# Phenotypes and Clinical Outcomes of Omalizumab and Mepolizumab treated Difficult Asthma patients

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**Abstract**

Introduction Real-world data on Omalizumab (OMA) and Mepolizumab (MEPO) can inform their use in severe asthma (SA). We studied patients in the Wessex AsThma CoHort of difficult asthma (WATCH) to: 1. Phenotypically compare OMA or MEPO treated patients against a SA, non-biologic group (SNB). 2. Assess clinical responses to OMA and MEPO. 3. Assess the spectrum of responses to these biologics. Methods We retrospectively phenotyped biologic naïve patients from WATCH (N=478) commenced on OMA (N=105) or MEPO (N=62) compared to SNB (N=178). Biologic response was gauged using standard criteria and response features were identified using logistic regression. Results OMA and MEPO patients were phenotypically distinct. Both drugs significantly reduced exacerbations, acute healthcare encounters (emergency department or hospital admissions), maintenance oral corticosteroid dose, and improved Asthma Control Questionnaire 6 (ACQ6) scores. OMA patients with more exacerbations at baseline (P=0.024), less acute healthcare encounters (P=0.050), and no anxiety (P=0.008) were more likely to respond to it. Lower baseline ACQ6 was independently associated with higher odds of MEPO response (P=0.007). Combined (OMA or MEPO) non-responders had significantly more psychological co-morbidities and worse baseline subjective disease markers compared to responder groups. Current criteria used to measure trial outcomes for MEPO, but not OMA, missed some modalities of response. Conclusion In a difficult asthma cohort, OMA and MEPO were used for distinct SA phenotypes, yet both were multidimensionally efficacious. Among these phenotypes, some clinical features associated with response were identified which emphasized the importance of addressing treatable traits when considering biologic therapy.

*Long title: Phenotypes and Clinical Outcomes of Omalizumab and Mepolizumab treated Difficult Asthma patients*

*Short title: Real-world Omalizumab and Mepolizumab outcomes*

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**ABSTRACT**

**Introduction**Real-world data on Omalizumab (OMA) and Mepolizumab (MEPO) can inform their use in severe asthma (SA). We studied patients in the Wessex AsThma CoHort of difficult asthma (WATCH) to: 1. Phenotypically compare OMA or MEPO treated patients against a SA, non-biologic group (SNB). 2. Assess clinical responses to OMA and MEPO. 3. Assess the spectrum of responses to these biologics.

**Methods**We retrospectively phenotyped biologic naïve patients from WATCH (N=478) commenced on OMA (N=105) or MEPO (N=62) compared to SNB (N=178). Biologic response was gauged using standard criteria and response features were identified using logistic regression.

**Results**OMA and MEPO patients were phenotypically distinct. Both drugs significantly reduced exacerbations, acute healthcare encounters (emergency department or hospital admissions), maintenance oral corticosteroid dose, and improved Asthma Control Questionnaire 6 (ACQ6) scores. OMA patients with more exacerbations at baseline (P=0.024), less acute healthcare encounters (P=0.050), and no anxiety (P=0.008) were more likely to respond to it. Lower baseline ACQ6 was independently associated with higher odds of MEPO response (P=0.007). Combined (OMA or MEPO) non-responders had significantly more psychological co-morbidities and worse baseline subjective disease markers compared to responder groups. Current criteria used to measure trial outcomes for MEPO, but not OMA, missed some modalities of response.

**Conclusion**

In a difficult asthma cohort, OMA and MEPO were used for distinct SA phenotypes, yet both were multidimensionally efficacious. Among these phenotypes, some clinical features associated with response were identified which emphasized the importance of addressing treatable traits when considering biologic therapy.

**Keywords: asthma, asthma treatment, biologics, epidemiology, personalized medicine**

*Introduction*

Biologic therapies have revolutionised Severe Asthma (SA) management, heralding a potential era of personalized medicine (1) that better addresses SA's heterogeneity. In the United Kingdom (UK), four biologics are currently approved for use in SA (2). The two in longest use are the anti-immunoglobulin E (IgE) biologic, Omalizumab (OMA) and the anti-interleukin-5 (IL-5) biologic, Mepolizumab (MEPO). Both agents proved 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 patients (7,8). Brown et al. highlighted that only 9.8% of their SA cohort met enrolment criteria of phase-III asthma biologic RCTs (9). Thus, as the portfolio of biologics continues to expand, real-world data on these drugs is urgently needed (10) to better understand their place in real-life SA management. Additionally, an evolving paradox of biologic choice places greater onus on clinicians to "get it right 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 the two widely used asthma biologics, OMA and MEPO, from the thoroughly characterised, longitudinal Wessex AsThma CoHort of difficult asthma (WATCH) (11).

*Methods*WATCH is a prospective observational study of patients managed in a tertiary 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 2016 (12) . Detailed study methodology is described elsewhere (11). The study had ethical approval (REC reference: 14/WM/1226) and written informed consent was obtained for all participants.

We conducted a retrospective study of biologic naïve patients from WATCH who were started on OMA or MEPO between June 2006 and May 2019. Biologic eligibility was based on National Institute for Health & Care Excellence (NICE) guidance (13,14) [supplementary table E1]. Our aims were three-fold. First, to define phenotypic characteristics of patients commencing OMA or MEPO against SA patients who remained biologic naive. Second, to assess clinical responses to both agents from biologic trial data and identify features associated with response. Finally, to assess the spectrum of responses to these biologics.

