Real-world Omalizumab and Mepolizumab treated Difficult Asthma Phenotypes and their Clinical Outcomes

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Data are available upon reasonable request from the corresponding author.

# Abstract

**Background**Omalizumab and Mepolizumab are biologic drugs with proven efficacy in clinical trials. However, a better understanding of their real-world effectiveness in severe asthma management is needed.

**Objectives**
To better understand the real-world effectiveness of Omalizumab and Mepolizumab, elucidate the clinical phenotypes of patients treated with these drugs, identify baseline characteristics associated with biologic response and assess the spectrum of responses to these medications.

**Methods**
Using real-world clinical data, we retrospectively phenotyped biologic naïve patients from the Wessex AsThma CoHort of difficult asthma (N=478) commenced on Omalizumab (N=105) or Mepolizumab (N=62) compared to severe asthma patients not receiving biologics (SNB, N=178). We also assessed multiple clinical endpoints and identified features associated with response.
**Results**
Compared to SNB, Omalizumab patients were younger, diagnosed with asthma earlier, and more likely to have rhinitis. Conversely, compared to SNB, Mepolizumab patients were predominantly older males, diagnosed with asthma later, and more likely to have nasal polyposis but less dysfunctional breathing. Both treatments reduced exacerbations, Acute Healthcare Encounters [AHE] (emergency department or hospital admissions), maintenance oral corticosteroid dose, and improved Asthma Control Questionnaire 6 (ACQ6) scores. Omalizumab response was independently associated with more baseline exacerbations (P=0.024) but fewer AHE (P=0.050) and absence of anxiety (P=0.008). Lower baseline ACQ6 was independently associated with Mepolizumab response (P=0.007). A composite group of non-responders demonstrated significantly more psychopathologies and worse baseline subjective disease compared to responder groups.

**Conclusions and Clinical Relevance**In a difficult asthma cohort, Omalizumab and Mepolizumab were used in distinct clinical phenotypes but were both multidimensionally efficacious. Certain baseline clinical characteristics were associated with poorer biologic responses, such as psychological co-morbidity, which may assist clinicians in biologic selection. These characteristics also emphasize the need for comprehensive approaches to support these patients.

# Abbreviations:

ACQ6: Asthma Control Questionnaire-6

AHE: Acute Healthcare Encounters

AQLQ: Asthma Quality of Life Questionnaire

FENO: Fractional Exhaled Nitric Oxide

FEV1% : Percent predicted forced expiratory volume in 1 second

HADS: Hospital anxiety and depression scale

IgE: Immunoglobulin E

IQR: Interquartile range

mOCS: Maintenance oral corticosteroid

MDT: Multi-Disciplinary Team

MID: Minimally important difference

NICE: National Institute for Health & Care Excellence

OCS: Oral corticosteroids

PBE: Peripheral blood eosinophil count

RCTs: Randomised controlled trials

SD: Standard deviation

SNB: severe asthma, non-biologic group

WATCH: Wessex AsThma CoHort of difficult asthma

# Introduction

Asthma biologic therapies herald a potential era of personalized medicine1 that better addresses severe asthma’s heterogeneity. In the United Kingdom (UK), four biologics are currently approved for use in severe asthma2. The two in longest use are the anti-immunoglobulin E (IgE) biologic, Omalizumab and the anti-interleukin-5 biologic, Mepolizumab. Both agents were highly effective in phase-III randomised controlled trials (RCTs)3–6 and have been widely adopted into clinical practice. However, RCT populations are not reflective of real-world patients7,8. Brown et al. highlighted that only 9.8% of their severe asthma cohort met enrolment criteria of Phase-III asthma biologic RCTs9. Thus, as the portfolio of biologics continues to expand, real-world data on these drugs are urgently needed10 to better understand their place in real-life severe asthma management. Additionally, an evolving paradox of biologic choice places a greater onus on clinicians to “get it right the first time”, to save costs and improve patient outcomes. To guide asthma biologic selection, it is imperative to understand patient phenotypes best suited for individual drugs, identify features associated with response, and also consider how best to judge clinical impact of these therapies. Therefore, to help address these needs, we present parallel real-world clinical data on two widely used asthma biologics, Omalizumab and Mepolizumab, from the thoroughly characterized, longitudinal Wessex AsThma CoHort of difficult asthma (WATCH)11.

# Methods

WATCH is a prospective observational study of patients managed in a tertiary difficult asthma clinic at University Hospital Southampton, UK with “high dose therapies” and/or “continuous or frequent use of oral corticosteroids (OCS)” as per the British Thoracic Society Adult Asthma Management Guidelines 201612. Detailed study methodology is described elsewhere11. The study had ethical approval from the West Midlands – Solihull Research Ethics Committee (14/WM/1226) and written informed consent was obtained for all participants.

We conducted a retrospective study of biologic naïve WATCH patients commenced on Omalizumab or Mepolizumab between June 2006 and May 2019. Our aims were to 1. define phenotypic characteristics of Omalizumab or Mepolizumab patients against severe asthma patients who remained biologic naive. 2. Better understand the real-world effectiveness of both agents from biologic trial data. 3. Identify baseline characteristics associated with response. 4. Assess the spectrum of responses to these biologics.

Biologic eligibility was based on conventional criteria following the National Institute for Health & Care Excellence (NICE) guidance13,14. Briefly, for Omalizumab13, eligibility criteria were: confirmed allergic IgE‑mediated asthma (perennial allergen sensitisation) and the continuous or frequent treatment with OCS (≥4 courses in the previous year) and met dosing criteria. For Mepolizumab14, eligibility criteria were defined as a peripheral blood eosinophil (PBE) count ≥300 cells/microlitre in the previous 12 months, and either having ≥4 OCS courses in the previous 12 months or being on maintenance OCS (mOCS) ≥5 mg per day over the previous 6 months.

