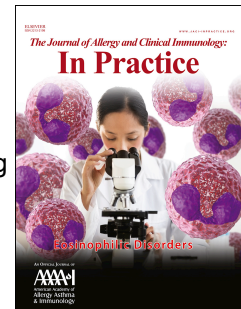


Journal Pre-proof

Optimizing omalizumab dosing in severe asthma – the exploration of therapeutic drug monitoring

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1 Optimizing omalizumab dosing in severe asthma – the exploration of therapeutic drug
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Clinical implication: We found a wide variability of omalizumab serum levels in a long-term responder population. Therefore, therapeutic drug monitoring might become viable in the near future, thereby improving the application of these expensive agents and further pursuing personalized medicine.

Therapeutic drug monitoring (TDM), measuring drug concentrations to adjust dosing and optimize treatment outcomes, is commonly applied to personalize costly biological treatment in rheumatoid arthritis and inflammatory bowel disease (IBD).⁽¹⁾ Currently, TDM is not used for the biologics applied in severe asthma, but might likewise help to optimize therapy efficacy, safety and cost-effectiveness.⁽²⁾ Studies evaluating variability in biologic serum levels in long-term responders, combined with clinical asthma outcomes, are lacking.

Omalizumab has been used in the treatment of severe allergic asthma since 2003. Therapy is evaluated after 16 weeks and continued in patients with good response.⁽³⁻⁵⁾ In early dose-finding trials, it was found that to achieve sufficient immunoglobulin E (IgE) suppression, omalizumab serum levels should be in serum-excess over baseline IgE of at least 15:1.⁽⁶⁾ This approach translated to the currently applied dosing table, incorporating baseline IgE and bodyweight.⁽⁷⁾ It is unknown to what end this 15:1 ratio is achieved or surpassed in patients receiving long-term (≥ 1 year) omalizumab therapy and what variability is seen in these ratios.

Despite being characterized by their pulmonologist as 'omalizumab responders' based on achieved improvements in clinical parameters, some patients still suffer from lack of control and need their next dose sooner than the standard dosing interval. On the other hand, some patients can maintain control with extended dosing intervals. Inadequate or excessive

biologic trough levels (the serum level before the next administration) might be related to this phenomenon.

Therefore, the variability in excess of omalizumab trough level over baseline IgE was determined in a real-world responder population, receiving long-term (≥ 1 year) omalizumab therapy for the treatment of severe asthma. In addition, the relationship between omalizumab trough levels and patient-reported need for the next administration was examined.

Patients recruited from a severe asthma centre in the Netherlands, all of whom were receiving long-term (≥ 1 year) omalizumab therapy for the treatment of severe allergic asthma by June 2019 were selected and informed consent was collected. In addition to the standard 6-monthly evaluation, recording questionnaires (Asthma Control Questionnaire (ACQ), Asthma-related Quality of Life Questionnaire (AQLQ)) and spirometry, omalizumab trough levels in serum were determined at the end of the dose interval. We used a modified patient-reported outcome measure BORG-scale ranging from 'no need' (score 0) to 'extreme need' (score 10) to quantify the patient-reported need for the next omalizumab administration.⁽⁸⁾ Patients were divided in subgroups with none to low need (0-2) and higher need (3-10). Inhalation medication was optimized before starting omalizumab treatment and monitored during the treatment.

27 severe asthma patients (GINA step 5) were included. Baseline characteristics are displayed in table 1.

The median omalizumab excess over baseline IgE was 72.5:1, ranging from 14.1:1 to 511.3:1 (Fig E1, online repository). All patients except one (96.3%) had an excess $\geq 15:1$. Median omalizumab trough-level was 50 $\mu\text{g/mL}$ (IQR 20-64), ranging from 9 $\mu\text{g/mL}$ to 100 $\mu\text{g/mL}$.

14 patients reported a low need for the next administration versus 13 with a high need for the next administration. Higher patient-reported need was associated with lower omalizumab trough levels ($\beta = -5.11$, 95% CI = -10.16 to -0.06, $p = 0.048$). Patients in the high need group had significantly lower median omalizumab trough levels as compared to the low need group (Fig 1A and 1B). No significant associations were found between omalizumab trough levels and other clinical parameters (exacerbation rate, ACQ, AQLQ, FEV1, FeNO). No significant associations were found between patient-reported need and gender, BMI, omalizumab interval, inhaled corticosteroid dose and reliever medication.

In this explorative study in long-term omalizumab treated patients, we found a large variability in omalizumab to baseline IgE ratios as well as omalizumab through levels, suggesting an opportunity to individualize treatment. These findings encourage to further explore the potential of TDM in omalizumab treatment.