Biologic trial data were collected at baseline (first biologic visit) and at subsequent treatment visits: 2-4 weekly for OMA and 4-weekly for MEPO. This included Asthma Control Questionnaire-6 (ACQ6), incidence of exacerbations (exacerbations requiring an acute oral corticosteroid [OCS] course / increase in maintenance OCS [mOCS]), incidence of emergency department or hospital admissions (Acute Healthcare Encounters [AHE]), current mOCS dose and Clinic percent predicted $FEV_1$ ($FEV_1$%). Hospital anxiety and depression scale (HADS) and Asthma Quality of Life Questionnaire (AQLQ) were collected at baseline and final visits for MEPO. Fractional Exhaled Nitric Oxide (FENO) was collected at all MEPO visits, but only at the baseline OMA visit. Co-morbidity, anthropometric and demographic data were extracted from the WATCH database. Maximum peripheral blood eosinophil count (PBE), total IgE, baseline exacerbations and AHE were from the 12 months prior to biologic approval. Exacerbations and AHE were annualised for comparisons.

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 either had [?]4 exacerbations or [?]1 AHE or were on mOCS in the past year but did not commence biologic therapy 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 described (15), to further characterise their phenotypic features.

Biologic response was determined by the clinical MDT (Multi-Disciplinary Team), based on NICE guidance (13,14). For OMA, response was assessed using the Global Evaluation of Treatment Effectiveness (GETE) (16–18). For MEPO, response was defined as a [?]50% reduction in exacerbations or in mOCS dose without

loss of asthma control. In borderline OCS responders, factors such as change in AHE, symptom control or quality-of-life would additionally guide MEPO continuation. Treatment trials typically ended at 16 weeks for OMA and 12 months for MEPO. However, equivocal trials were extended up to 32 weeks for OMA and 18 months for MEPO. We defined 'super-response' separately for both biologics. OMA super-responders were defined as 16-week responders who either 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 MEPO, super-responders were defined as 12-month responders who either 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. 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). Data were analysed using paired and unpaired t-tests, Mann-Whitney U test, Wilcoxon-Signed Rank test, Chi-square test, McNemar test or Fisher's exact test as appropriate. Multiple logistic regression (backward variable selection) was performed using variables trending towards significance (P<0.2). Statistical significance was set at P-value $< 0.05$.

*Results* Among the WATCH cohort, 37.7% (182/478) completed trials with either OMA or MEPO. Nearly two-thirds were with OMA (63.7%; 116/182) and the rest were with MEPO (36.3%; 66/182). Eleven from OMA analysis and four from MEPO analysis were excluded due to missing outcome data.

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

Compared to SNB subjects, neither biologic groups had significantly different baseline exacerbations or AHE (Table 1). However, they both showed other baseline severity markers, with significantly higher FENO, worse lung function and more mOCS dependency.

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

Conversely, compared to SNB subjects, MEPO subjects had a significantly higher maximum PBE (Table 1), were older, diagnosed with asthma later in life, and predominantly male. Additionally, they had a significantly higher prevalence of nasal polyps and nasal (polyps/sinus) surgery but less dysfunctional breathing.

*Omalizumab response*Overall, 99.0%,(104/105) patients completed OMA trials. One person withdrew due to side-effects. OMA (Figure 1) significantly reduced exacerbations [Median(IQR), baseline: 5(3) to 0(3) at end-of-trial, P<0.001], mOCS dose [Median(IQR), baseline: 10(10-20) to 10(5-15) at end-of-trial, P=0.002], AHE [Median(IQR), baseline: 1(2) to 0(0) at end-of-trial, P=0.003] and the proportion of patients with multiple (>1) AHE [Baseline: 36.5%,(38/104); end-of-trial: 15.4%,(16/104), P=0.007]. OMA (Figure 1) also significantly improved asthma control [Mean (SD) ACQ6, baseline: 2.96(1.26) to 1.64(1.12) at end-of-trial, P <0.001], Clinic $FEV_1$% [Mean(SD), baseline: 67.34(25.93) to 75.40(21.79) at end-of-trial, P<0.001] and reduced PBE (cells/μL) [Median(IQR) baseline: 200(400) to 200(200) at end-of-trial, P=0.002]. However, it did not significantly reduce mOCS dependency [Baseline: 48.1%, (50/104), end-of-trial: 41.6% (42/101), P=NS].

*Omalizumab responders vs non-responders*OMA response, as assessed by GETE, was achieved in 88.5%, (92/104) of subjects completing trials. OMA responders (supplementary table E2) 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%,(21/79) vs non-responder: 63.6%,(7/11), P=0.031]. In multivariate analysis (Table 2), anxiety and more AHE at baseline were independently associated with treatment failure, while more exacerbations at baseline was independently associated with treatment response.

*Omalizumab super-responders*

Based on our definition, 33.7%, (35/104) of OMA subjects who completed trials were super-responders. That constituted 38.0%, (35/92) of OMA responders. OMA Super-responders (supplementary Table E3) 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%,(5/35) vs non-super-responder: 65.2%,(45/69), P<0.001] and had a lower prevalence of anxiety [super-responder: 16.7%(5/30) vs non-super-responder: 38.3%,(23/60), P=0.036] and depression [super-responder: 17.2%,(5/29) vs non-super-responder: 39.3%,(24/61), P=0.036]. Absence of depression and not being on mOCS were independently associated with OMA super-response (Table 2).