Biologic trials were conducted and data were collected according to standard clinical practice in the UK. Specifically, data were collected at baseline (first biologic visit) and subsequent treatment visits: 2-4 weekly for Omalizumab and 4-weekly for Mepolizumab. Data collected at these visits included Asthma Control Questionnaire-6 (ACQ6), the incidence of exacerbations (exacerbations requiring an acute OCS course/increase in mOCS), the incidence of emergency department or hospital admissions (Acute Healthcare Encounters [AHE]), current mOCS dose and Clinic percent predicted FEV1 (FEV1%). Hospital anxiety and depression scale (HADS) and Asthma Quality of Life Questionnaire (AQLQ) were collected at baseline and final visits for Mepolizumab. Fractional Exhaled Nitric Oxide (FENO) was collected at all Mepolizumab visits, but only at the baseline Omalizumab visit, as per clinical practice in the prior decade. Co-morbidity, anthropometric and demographic data were extracted from the WATCH database. Exacerbations and AHE were annualised for comparisons.

Biologic response was determined by the clinical MDT (Multi-Disciplinary Team), using separate biologic-specific standard national criteria13,14. For Omalizumab, response was assessed using the ‘Global Evaluation of Treatment Effectiveness’ tool 15–17. For Mepolizumab, response was defined as a ≥50% reduction in exacerbations or mOCS dose without loss of asthma control14. In borderline responders based on standard criteria, factors such as changes in AHE, symptom control or quality-of-life would additionally guide Mepolizumab continuation. As per standard clinical practice in the UK, treatment trials were typically 16 weeks for Omalizumab and 12 months for Mepolizumab. However, equivocal trials were extended up to 32 weeks for Omalizumab and 18 months for Mepolizumab.

We defined ‘super-response’ separately for both biologics, given the separate eligibility and continuation criteria. Omalizumab super-responders were defined as 16-week responders who had the top quartile of percentage reduction in mOCS dose while being exacerbation and AHE free; or if not on mOCS, were exacerbation and AHE free. For Mepolizumab, super-responders were defined as 12-month responders who had the top quartile of percentage reduction in mOCS dose, while having a synchronous reduction in exacerbations; or if not on mOCS, had the top quartile of percentage reduction in exacerbations.

To describe the biologic-naïve characteristics of the biologic treated groups, a common comparator ‘severe asthma, non-biologic’ (SNB) group was extracted from WATCH. SNB subjects (N=178) were participants who in the past year either had ≥4 exacerbations or ≥1 AHE or were on mOCS, but did not commence biologics during the study period. Comparisons were made using baseline biologic data for the biologic treated groups and WATCH enrolment data for the SNB group. Additionally, biologic treated groups were mapped onto four age-of-onset/sex clinical clusters (male/early-onset [<18 years], female/early-onset, male/adult-onset [≥18 years], female/adult-onset) that we recently described18, for further phenotyping.

Statistical analysis was performed with SPSS 26 (IBM Corp, NY, USA), GraphPad Prism 9 (GraphPad Software, California, USA) and R (R Foundation, Vienna, Austria). Continuous variables were presented as Mean (Standard deviation[SD]) or Median (Interquartile range[IQR]). Categorical data were presented as percentage(frequency). Baseline characteristics were compared with unpaired t-tests, Mann-Whitney U tests, Chi-square tests and Fishers Exact tests as appropriate. Baseline data were compared against end-of-trial data using paired t-tests, Wilcoxon-Signed Rank test, and McNemar test as appropriate. Multiple logistic regression (backward variable selection) was performed using variables trending towards significance (P<0.2) at univariate analyses, to determine variables independently associated with response and super-response to the biologics. Statistical significance was set at P-value <0.05.

# Results

Among the WATCH cohort, 37.7% (182/478) commenced on biologic trials with either Omalizumab or Mepolizumab (Figure 1). Nearly two-thirds (Figure 1) were with Omalizumab (63.7%; 116/182) and the rest were with Mepolizumab (36.3%; 66/182). Eleven from Omalizumab analysis and four from Mepolizumab analysis were excluded due to unavailable biologic trial data (Figure 1).

**Baseline characteristics of Biologic Treated Groups vs SNB (comparator) group**

Compared to SNB subjects, neither biologic groups were significantly different in terms of baseline exacerbations or AHE (Table 1 and Table 2). However, the biologic treated groups had significantly higher FENO, worse lung function and more mOCS dependency (Table 1 and Table 2).

Compared to SNB subjects, Omalizumab treated subjects had a significantly younger age of asthma onset (Table 1). They were also more ethnically diverse, were all atopic and had a significantly greater prevalence of rhinitis, allergic bronchopulmonary aspergillosis, and nasal (polyps/sinus) surgery.

Conversely, compared to SNB subjects, Mepolizumab treated subjects had a significantly higher maximum PBE (Table 2), were older, diagnosed with asthma later in life, and predominantly male. Additionally, they had a significantly higher prevalence of nasal polyposis and nasal (polyps/sinus) surgery but less dysfunctional breathing.

**Omalizumab response**Overall, 99.0%,(104/105) patients completed Omalizumab trials (Figure 1). One person withdrew due to side-effects. Omalizumab (Figure 2) significantly reduced exacerbations [Median(IQR), baseline: 5(3) to 0(3), P<0.001], mOCS dose [Median(IQR), baseline: 10(10-20) to 10(5-15), P=0.002], AHE [Median(IQR), baseline: 1(2) to 0(0), P=0.003] and the proportion of patients with multiple (>1) AHE [Baseline: 36.5%,(38/104) to 15.4%,(16/104), P=0.007]. Omalizumab (Figure 2) also significantly improved asthma control [Mean(SD) ACQ6, baseline: 2.96(1.26) to 1.64(1.12), P <0.001], Clinic FEV1% [Mean(SD), baseline: 67.34(25.93) to 75.40(21.79), P<0.001] and reduced PBE (cells/μL) [Median(IQR) baseline: 200(400) to 200(200), P=0.002]. However, it did not significantly reduce mOCS dependency [Baseline: 48.1%, (50/104) to 41.6% (42/101), P=NS].

**Omalizumab responders, non-responders and super-responders**
Based on our definitions, of Omalizumab subjects who completed trials (Figure 1), 88.5%, (92/104) were responders and 33.7%, (35/104) were super-responders. Compared to Omalizumab non-responders, Omalizumab responders (Supplementary Table E1) were significantly older [Mean(SD) Age, Responder: 53(15) vs non-responder: 44(12), P=0.025] and had lower prevalence of anxiety [Responder: 26.6% vs non-responder: 63.6%, P=0.031]. In multivariate analysis (Table 3), anxiety and more AHE at baseline were independently associated with treatment failure, while more exacerbations at baseline were independently associated with treatment response.

