



Early View

Research letter

Predicting the benefits of type-2 targeted anti-inflammatory treatment with the prototype OxfoRd Asthma attaCk risk scaLE (ORACLE)

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TITLE: Predicting the benefits of type-2 targeted anti-inflammatory treatment with the prototype OxfoRd Asthma attaCk risk scaLE (ORACLE)

Running title: Predicting treatment benefits in asthma using ORACLE

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- Ethical approval: The studies described herein were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines. Study protocols received independent ethics committee approval at each study site.
- Informed consent: All patients included in the studies provided written informed consent.

Author contributions: SC analysed the data and drafted the manuscript. WILH participated in data analysis, developed the ORACLE web application. RB contributed primary data; WILH, RB and TSCH participated in data analysis and reviewed/approved the manuscript. IP is the guarantor of this publication, contributed to the writing of the manuscript and reviewed and approved the final version.

Conflicts of interest

SC received a non-restricted research grant from Sanofi-Genzyme for investigator-initiated type 2 innovation research and received speaker honoraria from GlaxoSmithKline, Sanofi-Regeneron and AstraZeneca; outside the submitted work. **WIHD** is co-founder and shareholder of the Albus Health company; outside the submitted work. **RB** has received honoraria for presentations or

consulting in Adboards from AstraZeneca, Asthma and Respiratory Foundation of New Zealand, Avillion, Cipla and Theravance; and research grants from AstraZeneca, CureKids (NZ), Genentech, and the Health Research Council of New Zealand. **TSCH:** has received grants from the Wellcome Trust, The Guardians of the Beit Fellowship, Pfizer Inc., Kymab Ltd, University of Oxford, Sensyne Health and Sanofi Genzyme; outside the submitted work. He has received personal fees from Astra Zeneca, personal fees from TEVA, personal fees from Omniprex and personal fees from Peer Voice outside the submitted work. **IDP:** In the last 5 years, IP has received speaker's honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Ingelheim, Aerocrine AB, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron, Menarini, and GSK, and payments for organising educational events from AstraZeneca, GSK, Sanofi/Regeneron, and Teva. He has received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi, and Knopp, and payments to support FDA approval meetings from GSK. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, AstraZeneca, Teva, and Chiesi. He has received grants from Chiesi and Sanofi Genzyme. He is co-patent holder of the rights to the Leicester Cough Questionnaire and has received payments for its use in clinical trials from Merck, Bayer, and Insmad. In 2014-2015 he was an expert witness for a patent dispute involving AstraZeneca and Teva.

Take Home Message: The prototype ORACLE scale based on two simple measures of type 2 airway inflammation – blood eosinophils and FeNO – quantifies the excess risk conferred by raised biomarkers which is removed by type-2 anti-inflammatory treatment in trial populations.

251/254 characters, including spaces

Plain Language Summary: Reduction of the risk of asthma attacks is a major goal of current international asthma management guidelines. We aimed to show that it is feasible to predict the excess risk of asthma attacks which can be removed by anti-inflammatory treatment using the prototype Oxford Risk of Asthma attacks scale (ORACLE). This scale is based on two simple tests combined with additional clinical considerations. The two tests are biomarkers of the airway inflammatory response known to cause asthma attacks: one involves counting eosinophils – a type of white blood cell – in a blood sample, and the other measures exhaled nitric oxide during a breathing test. The prototype ORACLE predicted the excess risk conferred by raised biomarkers which is removed by anti-inflammatory therapy (inhaled corticosteroids or biologics) in trial populations. We conclude that pursuing a refined version of the prototype is worthwhile, as it could potentially allow doctors and people with asthma to quantify their risk and the potential benefit of increasing or decreasing their type-2 anti-inflammatory treatment.

ABBREVIATIONS

FeNO: fractional exhaled nitric oxide

ICS: inhaled corticosteroids

ORACLE: OxfoRd Asthma attaCk risk scaLE

RCT: randomised controlled trial

INTRODUCTION

Reduction of the risk of severe asthma attacks is a major goal of current guidelines [1]. The observation that blood eosinophils and fractional exhaled nitric oxide (FeNO) identify the higher risk type-2 inflammatory phenotype in asthma is potentially relevant to this goal [2].