*Mepolizumab response*

MEPO 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. MEPO (Figure 1) significantly improved symptom control [Mean(SD), ACQ6 baseline: 2.71(1.26) vs 1.95(1.64) at end-of-trial, P<0.001], AQLQ [Mean(SD), baseline: 4.33(1.27) to 5.41(1.35) at the end-of-trial, P<0.001] and total HADS [Median(IQR), baseline: 9.5(10) to 6(9.5) at end-of-trial, P=0.012]. Furthermore, MEPO (Figure 1) significantly reduced exacerbations [Median(IQR), baseline: 4(3) vs 2(3) at the end-of-trial, P<0.001], AHE [Median(IQR), baseline: 0(1) to 0(0) at the end-of-trial, P=0.006], PBE (cells/μL) [Median(IQR), baseline: 500(350) to 100(100) at end-of-trial, P<0.001), mOCS dose [Median(IQR), baseline: 10(10) to 5(7) at end-of-trial, P<0.001], and mOCS dependency [Baseline: 70.7%,(41/58); end-of-trial: 56.1% ,(32/57), P=0.008]. However, it did not significantly improve Clinic $FEV_1$%, FENO nor the proportion of patients with multiple AHE.

*Mepolizumab responders and non-responders*

Among MEPO subjects who completed their trials, 74.1%, (43/58) subjects were responders based on NICE criteria. At baseline, MEPO responders were on a significantly lower mOCS dose (supplementary Table E4) [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%,(4/41) vs non-responder: 42.9%,(6/14), P=0.012] and depression [responder: 19.1%,(8/42) vs non-responder: 46.7%,(7/15), P=0.037]. In multivariate analysis (Table 2), only better ACQ6 at baseline was independently associated with MEPO response.

*Mepolizumab super-responders*

According to our definition, 19%, (11/58) of MEPO subjects who completed trials were super-responders, which constituted 25.6%, (11/43) of MEPO responders. At baseline, MEPO super-responders (supplementary Table E5) 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 $FEV_1$% [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 BMI [Median (IQR), super-responder: 25.1(5) vs non-super-responder: 29.9(12.3), P=0.009] and a lower prevalence of obesity (BMI[?]30 $kgm^{-2}$) [super-responders: 9.1%,(1/11) vs non-super-responder: 48.9%,(23/47), P= 0.019]. Multivariate analysis (Table 2) found that more exacerbations and better ACQ6 at baseline were independently associated with MEPO super-response.

*Overall biologic non-response*

All biologic non-responders, N=27 (OMA [44.4%,12/27], MEPO [55.6%,15/27]), were combined and compared with the SNB group and responder groups. Compared to SNB subjects, at baseline, combined non-responders (CNRs) (Table 3) had significantly more AHE, worse ACQ6 and worse lung function. Furthermore, they were significantly more mOCS dependent, more atopic and had a larger proportion of multiple

AHE.

Compared to both biologic responders, CNRs had significantly worse baseline ACQ6 and greater prevalence of anxiety. In comparison with MEPO responders, a significantly larger proportion of CNRs were female, had depression, dysfunctional breathing and multiple AHE. Furthermore, CNRs had significantly more AHE at baseline and had younger asthma onset. Compared to OMA responders, there were no notable differences apart from those conferred by qualifying criteria (more Atopy/ lower Maximum PBE).

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

Within our biologic (OMA+ MEPO) 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 GETE used in OMA (Figure 2a) 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).

In comparison, in MEPO, 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 2b). 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 MEPO responders did not show ACQ (21.0%, 8/38) nor AQLQ (30.8%, 8/26) responses.

*Discussion*

This is the first real-world study to compare the parallel biologic naïve characteristics of OMA and MEPO treated subjects against a common comparator that remained biologic naïve (SNB) within the same cohort. A key finding was that despite potentially overlapping clinical indications for these drugs, OMA and MEPO treated patients showed distinctive asthma phenotypes. Regardless of that, both biologic response rates were comparable to RCTs and other reports (19–26). In addition, for OMA, even though 43.3% (45/104) patients were potentially dual-eligible for MEPO, the OMA response rate was 88.5%, reiterating that OMA was efficacious in the phenotype that received it. Indeed, both OMA and MEPO conferred substantial multidimensional clinical benefit to the real-world populations which received them. This testifies to the success of both biologics in targeting treatable traits in difficult asthma patients. Nevertheless, non-responders emerged to both drugs, typically characterised by worse baseline disease and psychological comorbidity.

Of those with highest disease burden in our cohort (OMA, MEPO, SNB), 51.6% did not receive biologics. Both biologic receiving groups had hallmarks of greater disease severity with significantly worse lung function (Clinic $FEV_1$%), 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 a responsiveness to that conventional optimisation. Conversely, biologics treated subjects had already undergone substantial treatment optimisation, without sufficient response, prior to their characterisation in this study.

Although our three high burden groups were similar with regards to ACQ6, exacerbations and AHE, they were phenotypically distinct. OMA patients had a younger, early-onset, atopic phenotype, with high proportions of co-morbid ABPA and rhinitis. Conversely, MEPO patients had an older, male, late-onset, eosinophilic but less atopic phenotype, associated with higher prevalence of nasal polyposis but less dysfunctional breathing.