Compared to Omalizumab non-super-responders, Omalizumab super-responders (Supplementary Table E2) had significantly more exacerbations at baseline [Median(IQR), super-responder: 6(2) vs non-super-responder: 4(4), P=0.029], were less mOCS dependent [super-responder: 14.3%, vs non-super-responder: 65.2%, P<0.001] and had a lower prevalence of anxiety [super-responder: 16.7% vs non-super-responder: 38.3%, P=0.036] and depression [super-responder: 17.2% vs non-super-responder: 39.3%,P=0.036]. In multivariate analysis, absence of depression and not being on mOCS were independently associated with Omalizumab super-response (Table 3).

**Mepolizumab response**

Mepolizumab trials were completed by 93.6%, (58/62) patients, while 4.8%, (3/62) withdrew due to adverse effects and 1.6%, (1/62) withdrew due to logistical reasons (Figure 1). Mepolizumab (Figure 2) significantly improved symptom control [Mean(SD), ACQ6 baseline: 2.71(1.26) to 1.95(1.64), P<0.001], AQLQ [Mean(SD), baseline: 4.33(1.27) to 5.41(1.35), P<0.001] and total HADS [Median(IQR), baseline: 9.5(10) to 6(9.5), P=0.012]. Furthermore, Mepolizumab (Figure 2) significantly reduced exacerbations [Median(IQR), baseline: 4(3) to 2(3), P<0.001], AHE [Median(IQR), baseline: 0(1) to 0(0), P=0.006], PBE (cells/μL) [Median(IQR), baseline:500(350) to 100(100) P<0.001), mOCS dose [Median(IQR), baseline: 10(10) to 5(7), P<0.001], and mOCS dependency [Baseline: 70.7%,(41/58) to 56.1% ,(32/57), P=0.008]. However, it did not significantly improve Clinic FEV1%, FENO nor the proportion of patients with multiple AHE.
 **Mepolizumab responders, non-responders and super-responders**

Based on our definitions, among Mepolizumab subjects who completed their trials (Figure 1), 74.1%, (43/58) subjects were responders and 19%, (11/58) of Mepolizumab subjects were super-responders. At baseline, comapred to Mepolizumab non-responders, Mepolizumab responders were on a significantly lower mOCS dose (Supplementary Table E3) [Median(IQR), responder:10(6) vs non-responder:17(25), P=0.030], had better ACQ6 [Mean(SD), responder: 2.33(1.27) vs non-responder: 4(0.94), P <0.001] , better AQLQ [Mean(SD), responder: 4.53(1.19) vs non-responder: 3.57(1.19), P=0.021] , and significantly less AHE [Median(IQR), responder: 0(1) vs non-responder: 1(4), P=0.030]. A smaller proportion of responders had multiple AHE [responder: 9.8% vs non-responder: 42.9%, P=0.012] and depression [responder: 19.1% vs non-responder: 46.7%, P=0.037]. In multivariate analysis (Table 3), only better ACQ6 at baseline was independently associated with Mepolizumab response.

At baseline, compared to Mepolizumab non-super-responders, Mepolizumab super-responders (Supplementary Table E4) had significantly lower ACQ6 [Mean(SD), super-responder: 1.93(1.33) vs non-super-responder: 3.03(1.24), P=0.016], higher AQLQ [Mean(SD), super-responder: 5.16(1.40) vs non-super-responder: 4.09(1.13), P=0.018], more exacerbations [Median(IQR), super-responder: 7(5) vs non-super-responder: 4(5), P=0.010] and better Clinic FEV1% [Mean(SD), super-responder: 79.73(19.97) vs non-super-responder: 63.07(19.84), P=0.016]. Additionally, super-responders also had a significantly lower body mass index [Median (IQR), super-responder:25.1(5) vs non-super-responder: 29.9 (12.3), P=0.009] and a lower prevalence of obesity (Body Mass Index ≥30 kgm-2) [super-responders: 9.1% vs non-super-responder: 48.9%, P= 0.019]. Multivariate analysis (Table 3) found that more exacerbations and better ACQ6 at baseline were independently associated with Mepolizumab super-response.

Summary phenotypic features of Omalizumab and Mepolizumab treated patients and features independently associated with response and super-response to these drugs is displayed in Figure 3.

**Overall biologic non-response**

All biologic non-responders, N=27 (Omalizumab [44.4%,12/27], Mepolizumab [55.6%,15/27]), were combined and compared with the SNB group and responder groups. Compared to SNB subjects, at baseline, Combined non-responders (Supplementary Table E5) had significantly more AHE [Median (IQR) SNB: 0 (1) vs Combined non-responders: 1 (3), P = 0.028] , worse ACQ6 [Median (IQR) SNB: 3 (1.8) vs Combined non-responders: 3.67 (1.26) , P = 0.017] and worse lung function [Mean(SD) Clinic FEV1 % SNB: 76.78 (23.37) vs Combined non-responders: 61.64 (21.75), P = 0.003]. Furthermore, Combined non-responders were significantly more mOCS dependent (Combined non-responders: 66.7%, vs SNB: 30.6%, P=0.013) , more atopic (Combined non-responders: 74.0%, vs SNB: 52.8%, P=0.038) and had a larger proportion of multiple AHE (Combined non-responders: 48%%, vs SNB: 24.3%, P<0.001).

Compared to both biologic responders, combined non-responders had significantly worse baseline ACQ6 [Median(IQR) Mepolizumab responders: 2.33 (2.27) vs Combined non-responders: 3.67 (1.26), P<0.001] ; [Median(IQR) Omalizumab responders: 3 (1.83) vs Combined non-responders: 3.67 (1.26), P=0.036] and greater prevalence of anxiety [Median(IQR) Mepolizumab responders: 20.0% vs Combined non-responders: 50%, P=0.011] ; [Median(IQR) Omalizumab responders: 26.6% vs Combined non-responders: 50%, P=0.027]. In comparison with Mepolizumab responders, a significantly larger proportion of Combined non-responders was female (Mepolizumab responders, male proportion: 58.1% vs Combined non-responders: 33.3% , P=0.043), had depression (Mepolizumab responders: 19.1% vs Combined non-responders: 48%, P=0.012), dysfunctional breathing (Mepolizumab responders: 31.7% vs Combined non-responders: 59.3%, P=0.025) and multiple AHE (Mepolizumab responders: 9.8% vs Combined non-responders: 48%, P=0.001). Combined non-responders also had significantly more AHE at baseline [Median(IQR) Combined non-responders: 1 (3) vs Mepolizumab responders: 0 (1), P=0.002] and had younger asthma onset [Median(IQR) Combined non-responders: 12 (31) vs Mepolizumab responders: 33.5 (40.5), P=0.032]. Compared to Omalizumab responders, there were no notable differences apart from those conferred by qualifying criteria (more atopy/ lower maximum PBE).