Blood eosinophils and FeNO provide complementary mechanistic information on different immune compartments and inflammatory mediators involved in the pathogenesis of asthma: whereas blood eosinophils reflect the systemic pool of effector cells and circulating interleukin-5, FeNO identifies type-2 inflammation in the airway compartment [3]. In randomised controlled trials (RCT), blood eosinophils and FeNO are independently and additively associated with the risk of asthma attacks [4–8]. Importantly, this excess risk is reduced with appropriate treatment at all stages of the disease, be it inhaled corticosteroids (ICS) in mild asthma [9], a higher dose ICS in moderate asthma [5] or biological agents targeting type-2 cytokines in moderate-to-severe asthma [10, 11]. These observations are consistent with the treatable traits paradigm [12], which emphasizes the identification of patient characteristics to guide treatment.

To determine the feasibility of biomarker-stratified risk assessment, we previously derived a prototype OxfoRd Asthma attaCk risk scaLE (ORACLE) [2] using trial-level data from biomarker-stratified RCTs [4–8]. Here, we explore the hypothesis that the excess risk quantified by raised biomarkers in the prototype ORACLE is equivalent to the benefits of anti-inflammatory treatment observed in the derivation trials.

METHODS

Objective

To assess whether the anti-inflammatory treatment effect conferred by raised blood eosinophils and FeNO is predicted by the prototype ORACLE.

Study design

We performed a trial-level analysis of four RCTs in mild [9], moderate [5], and moderate-to-severe asthma [10, 11] comparing biomarker-stratified observed *vs* ORACLE-predicted effects of anti-inflammatory treatments (ICS or type-2 targeting biologics) on annualised severe asthma attack rates. Severe asthma attacks were defined as acute asthma requiring ≥ 3 days of systemic corticosteroids and/or hospitalisation [2].

Data collection

Observed biomarker-stratified attack rates. Observed annualised severe asthma attack rates of patients randomised to control and active arms were extracted from biomarker-stratified analyses of the Novel START (as-needed salbutamol *vs* low dose regular or as-needed ICS) [4], CAPTAIN (fluticasone furoate 100 *vs* 200 μ g/day-containing arms) [5], QUEST (placebo *vs* Dupilumab) [6, 8], and DREAM (placebo *vs* mepolizumab) [6] studies.

Several assumptions were made during the data collection which are consistent with those used to derive the prototype ORACLE [2]. For both the Novel START [4] and the CAPTAIN trials [7], data of patients with a baseline FeNO of 20-<50 ppb were regrouped into the 25-<50 ppb categories, as the difference of 5 ppb in FeNO is not clinically relevant [13]. For Novel START

[4], only the percentage of patients with one or more severe attacks(s) in the 52-weeks of follow-up was reported so an annualised rate was imputed as $-\log_{10}(1 - \% \text{incidence})$.

Predicted biomarker-stratified attack rates. A raw predicted rate was calculated by applying the prototype risk scale parameters in proportion to the reported clinical characteristics of each trial's control arm population [2]. 'Control' and 'active' arms' predicted biomarker-stratified attack rates were calculated based on our hypothesis that the type-2 anti-inflammatory treatment effect in type-2 high asthma (baseline blood eosinophils $\geq 0.15 \times 10^9/\text{L}$ and/or FeNO ≥ 25 ppb) is equivalent to the difference in predicted annualised asthma attack rate in any-biomarker-high stratum vs biomarker-low stratum (blood eosinophils $< 0.15 \times 10^9/\text{L}$ and FeNO < 25 ppb). We further assumed that there would be no anti-inflammatory treatment effect in patients with low baseline biomarkers.

Estimation of treatment effects

Individual trial treatment effects. For each trial, observed and predicted rate ratios were calculated between control and active arm attack rates in patients with any raised type-2 biomarker at baseline (blood eosinophils $\geq 0.15 \times 10^9/\text{L}$ and/or FeNO ≥ 25 ppb) and those with none (blood eosinophils $< 0.15 \times 10^9/\text{L}$ and FeNO < 25 ppb).