This adds further insight to preliminary suggestions of typical patient features for these biologics outlined by GINA (27). Additionally, stratification of biologic use by our recently described age-of-onset/sex phenotypes (15) further corroborate these findings, as we found significantly different biologic use across the four phenotypes. Notably, the female/early-onset phenotype showed highest prevalence of OMA and lowest prevalence of MEPO use, while the male/adult-onset phenotype showed highest prevalence of MEPO use. This may part explain a disparity in biologic effect, whereby OMA but not MEPO, significantly improved Clinic $FEV_1$%, mirroring findings of another real-world UK study (26). This observed difference could be partly explained by the higher representation of MEPO patients among the male/adult-onset phenotype which had poorest baseline lung function (15) in our cohort. Other reports have also confirmed that such patients have more severe, persistent airflow limitation (28), potentially explaining their limited lung function improvement. Another disparity was in steroid-sparing effect, whereby MEPO but not OMA, significantly reduced mOCS dependency. This may reflect different trial durations. Indeed, other studies which evaluated OMA beyond 16-weeks, found that it reduced the proportion of patients on mOCS (16,21,22,29,30). This may also reflect clinical practice during the single biologic phase, 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 OMA and MEPO response. A pooled analysis of seven clinical trials found that baseline characteristics were unable to reliably predict OMA benefit (23). For MEPO, post-hoc analyses of RCT data suggested that baseline PBE could be a useful predictor of response (31), but this was not consistently observed in real-world studies (24,26), including ours. Instead, our data suggests that patients with the most severe and poorly controlled baseline disease were poorest responders. Thus, for MEPO, better baseline asthma control was independently associated with response and super-response. This mirrored the findings of Kavanagh et al. (26), where in their cohort, poor disease control at baseline was independently associated with MEPO non-response. Similarly, in OMA, 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, Gastrointestinal reflux disease, dysfunctional breathing and psychological morbidity(32). 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 significantly(32). 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 OMA non-response while depression was independently associated with OMA non-super-response and was associated with MEPO 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 response (33). The impact of psychopathology on biologic outcome could be secondary to the well documented interplay between psychological disease and SA (34). Psychopathologies have been associated with worse asthma control, more exacerbations and more AHE (35–37). Furthermore, studies have shown that proinflammatory cytokines associated with asthma are raised in depression and anxiety (38,39), which may dampen biologic effect. Brown et al showed in a RCT that 12-week continuous escitalopram therapy for SA patients with co-morbid major depression significantly reduced OCS use and asthma control (40). 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 characterised 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 aug-

mented 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 use (15). This reiterates the importance of holistically addressing treatable traits, through addressing psychopathologies before biologic therapy.

Head-to-head comparisons between OMA and MEPO response rates were not appropriate in our data, given their different phenotypic traits, and the different response tools employed. However, notably,10/15 MEPO '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 MEPO patients were not classified as responders according to NICE criteria(14). A post-hoc analysis of two MEPO RCTs found that ACQ was unreliable in predicting MEPO response (41). Though important, their findings were based on RCT data which may have limited transferability to real-world patients (7–9). Additionally, ACQ is used to gauge MEPO response in the Australian Mepolizumab Registry, and shown to correlate with improvements in objective measures(25). Conversely, few MEPO responders did not sustain an ACQ or AQLQ response. This could be because 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 MEPO 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 MEPO 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 are the first to report detailed real-world clinical outcomes on both OMA and MEPO in parallel, against a non-biologic comparator in a difficult asthma cohort. Additionally, our cohort represents an extensively characterised 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 pooled analysis of the non-responder group and explored other definitions of response in MEPO, compared to OMA.

## CONCLUSION:

In summary, in this real-world difficult asthma cohort, OMA and MEPO 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 personalised and optimal use of biologic therapies, future research should develop a deeper endotypic understanding of asthma biologic need and responsiveness.

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*Table 1. Baseline characteristics of the Biologic cohorts vs severe asthma, non-biologics cohort*

| | **Omalizumab group, N= 105 (A)** | **Omalizumab group, N= 105 (A)** | **Mepolizumab group, N= 62 (B)** | **Mepolizumab group, N= 62 (B)** | **Severe asthma, non-biologic group, N=178 (C)** | **Severe asthma, non-biologic group, N=178 (C)** | **P-values** | **P-valu** |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) / Median (IQR) | Missing | Mean (SD) / Median (IQR) | Missing | Mean (SD) / Median (IQR) | Missing | **A vs C** | **B vs C** |
| **Annualised rate of exacerbations, median (IQR)** | 5 (3) + | 2 | 4 (5) + | 1 | 5 (3) ++ | 32 | 0.391 | 0.744 |
| **Annualised rate of AHE, median (IQR)** | 1 (2) + | 9 | 0 (1) + | 3 | 0 (1) ++ | 1 | 0.238 | 0.184 |
| **Μαξιμυμ Εος ϛουντ ιν τηε παστ ψεαρ, μεδιαν (IXP) - ϛελλς/μΛ** | 250 (400) + | 9 | 500(400) + | 0 | 200 (300) ++ | 49 | 0.052 | **<0.001** |
| **ACQ6, median (IQR)** | 3 (1.79) § | 25 | 2.67 (1.67) § | 3 | 3 (1.8) ++ | 11 | 0.594 | 0.795 |
| **FENO, median (IQR) - ppb** | 30 (38) § | 27 | 36 (52) § | 3 | 16.85 (24.65) ++ | 50 | **0.007** | **<0.001** |