**Age-of-onset/sex stratification of biologic use**

Within our biologic (Omalizumab + Mepolizumab) cohort, the female/early-onset cluster was most prevalent, while the male/early-onset group was the least. Although biologic use across these phenotypes (Table 4) was significantly different, there was no statistically significant difference in response for either biologic across these phenotypes.
**Alternative assessments of biologic outcomes**

The ‘Global Evaluation of Treatment Effectiveness’ tool used in Omalizumab (Figure 4a) captured all modalities of response. It captured all (100%, 32/32) patients who had an improvement of AHE status (≥1 AHE to 0 AHE), all (100%, 75/75) patients who had an OCS/Exacerbation response (≥50% reduction in mOCS dose or exacerbations) and 97.8%, (48/49) of patients who had an ACQ response (≥the minimally important difference [MID] of 0.5).

For Mepolizumab, 16.7%, (6/36) patients who had an ACQ response and 18.2%, (4/22) patients who had an AQLQ response (≥MID of 0.5) were not deemed responders based on NICE criteria (Figure 4b). Similarly, 30%, (3/10) subjects who had an improvement of AHE status were not deemed responders using conventional criteria. Additionally, NICE criteria did not capture three patients who responded in two separate domains (ACQ & AQLQ:2, AHE & ACQ:1). Conversely, some Mepolizumab responders did not show ACQ (21.0%,8/38) nor AQLQ (30.8%,8/26) responses.

# Discussion

This study adds further insight to a growing body of real-world data on the use of biologic drugs in more severe asthma. It uniquely characterised the parallel biologic naïve characteristics of Omalizumab and Mepolizumab treated subjects against a common comparator that remained biologic naïve (SNB) within the same difficult asthma cohort. A key finding was that despite potentially overlapping clinical indications for these drugs, Omalizumab and Mepolizumab treated patients showed distinctive asthma phenotypes. Regardless, both biologic response rates were comparable to RCTs and other reports19–26. In addition, for Omalizumab, even though 43.3% (45/104) patients were potentially dual-eligible for Mepolizumab, the Omalizumab response rate was 88.5%, reiterating that Omalizumab was efficacious in the phenotype that received it. Indeed, both Omalizumab and Mepolizumab conferred substantial multidimensional clinical benefit to the real-world populations which received them. This testifies to the success of both biologics in treating particular difficult asthma phenotypes. Nevertheless, non-responders emerged to both drugs, typically characterised by worse baseline disease and psychological comorbidity.

Of those with the highest disease burden in our cohort (Omalizumab, Mepolizumab, SNB), 51.6% did not receive biologics. Both biologic receiving groups had hallmarks of greater disease severity with significantly worse lung function (Clinic FEV1%), worse airway inflammation (FENO) and greater mOCS dependence compared to SNB. The SNB group are noteworthy as their characterisation derives from the timepoint of WATCH enrolment, when 42.3% of them were new clinic referrals, and thus at an early phase of conventional treatment optimisation. Their lack of subsequent biologic need infers responsiveness to that conventional optimisation. Conversely, biologics treated subjects had already undergone substantial treatment optimisation, without sufficient response, before their characterisation in this study.

Although our three high burden groups were similar with regards to ACQ6, exacerbations and AHE, both biologic treated groups showed clear evidence of Type 2 inflammation, as per Global Initiative for Asthma (GINA) guidelines27. Indeed, as mentioned earlier, both groups had significantly higher levels of FENO, greater than 20ppb, and blood eosinophils greater than ≥150 cells/µL, despite greater proportions of oral corticosteroid dependancy. Additionally, the biologic treated groups were alsophenotypically distinct. These findings substantiate but also add further insight to preliminary suggestions of typical patient features for these biologics outlined by the Global Initiative for Asthma 27. Thus, Omalizumab patients had a younger, early-onset, atopic phenotype, with high proportions of co-morbid allergic bronchopulmonary aspergillosis and rhinitis. Conversely, Mepolizumab patients had an older, male, late-onset, eosinophilic but less atopic phenotype, associated with a higher prevalence of nasal polyposis but less dysfunctional breathing. Additionally, stratification of biologic use by our recently described age-of-onset/sex phenotypes18 further corroborates these findings, as we found significantly different biologic use across the four phenotypes. Notably, the female/early-onset phenotype showed the highest prevalence of Omalizumab and lowest prevalence of Mepolizumab use, while the male/adult-onset phenotype showed the highest prevalence of Mepolizumab use. This may partly explain a disparity in biologic effect, whereby Omalizumab but not Mepolizumab, significantly improved Clinic FEV1%, mirroring findings of another real-world UK study26. This observed difference could be partly explained by the higher representation of Mepolizumab patients among the male/adult-onset phenotype which had poorest baseline lung function18 in our cohort. Other reports have also confirmed that such patients have more severe, persistent airflow limitation28, potentially explaining their limited lung function improvement. Another disparity was in steroid-sparing effect, whereby Mepolizumab but not Omalizumab, significantly reduced mOCS dependency. This may reflect different trial durations mandated in UK clinical practice. Indeed, other studies which evaluated Omalizumab beyond 16-weeks, found that it reduced the proportion of patients on mOCS15,21,22,29,30. This may also reflect clinical practice during the single biologic era, whereby a more conservative mOCS weaning approach may have been adopted, given the lack of alternatives.