The 15:1-excess mentioned in early omalizumab dose-finding trials is achieved in almost all patients. This implies that the currently applied dosing table probably succeeds in achieving sufficient IgE suppression. However, the excess generously surpasses the ratio found in early trials in most patients, indicating possible overtreatment with omalizumab in these long-term responders. Interindividual trough levels varied greatly, as was the case in a similar study evaluating infliximab levels in IBD patients. In the latter study, an association between remission and infliximab trough levels was found.⁽⁹⁾ These and similar results led to the incorporation of TDM in the application of biologics for IBD, personalizing the treatment and optimizing clinical outcomes. The large variability we observed in this explorative study in omalizumab responders after at least 1 year of treatment encourages to exploring whether

inadequate omalizumab levels are associated with different levels of response to therapy in a more diverse population with responders, partial responders and non-responders.

The observed association between patient-reported need and omalizumab trough level is remarkable. Despite being an 'omalizumab responder', some patients indicate that the applied dosing regime is not optimal. A possible explanation might be that patients with higher blood levels clear omalizumab more slowly, resulting in more stable and adequate omalizumab levels and smaller fluctuations in unbound IgE. Fluctuations in unbound IgE might lead to a relative loss of control, leading to the feeling of needing the next administration. We were not able to test this hypothesis since no assay for measuring unbound IgE was available. However, the excess of omalizumab to baseline IgE found in our population seems to negate this explanation.

This proof of principle study is the first to evaluate the variability of omalizumab trough levels in severe asthma patients treated for more than one year and patient-reported need for the next administration and provides an opportunity to individualize treatment, adjusting the currently applied dosing schedule. The focus on therapeutic drug monitoring is an innovative approach towards personalized medicine in severe asthma care. The study includes a complete single centre responder population, but the number of participants remains limited. Data on the variability in serum levels of other biologics used in the treatment of severe asthma is currently lacking. Therefore larger studies are warranted in more diverse populations, focusing on the applicability of TDM in the recently approved biologics for severe asthma. The incorporation of serum level measurements of biological therapy has led to successful individualization of medicine in other diseases, increasing

117 efficacy, patient wellbeing, patient safety and cost-effectiveness, an addition which
118 undoubtedly will be welcomed in severe asthma clinical care.

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Legend section

Figure 1:

1A: Omalizumab trough levels ranging from high to low. Each bar represents a trough level of a patient. The high or low patient-reported need for the next gift is represented by the respective gray and white bars.

1B: Boxplot of the omalizumab trough levels and patient-reported need subgroups. Patients in the low need group had significantly higher omalizumab trough levels as compared to the high need group: 59 $\mu\text{g/mL}$ (IQR 40-98) vs 34 $\mu\text{g/mL}$ (IQR 20-53), $p=0.041$.