| | **Omalizumab group, N= 105 (A)** | **Omalizumab group, N= 105 (A)** | **Mepolizumab group, N= 62 (B)** | **Mepolizumab group, N= 62 (B)** | **Severe asthma, non-biologic group, N=178 (C)** | **Severe asthma, non-biologic group, N=178 (C)** | **P-values** | **P-valu** |
|---|---|---|---|---|---|---|---|---|
| **Clinic $FEV_1$ %, mean (SD)** | 66.59 (20.77) § | 6 | 67.1 (20.77) § | 2 | 76.78 (23.37) ++ | 57 | **0.001** | **0.007** |
| **Maintenance OCS dose, median (IQR) - mg** § | 10 (10) | 1 | 10 (10) | 0 | n/a | n/a | n/a | n/a |
| **BMI, median (IQR) – $kgm^{-2}$** ++ | 30.60 (9.75) | 0 | 28.95 (28.95) | 0 | 30.8 (10.8) | 3 | 0.502 | 0.214 |
| **Age of asthma diagnosis, median (IQR) - y** | 10 (25) | 4 | 28 (38.5) | 1 | 20 (35) | 9 | **0.007** | **0.039** |
| **Age, median (IQR) - y** | 52 (18.5) | 0 | 61 (19) | 0 | 54.5 (25) | 0 | 0.643 | **0.015** |
| | **Percentage (N)** | Missing | **Percentage (N)** | Missing | **Percentage (N)** | Missing | **P-value** | **P-valu** |
| **Multiple AHE (>1), Yes** | 31.3% (30) + | 9 | 16.9% (10) + | 3 | 24.3% (43) ++ | 5 | 0.215 | 0.242 |
| **On Maintenance OCS, Yes** | 47.6% (50) § | 0 | 72.6% (45) § | 0 | 30.6% (53) ++ | 1 | **0.004** | **<0.001** |
| **Adult-onset asthma, Yes** | 37.6% (38) | 4 | 60.7% (37) | 1 | 52.7% (89) | 9 | **0.017** | 0.282 |

| | **Omalizumab group, N= 105 (A)** | **Omalizumab group, N= 105 (A)** | **Mepolizumab group, N= 62 (B)** | **Mepolizumab group, N= 62 (B)** | **Severe asthma, non-biologic group, N=178 (C)** | **Severe asthma, non-biologic group, N=178 (C)** | **P-values** | **P-valu** |
|---|---|---|---|---|---|---|---|---|
| **Sex, Male** | 33.3% (35) | 0 | 53.2% (33) | 0 | 29.8% (53) | 0 | 0.532 | **0.001** |
| **Ethnicity, White** | 87.6% (92) | 0 | 91.9% (57) | 0 | 94.9% (169) | 0 | **0.026** | 0.362 |
| **Rhinitis, Ever** ++ | 73.6% (64) | 18 | 72.9% (43) | 3 | 60.1% (95) | 10 | **0.035** | 0.082 |
| **GORD, Ever** ++ | 64.4% (67) | 1 | 67.2% (41) | 1 | 65.3% (111) | 8 | 0.883 | 0.875 |
| **Smoking, Ever** ++ | 43.8% (46) | 0 | 56.5% (35) | 0 | 47.5% (84) | 1 | 0.552 | 0.223 |
| **Atopy (SPT / sIgE positive)** ++ | 100% (105) | 0 | 50.0% (31) | 0 | 52.8% (94) | 0 | **<0.001** | 0.703 |
| **Obesity (BMI[?]30kg/m$^2$), Ever** ++ | 52.4% (55) | 0 | 41.9% (26) | 0 | 52.6% (92) | 3 | 0.975 | 0.097 |
| **Admitted to ICU for asthma, Ever** ++ | 27.9% (29) | 1 | 35.5% (22) | 0 | 32.6% (58) | 0 | 0.410 | 0.677 |
| **Intubated for Asthma, Ever** ++ | 14.4% (15) | 1 | 14.5% (9) | 0 | 17.4% (31) | 0 | 0.512 | 0.598 |
| **Dysfunctional breathing, Ever** ++ | 51.5% (51) | 6 | 40.0% (24) | 2 | 55.1% (92) | 11 | 0.572 | **0.045** |
| **ILO, Ever** ++ | 19.4% (18) | 12 | 13.8% (8) | 4 | 13.2% 921) | 19 | 0.193 | 0.911 |

| | **Omalizumab group, N= 105 (A)** | **Omalizumab group, N= 105 (A)** | **Mepolizumab group, N= 62 (B)** | **Mepolizumab group, N= 62 (B)** | **Severe asthma, non-biologic group, N=178 (C)** | **Severe asthma, non-biologic group, N=178 (C)** | **P-values** | **P-valu** |
|---|---|---|---|---|---|---|---|---|
| **Depression, Ever ++** | 31.9% (29) | 14 | 28.3% (17) | 2 | 42.8% (68) | 19 | 0.089 | 0.051 |
| **Anxiety, Ever ++** | 30.8% (28) | 14 | 27.1% (16) | 3 | 38.0% (60) | 19 | 0.252 | 0.136 |
| **Bronchiectasis, Ever ++** | 15.5% (16) | 2 | 19.4% (12) | 0 | 14.2% (25) | 2 | 0.762 | 0.336 |
| **Salicylate sensitivity, Ever ++** | 33.0% (34) | 2 | 19.4% (12) | 0 | 27.8% (49) | 2 | 0.416 | 0.188 |
| **ABPA, Ever ++** | 12.6% (13) | 2 | 12.9% (8) | 0 | 5.2% (9) | 4 | **0.027** | 0.081 |
| **Sulphite sensitivity, Ever ++** | 8.7% (9) | 2 | 9.7 % (6) | 0 | 7.4% (13) | 3 | 0.696 | 0.590 |
| **COPD, Ever ++** | 5.8% (6) | 2 | 9.7 % (6) | 0 | 10.8% (19) | 2 | 0.161 | 0.805 |
| **Nasal polyps, Ever ++** | 21.4% (21) | 7 | 34.5% (20) | 4 | 19% (31) | 15 | 0.635 | **0.019** |
| **Nasal (polyps / sinus) surgery, Ever ++** | 31.6% (30) | 10 | 31.7% (19) | 2 | 19.3% (31) | 17 | **0.025** | **0.050** |
| **Urticaria or Angioedema, Ever ++** | 12.6% (13) | 2 | 8.1% (5) | 0 | 6.8% (12) | 2 | 0.101 | 0.776 |
| **OSA, Ever ++** | 4.9% (5) | 2 | 6.5% (4) | 0 | 11.5% (20) | 4 | 0.062 | 0.259 |