Overall, there is limited knowledge on clinical predictors of Omalizumab and Mepolizumab response. A pooled analysis of seven clinical trials found that baseline characteristics were unable to reliably predict Omalizumab benefit23. For Mepolizumab, GINA guidelines 27and post-hoc analyses of RCT data suggested that baseline PBE could be a useful predictor of response31, but this was not consistently observed in real-world studies24,26, including ours. Additionally, the GINA guidelines have also suggested childhood-onset, atopic asthma as a predictor of good response to Omalizumab. Furthermore, the aforementioned guideline also suggested that features such as Nasal polyposis, adult-onset asthma, higher number of severe exacerbations and maintainence OCS at baseline to be potential predictors of good response for Mepolizumab. While all those phenotypic features were indeed observed in our Omalizumab and Mepolizumab treated patients, our data did not find them to be associated with actual biologic response. Instead, our data suggest that patients with the most severe and poorly controlled baseline disease were poorest responders. Thus, for Mepolizumab, better baseline asthma control was independently associated with response and super-response. This mirrored the findings of Kavanagh et al26, where in their cohort, poor disease control at baseline was independently associated with Mepolizumab non-response. Similarly, in Omalizumab, more ‘severe’ exacerbations, AHE, at baseline were associated with non-response, while being on mOCS, was associated with non-super-response. However, while AHE may represent more ‘severe’ asthma exacerbations, they may also reflect impact of multiple influences beyond just airways disease. Indeed, Burke et al. identified that those with repeated AHE were a subgroup of difficult asthma patients with multiple aggravating comorbidities including obesity, gastro-oesophageal reflux disease, dysfunctional breathing and psychological morbidity32. Such complex multifactorial health events may be less responsive to a simple biologic approach. It is notable that by adopting a holistic, asthma MDT approach, they reduced AHE significantly32. Collectively these findings emphasise the importance of comprehensive, up-front characterisation of difficult asthma patients, focused on addressing all treatable traits to maximise biologic outcome.

Reinforcing this, our data uniquely showed that psychological co-morbidities may be associated with biologic non-response, an unexplored aspect by other real-world biologic studies. Anxiety was independently associated with Omalizumab non-response while depression was independently associated with Omalizumab non-super-response and was associated with Mepolizumab non-response. Psychopathologies have been associated with biologic non-response in other diseases. Analysis of the British Society for Rheumatology Biologics registry showed that depression reduced the odds of biologic response33. The impact of psychopathology on biologic outcome could be secondary to the well-documented interplay between psychological disease and SA34. Psychopathologies have been associated with worse asthma control, more exacerbations and more AHE35–37. Furthermore, studies have shown that proinflammatory cytokines associated with asthma are raised in depression and anxiety38,39, which may dampen biologic effect. Brown et al showed in an RCT that 12-week continuous escitalopram therapy for severe asthma patients with co-morbid major depression significantly reduced OCS use and improved asthma control40. As such, our findings encourage proactive management of psychological comorbidity alongside consideration of asthma biologics.

Analysis of our pooled biologic data allowed us to describe an overall biologic unresponsive group. They had early-onset asthma, were predominantly female yet had comparable exacerbations, mOCS dependence, FENO, lung function and asthma ICU admissions to responders. However, they were characterized by more AHE, a larger proportion of multiple AHE, significantly worse baseline asthma control, alongside greater proportions of anxiety and depression. We postulate their biologic unresponsiveness may have been augmented by their high burden of psychopathologies as although their objective disease markers and clinical co-morbidities were equivalent, their subjective markers of disease were not. Our recent work has shown that this group of early-onset, female patients have the highest prevalence of psychological co-morbidities, yet also have the highest frequency of biologic use18. This reiterates the importance of holistically addressing treatable traits, through addressing psychopathologies before biologic therapy.

Head-to-head comparisons between Omalizumab and Mepolizumab response rates were not appropriate in our data, given their different phenotypic traits, and the different response tools employed. However, notably,10/15 Mepolizumab ‘non-responders’ displayed responses in domains outside NICE criteria. Particularly noteworthy were those who sustained an improvement in AHE status, including one who had both ACQ and AHE status response. However, despite improvements in disease control and healthcare utilisation, important markers of economic and patient-centred efficacy, these Mepolizumab patients were not classified as responders according to NICE criteria14. A post-hoc analysis of two Mepolizumab RCTs found that ACQ was unreliable in predicting Mepolizumab response41. Though important, their findings were based on RCT data which may have limited transferability to real-world patients7–9. Additionally, ACQ is used to gauge Mepolizumab response in the Australian Mepolizumab Registry, and shown to correlate with improvements in objective measures25. Conversely, few Mepolizumab responders did not sustain an ACQ or AQLQ response. This could be because an improvement in NICE defined domains may not equate to the patient’s perception of better asthma control or quality-of-life. Thus, in those who are borderline responders, consideration might be made to measure Mepolizumab response more holistically, perhaps by taking into account a wider range of measures. However, the economic implications of any such move need careful deliberation.

Our study had limitations. Inherent to real-world observational studies, we had some missing data. However, real-world data capture is representative of clinical populations receiving these treatments. Our report is also limited by the small numbers in the Mepolizumab group, which prevented us from uncovering whether the different age-of-onset/sex phenotypes had differing response predictors. Therefore, future studies are needed to clarify these findings and further explore age-of-onset/sex-related signals. Our study had several strengths. We report detailed real-world clinical outcomes on both Omalizumab and Mepolizumab in parallel, against a non-biologic comparator in a difficult asthma cohort, adding to the growing real world dataset on these drugs. Additionally, our cohort represents an extensively characterized difficult asthma population from a wide geographical catchment, enhancing generalisability of findings. This allowed mapping of previously described clinical clusters onto our data, consolidating our observations. We also undertook a pooled analysis of the non-responder group and explored other definitions of response in Mepolizumab, compared to Omalizumab.

# Conclusion:

In summary, in this real-world difficult asthma cohort, Omalizumab and Mepolizumab were used for distinct SA phenotypes in which they were both multidimensionally effective. Among these phenotypes, we identified some features independently associated with response, which may assist clinicians. In turn, those findings reiterated the importance of detailed characterisation and addressing treatable traits alongside consideration of biologics use in more severe asthma. To further enhance the personalized and optimal use of biologic therapies, future research should develop a deeper endotypic understanding of asthma biologic need and responsiveness.