Comparing the aggregate observed versus predicted impact of anti-inflammatory treatments. The control vs treatment arm rate ratios calculated for the observed and predicted biomarker-stratified data were tabulated across individual trials. The main outcome was the comparison of the frequency-weighted mean rate ratio for all observed vs predicted treatment effects.

RESULTS

The observed *vs* ORACLE-predicted biomarker-stratified annual asthma attack rates and anti-inflammatory treatment benefits are shown in the table. For the 3925 patients with any type-2 biomarker high at baseline, the observed *vs* predicted frequency-weighted mean rate ratios were 0.59 *vs* 0.58; the corresponding percentages reduction in asthma attacks were 41% and 42%, respectively. In contrast, the 814 patients with both biomarkers low at baseline had observed *vs* predicted rate ratios of 0.86 *vs* 1.00; the corresponding percentages reduction in asthma attacks were 14% and 0%, respectively. Finally, an exploratory analysis for the 243 patients with both biomarkers very high (*i.e.*: blood eosinophils $\geq 0.30 \times 10^9/L$ and FeNO ≥ 50 ppb), restricted to the Novel START and CAaPTAIN studies due to data availability, confirmed a biomarker-dependent treatment response quantified by the prototype ORACLE (observed *vs* predicted percentages reduction in asthma attacks: 69% *vs* 72%).

DISCUSSION

We found using trial-level data that the prototype ORACLE scale may quantify the excess risk conferred by raised biomarkers which is removed by type-2 anti-inflammatory therapy in trial populations. As is the case with cardiovascular risk and management, the relative treatment benefit associated with these biomarkers was consistent across populations, but the absolute treatment benefit conferred by type-2 airway inflammation was greater in a population with higher baseline biomarkers and background risk. This information may help doctors and patients make predictions about the likely benefit of type-2 anti-inflammatory treatment to prevent asthma attacks.

To our knowledge, this analysis is the first to suggest a potential theragnostic (*i.e.*: predicting treatment responsiveness) utility of a risk prediction model in asthma. Similarities in the visual display, predictive value, and utility of cardiovascular risk charts and the prototype ORACLE [2] can be drawn; these are not accidental. Just as high blood pressure and cholesterol levels are regularly assessed to estimate and to prevent the risk of heart attacks, we propose that blood eosinophils and FeNO are airway equivalents which measure the modifiable risk of asthma attacks. The demonstration that the ORACLE framework has prognostic and theragnostic value supports our efforts to derive and validate a more robust ORACLE using individual-participant control arm data [14].

We emphasize that our estimations of treatment benefits were derived from trial-level analyses involving several assumptions and that, although promising, several deficiencies mean the prototype ORACLE is not yet validated for clinical practice. First, we were unable to calculate confidence intervals due to regrouping of trial arms and biomarker strata. We thus assessed the theragnostic value of ORACLE based on point estimates, clinical significance [15], and the positive results of anti-inflammatory treatments in type-2 high trial populations [4–6]. Second, our analyses were performed using data from four of the eight RCTs included in the prototype derivation [2] because the other derivation RCTs' did not report on the composite biomarker definitions of interest. Despite a systematic review of the literature [14], it was not possible to find external trials reporting on the appropriate composite biomarker-stratified subgroups' control and active treatment attack rates in a manner which allows ORACLE-predicted rates to be calculated. Third, we concede that the estimation of the theragnostic utility of ORACLE in mild asthma trial populations was less precise because of small patient numbers and the rarity of the outcome of interest. Although there was a discrepancy between observed *vs* predicted treatment benefits in mild asthma with low type-2 biomarkers, we still consider that the prognostic

importance of blood eosinophils remains relevant in this patient group [4]. Furthermore, the concordance between observed vs predicted treatment benefits across moderate-to-severe type-2 low and type-2 high asthma supports the notion that blood eosinophils and FeNO are especially useful to gauge the potential benefits of anti-inflammatory treatment beyond low-dose ICS. Fourthly, we assessed different anti-inflammatory treatments in asthma of different severities with and without long-acting bronchodilators, which reduces internal validity for specific combinations, although enhances external validity for anti-inflammatory dosing. Finally, the prototype ORACLE's predictions are based on biomarkers measured at stable state; their value at the time of an exacerbation remains unclear.