| | **Omalizumab group, N= 105 (A)** | **Omalizumab group, N= 105 (A)** | **Mepolizumab group, N= 62 (B)** | **Mepolizumab group, N= 62 (B)** | **Severe asthma, non-biologic group, N=178 (C)** | **Severe asthma, non-biologic group, N=178 (C)** | **P-values** | **P-valu** |
|---|---|---|---|---|---|---|---|---|
| **Eczema, Ever ++** | 31.7% (33) | 1 | 27.4% (17) | 0 | 21.6% (38) | 2 | 0.060 | 0.349 |

Categorical data are presented as proportions and numbers. Continuous data are either presented as Median + Interquartile range (IQR) or Mean + standard deviation (SD). +: In the preceding 12 months prior to biologic approval. ++: at WATCH enrolment. §: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. EOS: 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. $FEV_1$: forced expiratory volume in one second. Adult-onset: Age of asthma onset [?]18 years. GORD: Gastrointestinal 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 features 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 $FEV_1$%, Age, BMI, Sex, Baseline annualised rate of exacerbations, Multiple AHE, Annualised rate of AHE, Anxiety. | Baseline annualised rate of exacerbations | 0.024 | 1.622 (1.065-2.469) | 0.856 |
| | | | Lower baseline annualised 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 annualised rate of exacerbations, 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** | **Mepolizumab models Cases included** | **Mepolizumab models Variables included** | **Mepolizumab models Final variables** | **Mepolizumab models P-value** | **Mepolizumab models OR; 95 CI** | **Mepolizumab models AUC of model** |
| Mepolizumab responders vs non-responders | 42/58, 72.4% | ACQ6, Multiple AHE, Depression, Anxiety, AQLQ baseline, Total HADS baseline, Baseline annualised rate of AHE, 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 annualised rate of exacerbations ACQ6, Clinic $FEV_1$%, 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 annualised rate of exacerbations | 0.023 | 1.487 (1.046-2.115) |

$FEV_1$: 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 3: Baseline characteristics of combined biologic non-responders vs SNB and responders*

**Combined non-responder group, N=27 (A)**

**Combined non-responder group, N=27 (A)**

**Omalizumab responder,**

N=92 (B)

**Omalizumab responder,**

N=92 (B)

**Mepolizumab responder,**

N=43 (C)

**Mepolizumab responder,**

N=43 (C)

**Severe asthma, non-biologic group, N=178 (D)**

**Severe asthma, non-biologic group, N=178 (D)**

**P values**

**P values**

**P values**

Mean (SD) / Median (IQR)

Missing

Mean (SD) / Median (IQR)

Missing

Mean (SD) / Median (IQR)

Missing

Mean (SD) / Median (IQR)

Missing

*A vs B*

*A vs C*

*A vs D*

**Annualised rate of exacerbations, median (IQR)**

4 (5) +

2

5 (2) +

1

4 (5) +

1

5 (3) ++

32

0.526

0.864

0.978

**Annualised rate of AHE, median (IQR)**

1 (3) +

1

0 (2) +

8

0 (1) +

2

0 (1) ++

1

0.095

**0.002**

**0.028**

**Μαξιμυμ Εος ςουντ ιν τηε παστ ψεαρ, μεδιαν (IXP) - ςελλς/μΛ**

400 (400) +

2

200 (400) +

7

500 (500) +

0

200 (300) ++

49

**0.005**

0.178

**<0.001**

**ACQ6, median (IQR)**

3.67 (1.26) §

6

3 (1.83) §

20

2.33 (2.27) §

2

3 (1.8) ++

11

**0.036**

**<0.001**

**0.017**

**FENO, median (IQR) - ppb**

22 (59.6) SS

4

29.5 (37) SS

24

37 (46.5) SS

2

16.85 (24.65) ++

50

0.514

0.129

0.383

**Clinic $FEV_1$ %, mean (SD)**

61.64 (21.75) SS

1

68.13 (20.49) SS

6

67% (20.1) SS

1

76.78 (23.37) ++

57

0.483

0.909

**0.003**

**BMI, median (IQR) -kgm$^{-2}$** ++

30.6 (15.9)

0

30.36 (5.99)

0

29.1 (11.5)

0

30.8 (10.8)

3

0.194

0.160

0.469

**Age at asthma diagnosis, median (IQR) - y** ++

12 (31)

0

11 (25.5)

3

33.5 (40.5)

1

20 (35)

9

0.627

**0.032**

0.355

**Age, median (IQR) - y**

54 (28)

0

53 (20.5)

0

61 (19)

0

54.5 (25)

0

0.871

0.110

0.997

**Percentage (N)**

Missing

**Percentage (N)**

Missing

**Percentage (N)**

Missing

**Percentage (N)**

Missing

*A vs B*

*A vs C*

*A vs D*

**Multiple (>1) AHE, Yes**

48% (12) +

2

27.4% (23) +

8

9.8% (4) +

2

24.3% (43) ++

5

0.053

**0.001**

**<0.001**

**On maintenance OCS, Yes**

66.7% (18) SS

0

46.7% (43) SS

0

69.8% (30) SS

0

30.6% (53) ++

1

0.069

0.797

**0.013**

**Adult-onset asthma**, **Yes**

38.5% (10)