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# Tables

**Table 1. Baseline characteristics of the Omalizumab group vs severe asthma, non-biologic group**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Omalizumab group,N= 105  | Severe asthma, non-biologic group, N=178  | P-value |
|  | Mean (SD) / Median (IQR) | Missing | Mean (SD) / Median (IQR) | Missing |  |
| **Annual rate of exacerbations in the past year, median (IQR)** a,b | 5 (3)  | 2 | 5 (3)  | 32 | 0.391 |
| **Annual rate of AHE in the past year, median (IQR)** a,b | 1 (2)  | 9 | 0 (1)  | 1 | 0.238 |
| **Maximum PBE count in the past year, median (IQR) - cells/µL** a,b | 250 (400) | 9 | 200 (300)  | 49 | 0.052 |
| **Baseline ACQ6, median (IQR)** b,c | 3 (1.79)  | 25 | 3 (1.8)  | 11 | 0.594 |
| **Baseline FENO, median (IQR) – ppb** b,c | 30 (38)  | 27 | 16.85 (24.65)  | 50 | **0.007** |
| **Baseline Clinic FEV1 %, mean (SD)** b,c | 66.59 (20.77)  | 6 | 76.78 (23.37)  | 57 | **0.001** |
| **BMI, median (IQR) – kgm-2**  | 30.60 (9.75) | 0 | 30.8 (10.8) | 3 | 0.502 |
| **Age of asthma diagnosis, median (IQR) - y** | 10 (25) | 4 | 20 (35) | 9 | **0.007** |
| **Age, median (IQR) - y** | 52 (18.5) | 0 | 54.5 (25) | 0 | 0.643 |
|  | **Percentage (N)** | Missing | **Percentage (N)** | Missing | **P-value** |
| **Multiple AHE (>1), Yes** a,b | 31.3% (30)  | 9 | 24.3% (43)  | 5 | 0.215 |
| **On Maintenance OCS at baseline, Yes** b,c | 47.6% (50)  | 0 | 30.6% (53)  | 1 | **0.004** |
| **Adult-onset asthma, Yes** | 37.6% (38) | 4 | 52.7% (89) | 9 | **0.017** |
| **Sex, Male**  | 33.3% (35) | 0 | 29.8% (53) | 0 | 0.532 |
| **Ethnicity, White** | 87.6% (92) | 0 | 94.9% (169) | 0 | **0.026** |
| **Rhinitis, Ever**  | 73.6% (64) | 18 | 60.1% (95) | 10 | **0.035** |
| **GORD, Ever**  | 64.4% (67) | 1 | 65.3% (111) | 8 | 0.883 |
| **Smoking, Ever**  | 43.8% (46) | 0 | 47.5% (84) | 1 | 0.552 |
| **Atopy (SPT / sIgE positive)**  | 100% (105) | 0 | 52.8% (94) | 0 | **<0.001** |
| **Obesity (BMI≥30kgm-2), Ever**  | 52.4% (55) | 0 | 52.6% (92) | 3 | 0.975 |
| **Admitted to ICU for asthma, Ever**  | 27.9% (29) | 1 | 32.6% (58) | 0 | 0.410 |
| **Intubated for Asthma, Ever**  | 14.4% (15) | 1 | 17.4% (31) | 0 | 0.512 |
| **Dysfunctional breathing, Ever** | 51.5% (51) | 6 | 55.1% (92) | 11 | 0.572 |
| **ILO, Ever**  | 19.4% (18) | 12 | 13.2% 921) | 19 | 0.193 |
| **Depression, Ever**  | 31.9% (29) | 14 | 42.8% (68) | 19 | 0.089 |
| **Anxiety, Ever**  | 30.8% (28) | 14 | 38.0% (60) | 19 | 0.252 |
| **Bronchiectasis, Ever**  | 15.5% (16) | 2 | 14.2% (25) | 2 | 0.762 |
| **Salicylate sensitivity, Ever**  | 33.0% (34) | 2 | 27.8% (49) | 2 | 0.416 |
| **ABPA, Ever**  | 12.6% (13) | 2 | 5.2% (9) | 4 | **0.027** |
| **Sulphite sensitivity, Ever**  | 8.7% (9) | 2 | 7.4% (13) | 3 | 0.696 |
| **COPD, Ever**  | 5.8% (6) | 2 | 10.8% (19) | 2 | 0.161 |
| **Nasal polyps, Ever**  | 21.4% (21) | 7 | 19% (31) | 15 | 0.635 |
| **Nasal (polyps / sinus) surgery, Ever**  | 31.6% (30) | 10 | 19.3% (31) | 17 | **0.025** |
| **Urticaria or Angioedema, Ever**  | 12.6% (13) | 2 | 6.8% (12) | 2 | 0.101 |
| **OSA, Ever**  | 4.9% (5) | 2 | 11.5% (20) | 4 | 0.062 |
| **Eczema, Ever**  | 31.7% (33) | 1 | 21.6% (38) | 2 | 0.060 |

Categorical data presented as proportions and numbers. Continuous data presented Median + Interquartile range (IQR) or Mean + standard deviation (SD). a: For biologic groups, In the preceding 12 months before biologic approval. b: For the non-biologic group, at WATCH enrolment. c: for biologic groups, at baseline biologic visit. Exacerbations: incidence of exacerbations requiring OCS / increase in maintenance OCS in the past 12 months before biologic approval. AHE: acute healthcare encounters, which include Emergency department/ hospital admissions. PBE: peripheral blood eosinophils. µL: microlitre. ACQ6: Asthma Control Questionnaire 6. FENO: fractional exhaled nitric oxide. ppb: parts per billion. IgE: immunoglobulin E. kU/L: kilounits per litre. OCS: oral corticosteroids. mg: milligrams. FEV1: forced expiratory volume in one second. Adult-onset: Age of asthma onset ≥18 years. GORD: Gastro-oesophageal reflux disease. SPT: skin prick test. sIgE: specific IgE. ICU: intensive care unit. ILO: intermittent laryngeal obstruction. ABPA: allergic bronchopulmonary aspergillosis. COPD: chronic obstructive pulmonary disease. OSA: obstructive sleep apnoea. The severe asthma, non-biologic (SNB) group is a common comparator group extracted from WATCH. They were participants who either had ≥4 exacerbations or ≥1 AHE or were on maintenance OCS in the past year but did not commence biologic therapy during the study period. Unpaired t-tests, Mann-Whitney U test, Chi-square tests or Fisher’s exact tests were used, where appropriate, to calculate P-values.