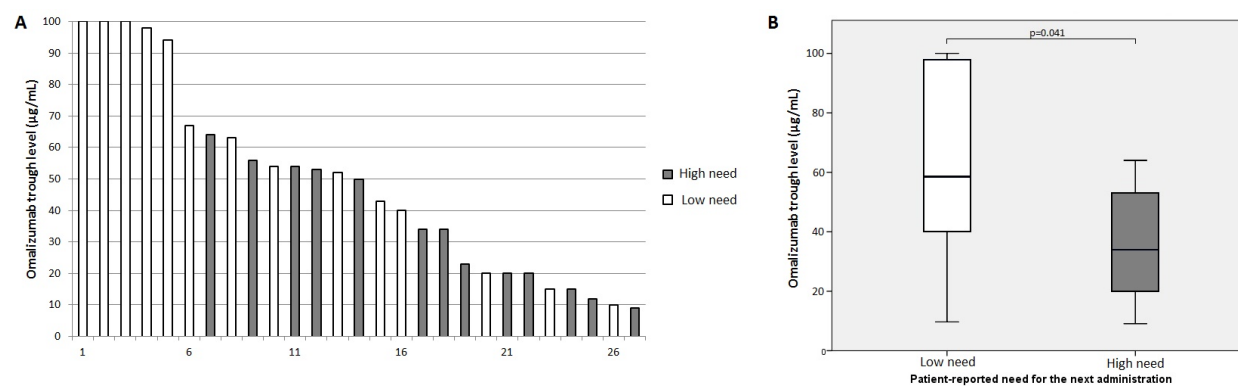
156 Table section

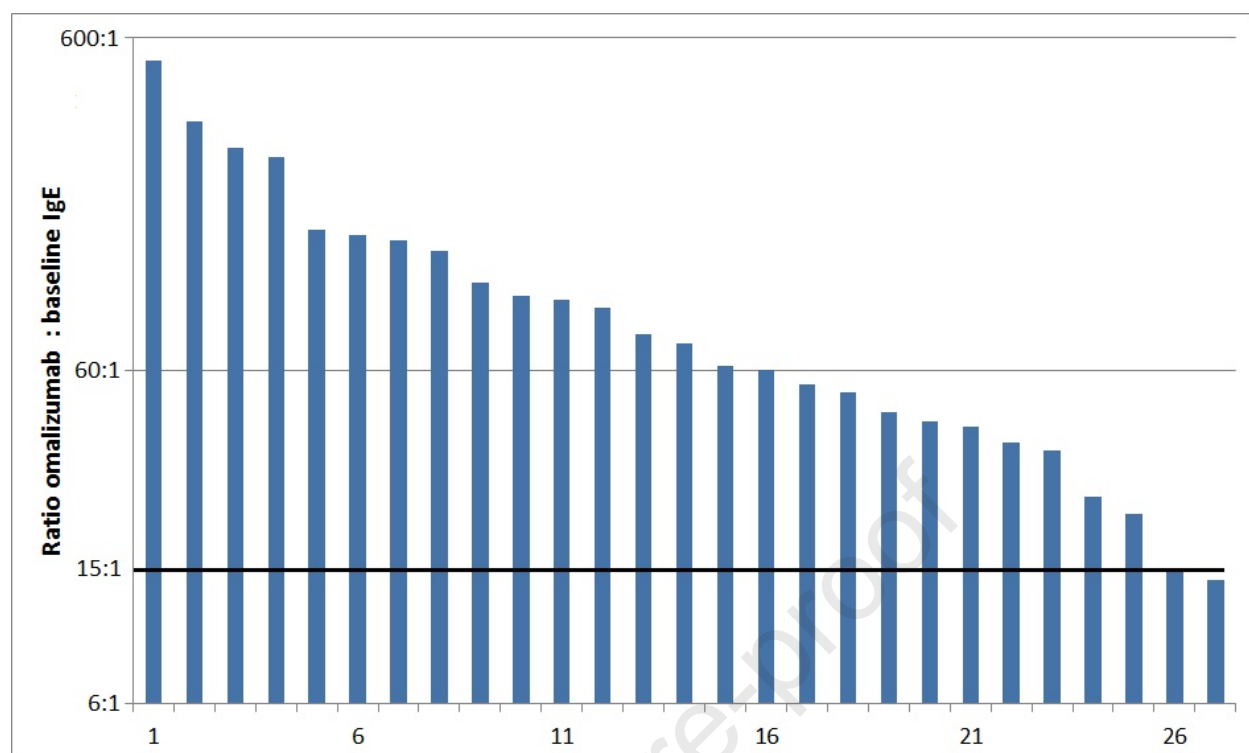
157 Table 1: Baseline characteristics.

Characteristic	N=27
Age (years, median; IQR)	54 (33-59)
Gender (Male; N; %)	10 (37%)
Bodyweight (kg, median; IQR)	88 (76-95)
BMI (median; IQR)	27.7 (25.1-33.6)
Inhaled fluticasone equivalents (mg/day, median; IQR)	1000 (500-1000)
Inhaled formoterole equivalents (mg/day, median; IQR)	24 (24-24)
Treatment duration (months, median; IQR)	38 (24-58)
Omalizumab dose (mg, range)	150 – 600
Omalizumab interval (weeks, range)	2 – 6
Dose per 4 weeks (mg, median; IQR)	450 (300-750)
Annual exacerbation rate (median; IQR; range)	0 (0-1), (0-1)
ACQ-score (median; IQR)	0.83 (0.50-2.17)
AQLQ-score (median; IQR)	6.07 (5.26-6.35)
FEV1 pre-salbutamol (%predicted, median; IQR)	79 (73-94)
Fractional exhaled Nitric Oxide (FeNO) (ppb, median; IQR)	20 (13-40)

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159 Abbreviations: ACQ = Asthma control questionnaire, AQLQ = Asthma-related quality of life
 160 questionnaire, FeNO = Fractional exhaled nitric oxide, FEV1 = Forced expiratory volume in 1
 161 second, IQR = Interquartile range.





- 1 Legend section online repository
- 2 Figure E1 (online repository): Ratios omalizumab to baseline IgE ranging from high to low.
- 3 Each bar represents a ratio of a patient. The 15:1 threshold found in early dose-finding trials
- 4 is indicated by the black horizontal line.
- 5