0

39.3% (35)

1

61.9% (26)

1

52.7% (89)

9

1.000

0.060

0.178

**Sex, Male**

33.3% (9)

0

35.9% (33)

0

58.1% (25)

0

29.8% (53)

0

1.000

**0.043**

0.822

**Ethnicity, White**

92.6% (25)

0

89.1% (82)

0

90.7% (39)

0

94.9% (169)

0

0.732

1.000

0.642

**Rhinitis, Ever ++**

80.8% (21)

1

73.0% (54)

22

68.3% (28)

2

60.1% (95)

10

0.430

0.262

**0.043**

**GORD, Ever ++**

73.1% (19)

1

64.1% (59)

0

61.9% (26)

1

65.3% (111)

8

0.485

0.344

0.434

**Smoking, Ever ++**

51.9% (14)

0

43.5% (40)

0

53.5% (23)

0

47.5% (84)

1

0.442

0.894

0.670

**Atopy (SPT /sIgE positive) ++**

74.0% (20)

0

100% (92)

0

51.2% (22)

0

52.8% (94)

0

**<0.001**

0.057

**0.038**

**Obesity (BMI[?]30kgm$^{-2}$), Ever ++**

55.6% (15)

0

50.0% (46)

0

41.9% (18)

0

52.6% (92)

3

0.612

0.190

0.772

**ICU admission for asthma, Ever ++**

33.3% (9)

0

26.4% (24)

1

37.2% (16)

0

32.6% (58)

0

0.479

0.802

1.000

**Intubated for Asthma, Ever ++**

18.5% (5)

0

14.3% (13)

1

9.3% (4)

0

17.4% (31)

0

0.591

0.292

1.000

**Dysfunctional breathing, Ever ++**

59.3% (16)

0

48.8% (42)

6

31.7% (13)

2

55.1% (92)

11

0.345

**0.025**

0.686

**ILO, Ever** ++

25.9% (7)

0

17.5% (14)

12

7.7% (3)

4

13.2% (21)

19

0.340

0.077

0.140

**Depression, Ever** ++

48% (12)

2

30.4% (24)

13

19.1% (8)

1

42.8% (68)

19

0.107

**0.012**

0.624

**Anxiety, Ever** ++

50% (13)

1

26.6% (21)

13

20.0% (8)

3

38.0% (60)

19

**0.027**

**0.011**

0.245

**Bronchiectasis, Ever ++**

18.5% (5)

0

14.4% (13)

2

18.6% (8)

0

14.2% (25)

2

0.560

1.000

0.563

**Salicylate sensitivity, Ever ++**

18.5% (5)

0

33.3% (30)

2

18.6% (8)

0

27.8% (49)

2

0.140

1.000

0.307

**ABPA, Ever ++**

14.8% (4)

0

12.2% (11)

2

14.0% (6)

0

5.2% (9)

4

0.746

1.000

0.079

**Sulphite sensitivity, Ever ++**

7.4% (2)

0

7.8% (7)

2

11.6% (5)

0

7.4% (13)

3

1.000

0.699

1.000

**COPD, Ever ++**

7.4% (2)

0

6.7% (6)

2

9.3% (4)

0

10.8% (19)

2

1.000

1.000

0.746

**Nasal polyps, Ever ++**

24% (6)

2

20.9% (18)

6

37.5% (15)

3

19% (31)

15

0.743

0.258

0.591

**Nasal (polyps / sinus) surgery, Ever ++**

32% (8)

2

31.3% (26)

13

35.7% (15)

1

19.3% (31)

17

0.949

0.757

0.145

**Urticaria or Angioedema, Ever ++**

7.4% (2)

0

13.3% (12)

2

7.0% (3)

0

6.8% (12)

2

0.517

1.000

1.000

**OSA, Ever ++**

11.1% (3)

0

4.4% (4)

2

4.7% (2)

0

11.5% (20)

4

0.350

0.367

1.000

**Eczema, Ever ++**

25.9% (7)

0

33.0% (30)

1

25.6% (11)

0

21.6% (38)

2

0.489

1.000

0.614

Categorical data are presented as proportions and numbers. Continuous data is either presented as Median + Interquartile range (IQR) or Mean + standard deviation (SD). +: In the preceding 12 months prior to biologic approval. ++: at WATCH enrolment. SS: at baseline biologic visit. Exacerbations: incidence of exacerbations requiring OCS / increase in maintenance OCS. AHE: acute healthcare encounters, which include Emergency department/ hospital admissions. EOS: 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. $FEV_1$: forced expiratory volume in one second. Adult-onset: Age of asthma onset [?]18 years GORD: Gastrointestinal 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. Combined non-responders were a combined group of Omalizumab non-responders (N=12) and Mepolizumab responders (N=15). Unpaired t-tests, Mann-Whitney U test, Chi-square tests or Fisher's exact tests were used, where appropriate, to calculate P-values.