**Table 2. Baseline characteristics of the Mepolizumab group vs severe asthma, non-biologic group**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mepolizumab group, N= 62  | Severe asthma, non-biologic group, N=178  | P-value |
|  | Mean (SD) / Median (IQR) | Missing | Mean (SD) / Median (IQR) | Missing |  |
| **Annual rate of exacerbations in the past year, median (IQR)** a,b | 4 (5) | 1 | 5 (3)  | 32 | 0.744 |
| **Annual rate of AHE in the past year, median (IQR)** a,b | 0 (1) | 3 | 0 (1)  | 1 | 0.184 |
| **Maximum PBE count in the past year, median (IQR) - cells/µL** a,b | 500(400)  | 0 | 200 (300)  | 49 | **<0.001** |
| **Baseline ACQ6, median (IQR)** b,c | 2.67 (1.67)  | 3 | 3 (1.8)  | 11 | 0.795 |
| **Baseline FENO, median (IQR) – ppb** b,c | 36 (52)  | 3 | 16.85 (24.65)  | 50 | **<0.001** |
| **Baseline Clinic FEV1 %, mean (SD)** b,c | 67.1 (20.77)  | 2 | 76.78 (23.37)  | 57 | **0.007** |
| **BMI, median (IQR) – kgm-2**  | 28.95 (28.95) | 0 | 30.8 (10.8) | 3 | 0.214 |
| **Age of asthma diagnosis, median (IQR) - y** | 28 (38.5) | 1 | 20 (35) | 9 | **0.039** |
| **Age, median (IQR) - y** | 61 (19) | 0 | 54.5 (25) | 0 | **0.015** |
|  | Percentage (N) | Missing | Percentage (N) | Missing | P-value |
| **Multiple AHE (>1), Yes** a,b | 16.9% (10)  | 3 | 24.3% (43)  | 5 | 0.242 |
| **On Maintenance OCS at baseline, Yes** b,c | 72.6% (45)  | 0 | 30.6% (53)  | 1 | **<0.001** |
| **Adult-onset asthma, Yes** | 60.7% (37) | 1 | 52.7% (89) | 9 | 0.282 |
| **Sex, Male**  | 53.2% (33) | 0 | 29.8% (53) | 0 | **0.001** |
| **Ethnicity, White** | 91.9% (57) | 0 | 94.9% (169) | 0 | 0.362 |
| **Rhinitis, Ever**  | 72.9% (43) | 3 | 60.1% (95) | 10 | 0.082 |
| **GORD, Ever**  | 67.2% (41) | 1 | 65.3% (111) | 8 | 0.875 |
| **Smoking, Ever**  | 56.5% (35) | 0 | 47.5% (84) | 1 | 0.223 |
| **Atopy (SPT / sIgE positive)**  | 50.0% (31) | 0 | 52.8% (94) | 0 | 0.703 |
| **Obesity (BMI≥30kgm-2), Ever**  | 41.9% (26) | 0 | 52.6% (92) | 3 | 0.097 |
| **Admitted to ICU for asthma, Ever**  | 35.5% (22) | 0 | 32.6% (58) | 0 | 0.677 |
| **Intubated for Asthma, Ever**  | 14.5% (9) | 0 | 17.4% (31) | 0 | 0.598 |
| **Dysfunctional breathing, Ever** | 40.0% (24) | 2 | 55.1% (92) | 11 | **0.045** |
| **ILO, Ever**  | 13.8% (8) | 4 | 13.2% 921) | 19 | 0.911 |
| **Depression, Ever**  | 28.3% (17) | 2 | 42.8% (68) | 19 | 0.051 |
| **Anxiety, Ever**  | 27.1% (16) | 3 | 38.0% (60) | 19 | 0.136 |
| **Bronchiectasis, Ever**  | 19.4% (12) | 0 | 14.2% (25) | 2 | 0.336 |
| **Salicylate sensitivity, Ever**  | 19.4% (12) | 0 | 27.8% (49) | 2 | 0.188 |
| **ABPA, Ever**  | 12.9% (8) | 0 | 5.2% (9) | 4 | 0.081 |
| **Sulphite sensitivity, Ever**  | 9.7 % (6) | 0 | 7.4% (13) | 3 | 0.590 |
| **COPD, Ever**  | 9.7 % (6) | 0 | 10.8% (19) | 2 | 0.805 |
| **Nasal polyps, Ever**  | 34.5% (20) | 4 | 19% (31) | 15 | **0.019** |
| **Nasal (polyps / sinus) surgery, Ever**  | 31.7% (19) | 2 | 19.3% (31) | 17 | **0.050** |
| **Urticaria or Angioedema, Ever**  | 8.1% (5) | 0 | 6.8% (12) | 2 | 0.776 |
| **OSA, Ever**  | 6.5% (4) | 0 | 11.5% (20) | 4 | 0.259 |
| **Eczema, Ever**  | 27.4% (17) | 0 | 21.6% (38) | 2 | 0.349 |

Categorical data presented as proportions and numbers. Continuous data presented Median + Interquartile range (IQR) or Mean + standard deviation (SD). a: For biologic groups, In the preceding 12 months before biologic approval. b: For the non-biologic group, at WATCH enrolment. c: for biologic groups, at baseline biologic visit. Exacerbations: incidence of exacerbations requiring OCS / increase in maintenance OCS in the past 12 months before biologic approval. AHE: acute healthcare encounters, which include Emergency department/ hospital admissions. PBE: peripheral blood eosinophils. µL: microlitre. ACQ6: Asthma Control Questionnaire 6. FENO: fractional exhaled nitric oxide. ppb: parts per billion. IgE: immunoglobulin E. kU/L: kilounits per litre. OCS: oral corticosteroids. mg: milligrams. FEV1: forced expiratory volume in one second. Adult-onset: Age of asthma onset ≥18 years. GORD: Gastro-oesophageal reflux disease. SPT: skin prick test. sIgE: specific IgE. ICU: intensive care unit. ILO: intermittent laryngeal obstruction. ABPA: allergic bronchopulmonary aspergillosis. COPD: chronic obstructive pulmonary disease. OSA: obstructive sleep apnoea. The severe asthma, non-biologic (SNB) group is a common comparator group extracted from WATCH. They were participants who either had ≥4 exacerbations or ≥1 AHE or were on maintenance OCS in the past year but did not commence biologic therapy during the study period. Unpaired t-tests, Mann-Whitney U test, Chi-square tests or Fisher’s exact tests were used, where appropriate, to calculate P-values.