To conclude, the prototype ORACLE shows potential to quantify the excess risk of asthma attacks in type-2 high asthma which is removed by anti-inflammatory therapy. Such a scale discriminating between high-risk/high-stake and low-risk/low-stake asthma is needed in clinical practice, where anti-inflammatory treatment can have a very positive impact when targeted appropriately but can also be escalated without any predictable benefit.

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TABLE
Predicted vs observed impact of anti-inflammatory treatments according to baseline biomarkers

| Baseline biomarkers | Annual severe asthma attack rate | Included trial: control vs active interventions (n) | | | | <u>Weighted mean % reduction</u> Control vs Active | |
|--|----------------------------------|--|---|---|---|---|------------------|
| | | <u>Novel START</u> Salbutamol vs Any low-dose ICS*† | <u>CAPTAIN</u> FF100 vs FF200* | <u>QUEST</u> Placebo vs Dupi 200 | <u>DREAM</u> Placebo vs Any Mepo | | |
| Type-2 Low Blood Eos <0.15×10 ⁹ cells/L and FeNO <25 ppb | Observed | | (n=18 vs 60) | (n=194 vs 211) | (n=106 vs 139) | (n=23 vs 63) | (n=341 vs 473) |
| | | Control arm | 0.05 | 0.27 | 0.56 | 1.98 | |
| | | Active arm | 0.03 | 0.22 | 0.58 | 1.71 | |
| | Predicted | % Reduction | 41% | 20% | -4% | 14% | 14% |
| | | Control arm | 0.07 | 0.19 | 0.53 | 0.74 | |
| | | Active arm | 0.07 | 0.19 | 0.53 | 0.74 | |
| % Reduction | 0% | 0% | 0% | 0% | 0% | | |
| Type-2 High Blood Eos ≥0.15×10 ⁹ cells/L or FeNO ≥25 ppb | Observed | | (n=201 vs 377) | (n=903 vs 909) | (n=514 vs 484) | (n=145 vs 392) | (n=1763 vs 2162) |
| | | Control arm | 0.05 | 0.40 | 1.07 | 2.46 | |
| | | Active arm | 0.03 | 0.26 | 0.41 | 1.19 | |
| | Predicted | % Reduction | 35% | 35% | 62% | 52% | 41% |
| | | Control arm | 0.13 | 0.32 | 0.93 | 1.28 | |
| | | Active arm | 0.07 | 0.19 | 0.53 | 0.74 | |
| % Reduction | 42% | 42% | 42% | 42% | 42% | | |
| Type-2 Very High Blood Eos ≥0.30×10 ⁹ cells/L and FeNO ≥50 ppb | Observed | | (n=51 vs 54) | (n=67 vs 71) | n/a | n/a | (n=118 vs 125) |
| | | Control arm | 0.13 | 0.62 | n/a | n/a | |
| | | Active arm | 0.02 | 0.25 | n/a | n/a | |
| | Predicted | % Reduction | 81% | 60% | n/a | n/a | 69% |
| | | Control arm | 0.26 | 0.65 | 1.88 | 2.60 | |
| | | Active arm | 0.07 | 0.19 | 0.82 | 1.14 | |
| % Reduction | 72% | 72% | 72% | 72% | 72% | | |

*For both the Novel START and CAPTAIN studies, data of patients with a baseline fractional exhaled nitric oxide (FeNO) of <20 ppb were regrouped into the <25 ppb group, as the difference of 5 ppb in FeNO is not clinically relevant [13]. †For Novel START, only the percentage of patients with one or more severe attacks(s) in the 52-weeks of follow-up was reported so a rate was imputed as -log10(1 - %incidence). Blood Eos, peripheral blood eosinophil cell count; Dupi 200, dupilumab 200 mg/2w ; FF100-200, fluticasone furoate 100 or 200µg/d-containing regimen; ICS, inhaled corticosteroid; Mepo, mepolizumab; n/a, data not available. Data from [4–6, 8], applied to the prototype scale reported in [2].