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

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

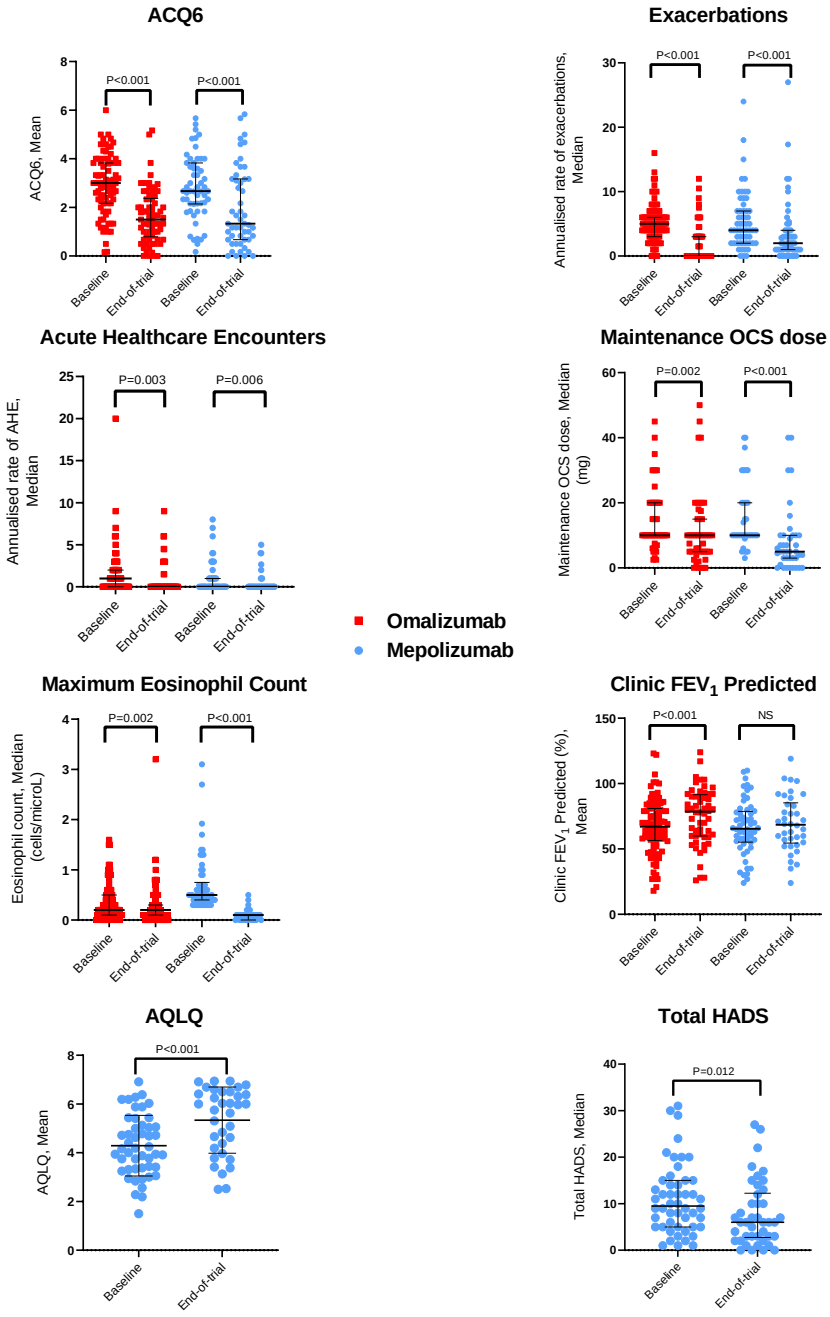
| **Phenotype and Proportions within overall WATCH cohort** | **Phenotype and Proportions within overall WATCH cohort** | **Male, early-onset (14.0%)** | **Male, early-onset (14.0%)** | **Female, early-onset (34.7%)** | **Male, adult-onset (20.8%)** | **Female, adult-onset (30.5%)** |
|---|---|---|---|---|---|---|
| | | B | 0.135 | 0.135 | 0.135 | 0.135 |
| | | C | 0.893 | 0.893 | 0.893 | 0.893 |

Early-onset is defined as having an age of asthma onset<18 years. Adult-onset is defined as having an age of asthma onset [?]18 years. + of those who completed biologic trials, i.e.: did not withdraw due to any reason. A= Chi-squared tests were performed to assess biologic use across the four age-of-onset/sex clusters. 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: 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. $FEV_1$: forced expiratory volume in one second. AQLQ: Asthma Quality of Life Questionnaire. HADS: Hospital anxiety and depression scale.

Figure 2: Alternative assessments of biologic outcomes. Figure 2a: Side-by-side comparisons of different measures of biologic response. Figure 2b: Mepolizumab focused measures of biologic response. Numbers represent patient counts. ACQ: Asthma Control Questionnaire 6. AHE: acute healthcare encounters, which include Emergency department/ hospital admissions. OCS: Response with regard to exacerbations (incidence of exacerbations needing an acute OCS course or an increase in maintenance OCS dose). AQLQ: Asthma Quality of Life Questionnaire. MDT: multi-disciplinary team decision. Response for ACQ and AQLQ was defined as a reduction greater than the minimally important difference of [?]0.5. AHE response was defined as patients who had [?]1 AHE at baseline but now currently have no AHE. OCS response is defined as a reduction of maintenance OCS dose or exacerbations by [?]50%. MDT response is defined earlier in the methods. The blue outlier in figure 2a and 2b is a patient who reduced his maintenance OCS from 10-7mg and had no exacerbations nor AHE in the trial period (from a baseline of 0), and thereby had a positive trial.




## Hosted file

Figure 2.pdf available at https://authorea.com/users/469021/articles/562171-phenotypes-and-clinical-outcomes-of-omalizumab-and-mepolizumab-treated-difficult-asthma-patients