**Table 3: Baseline features Independently Associated with Biologic Responses**

|  |
| --- |
| **Omalizumab models** |
| **Model name** | **Cases included** | **Variables included** | **Final variables** | **P-value** | **OR; 95 CI** | **AUC of model** |
| Omalizumab response vs non-response | 78/104, 75% | Clinic FEV1%, Age, BMI, Sex, Baseline annual rate of exacerbations in the past year, Multiple AHE, Annual rate of AHE in the past year, Anxiety. | Baseline annual rate of exacerbations  | 0.024 | 1.622 (1.065-2.469) | 0.856 |
| Lower baseline annual rate of AHE | 0.050 | 1.297 (1.000-1.681) |
| No Anxiety | 0.008 | 8.772 (1.745-43.478) |
| Omalizumab super-response vs non-super-response | 75/104, 72.1% | Baseline annual rate of exacerbations in the past year, Multiple AHE, on mOCS, Adult-onset, Obesity, ICU admission for asthma ever, Anxiety, Depression. | Not on maintenance OCS | <0.001 | 18.182 (4.484-71.429) | 0.809 |
| No Depression | 0.009 | 4.784 (1.623-29.412) |
| **Mepolizumab models** |
| **Model name** | **Cases included** | **Variables included** | **Final variables** | **P-value** | **OR; 95 CI** | **AUC of model** |
| Mepolizumab responders vs non-responders | 42/58, 72.4% | ACQ6, Multiple AHE, Depression, Anxiety, AQLQ baseline, Total HADS baseline, Baseline annual rate of AHE in the past year, Dysfunctional Breathing. | Lower ACQ6 at baseline | 0.007 | 4.651 (1.513-14.286) | 0.859 |
| Mepolizumab super- responders vs non-super-responders | 47/58, 81% | Baseline annual rate of exacerbations in the past year, ACQ6, Clinic FEV1%, AQLQ baseline, BMI, on mOCS, Adult-onset, Atopy, Smoking ever, Bronchiectasis ever | Lower ACQ6 at baseline | 0.025 | 3.401 (1.167-9.901) | 0.811 |
| Baseline annual rate of exacerbations | 0.023 | 1.487 (1.046-2.115) |

FEV1: forced expiratory volume in one second. BMI: Body mass index. Exacerbations: incidence of exacerbations requiring OCS / increase in maintenance OCS in the past 12 months before biologic approval. AHE: acute healthcare encounters, which include Emergency department/ hospital admissions. Multiple AHE: >1 AHE in the past 12 months before biologic approval. mOCS: maintenance oral corticosteroids. BMI: Body mass index. Obesity: BMI≥30kgm-2. ICU: Intensive care unit. ACQ6: asthma control questionnaire 6. AQLQ: Asthma Quality of Life Questionnaire. HADS: hospital anxiety and depression scale. Adult-onset: asthma age of onset ≥18 years. Multiple logistic regression was performed (backward variable selection) using baseline variables trending towards significance (P<0.2). AUC: Area under the Receiver operating characteristic curve.

**Table 4: Stratification of biologic use and outcomes within Age-of-onset/sex clusters**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Phenotype and Proportions within overall WATCH cohort** | **Male, early-onset****(14.0%)** | **Female, early-onset (34.7%)** | **Male, adult-onset****(20.8%)** | **Female, adult-onset (30.5%)** |
| **Proportions within biologic cohorts (%, n/N)** | Overall,N= 167 (A) | 17.4% (29/167) | 34.7% (58/167) | 23.4% (39/167) | 24.6% (41/167) |
| Omalizumab, N=105 | 15.2% (16/105) | 44.8% (47/105) | 18.1% (19/105) | 21.9% (23/105) |
| Mepolizumab, N=62 | 21.0% (13/62) | 17.7% (11/62) | 32.3% (20/62) | 29.0% (18/62) |
| **Biologic response within each phenotype (%, n/N) a** | Omalizumab responder (B) | 100% (16/16) | 80.9% (38/47) | 94.4% (17/18) | 91.3% (21/23) |
| Mepolizumab responder (C) | 69.2% (9/13) | 70% (7/10) | 80% (16/20) | 73.3% (11/15) |
| **P-values** | A | **0.004**  |
| B | 0.135 |
| C | 0.893 |

Early-onset: age of asthma onset<18 years. Adult-onset: age of asthma onset ≥18 years. a: those who completed biologic trials, i.e.: did not withdraw due to any reason. A= Chi-squared tests were performed to assess the distribution of the four age-of-onset/sex clusters across both biologics. B= Chi-squared tests were performed to assess biologic response to Omalizumab across the four age-of-onset/sex clusters. C= Chi-squared tests were performed to assess biologic response to Mepolizumab across the four age-of-onset/sex clusters.

# Figure legends

Figure 1: Consort diagram of participants in the study and included in the various stages of analysis.

Figure 2: Biologic outcomes for Omalizumab and Mepolizumab at the end-of-trial. ACQ6: Asthma Control Questionnaire 6. AHE: acute healthcare encounters, which include Emergency department/ hospital admissions. OCS: oral corticosteroids. mg: milligrams. FEV1: forced expiratory volume in one second. AQLQ: Asthma Quality of Life Questionnaire. HADS: Hospital anxiety and depression scale.

Figure 3: Summary of baseline phenotypic features of Omalizumab and Mepolizumab treated patients and factors independently associated with response and super-response to these drugs. ABPA: allergic bronchopulmonary aspergillosis. AHE: acute healthcare encounters, which include Emergency department/ hospital admissions. ACQ6: Asthma Control Questionnaire 6. mOCS: maintenance oral corticosteroids. WATCH: Wessex AsThma CoHort of difficult asthma.

Figure 4: Alternative assessments of biologic outcomes. 4a: Side-by-side comparisons of different response measures. 4b: Alternative Mepolizumab response measures. ACQ: Asthma Control Questionnaire 6. AHE: acute healthcare encounters. OCS: exacerbations. AQLQ: Asthma Quality of Life Questionnaire. MDT: multi-disciplinary team decision. Blue outlier: a patient who had maintenance OCS reduction (10-7mg) and had no exacerbations nor AHE (baseline:0), and thereby had a positive trial.