baseline and no more than 10% decline from baseline.[14,15] Our data show the impact of these criteria on the remission definition. However, lung function criteria need to be further streamlined in future studies. We have also assessed various

ACQ-5 cut-offs and assessed ACQ-5 at multiple time points (to establish the sustained absence of symptoms) in sensitivity analyses. The most stringent definition we used in the sensitivity analysis was no exacerbations and no OCS use in the previous 6 months, ACQ-5 ≤1 at both 6 and 12 months and optimization or stabilization of lung function at 12 months. A subgroup in both mepolizumab (18.1%) and omalizumab (10.6%) cohort met this stricter criterion raising the hope for next-generation asthma management goals.

Future pre-planned remission studies may also establish complete remission using specific biomarkers considering baseline pathobiology of the disease (e.g. sputum/blood eosinophils for eosinophilic asthma, sputum neutrophils for neutrophilic asthma, fractional exhaled nitric oxide [FeNO] for allergic asthma, etc.). Future studies may also consider a longer-term follow-up as disease stabilization and relapse may depend on the length of remission.

Regression analysis found that the lower BMI; higher FEV1% predicted pre-BD (an indicator of lung function); and baseline ACQ score, maintenance OCS use status and hospitalization history (indicators of asthma severity) were predictive of remission. Comorbidities such as obesity, depression and osteoporosis were also associated with reduced odds of remission, indicating the potential importance of the treatable traits approach (identifying and treating all measurable and treatable clinically relevant factors) in addition to biologic therapy to achieve remission.[25] These findings reiterate the association between baseline asthma severity, lung function and comorbidities with clinical remission.[3,16]

The study used data from two large real-world datasets. The specific strengths and limitations of these datasets were published elsewhere.[23,26,27] Limitations of the current analysis are the retrospective nature of the analysis, regression to the mean (i.e. some of the observed remissions in this study might be a natural phenomenon) and the uncertainty of the current definitions of asthma remission (the definitions might change in future).

5 | CONCLUSION

This study confirmed that clinical remission is possible in a subset of severe asthma patients undergoing biologic therapies. The positive trend observed among these patients raises the hope of asthma remission as a realistic therapeutic goal.

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AUTHOR CONTRIBUTIONS

Peter G. Gibson, Dennis Thomas and Vanessa M. McDonald developed the concept. Peter G. Gibson is the data custodian of AMR and AXR datasets. Sean Stevens is the statistician who conducted the data analysis. All authors contributed towards developing the remission definition and revising and finalizing the manuscript.

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CONFLICT OF INTEREST STATEMENT

D. Thomas reports grants from GlaxoSmithKline, outside the submitted work. V.M. McDonald reports grants and personal fees from GlaxoSmithKline, AstraZeneca and Menarini, outside the submitted work. S. Stevens has nothing to disclose. E.S. Harvey reports grants from GlaxoSmithKline that were paid to her employer, during the conduct of the study. M. Baraket has nothing to disclose. P. Bardin reports per patient trial participation fees from Monash Lung and Sleep, during the conduct of the study; personal fees for advisory board work, outside the submitted work. J. Bowden reports personal fees for advisory board work from GlaxoSmithKline, AstraZeneca and Novartis, outside the submitted work. S. Bowler reports personal fees for advisory board work from GlaxoSmithKline, outside the submitted work. J. Chien reports personal fees from GlaxoSmithKline, outside the submitted work. L.P. Chung reports honorariums for educational activities and /or consultation fees from AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Boehringer Ingelhein and Menarini, outside the submitted work. A. Gillman reports personal fees for advisory board work and education from GlaxoSmithKline, outside the submitted work. M. Hew reports grants and personal fees from AstraZeneca, GlaxoSmithKline and Novartis, personal fees from Sanofi, Teva and Seqirus, outside the submitted work; all paid to his institutional employer Alfred Health. S. Hodge has nothing to disclose. A. James has nothing to disclose. C. Jenkins reports personal fees for advisory board work, conducting meetings and developing educational content, and non-financial support from AstraZeneca, personal fees for advisory board work from Boehringer Ingleheim, grants and personal fees for advisory board work from GlaxoSmithKline, personal fees for advisory board work, facilitating symposia and developing educational content from Novartis, outside the submitted work. C. Katelaris reports grants from GlaxoSmithKline, during the conduct of the study; grants and personal fees for advisory board work and lectures from Sanofi, Novartis and CSL, personal fees from Seqirus and Takeda, outside the submitted work. G.P. Katsoulotos has nothing to disclose. D. Langton has received fees from GlaxoSmithKline for participation in severe asthma advisory boards. J. Lee has received fees for providing unrelated independent medical advice for GlaxoSmithKline and has received speaker fees for medical education purposes from Boehringer Ingelheim, GlaxoSmithKline and AstraZeneca. G. Marks has nothing to disclose. M. Peters reports personal fees for advisory board work from Sanofi Genzyme, Novartis Pharmaceuticals and AstraZeneca, outside the submitted work. N. Radhakrishna reports grants from Sanofi and speaker fees from GSK, AstraZeneca, Mundipharma, Sanofi and Mylan. P.N. Reynolds has nothing to disclose. J. Rimmer reports speaker/sponsorship fees from GSK, Stallergenes and Sanofi. P. Sivakumaran has nothing to disclose. J. W. Upham has received speaker fees, conference travel support and consultancy fees from AstraZeneca, GSK, Novartis, Boehringer Ingelheim and Sanofi. P. Wark reports grant from GlaxoSmithKline. I.A. Yang has nothing to disclose. Gibson reports grants from GlaxoSmithKline, during the conduct of the study; personal fees for lectures from AstraZeneca, GlaxoSmithKline and Novartis, grants from AstraZeneca and GlaxoSmithKline, outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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