

Application of Model-Based Meta-Analysis to evaluate the relationship between early biomarker to late stage clinical endpoints for the development of anti-asthmatic drugs

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Background

A significant unmet medical need remains for severe asthmatics. The key challenge in the development of drug with improved clinical benefit in patients with severe asthma is to establish a robust clinical development plan from proof of concept studies through phase II/III. Such a development may benefit from the ability to translate of phase I/IIa clinical signal such as Forced Expiratory Volume (FEV1), to late stage (phase III/IV) clinical outcomes such as reductions in clinical asthma exacerbation rates. Model-based meta-analysis (MBMA) of relevant clinical trial data allows evaluating such a translational opportunity.

Objectives

- To perform an MBMA of comparative effectiveness of biologics for the treatment of moderate to severe asthma
- To develop a joint MBMA model that relates early clinical well-established endpoints (FEV1) to late stage clinical outcomes (exacerbation rate)

Methods

General model for continuous response endpoint (FEV1)

$$Y_{ij} = E0_{ij} + E_{TOT,ij} + \varepsilon(N_{ij}) \quad \varepsilon(N_{ij}) \sim N\left(0, \frac{\sigma^2}{N_{ij}}\right)$$

$E0_{ij}$ = placebo response; Y_{ij} = mean FEV1 response; ε_{ij} = residual (within-trial) variability assumed to be normally distributed; N_{ij} = the sample size

General model for event rate endpoint (exacerbation rate)

$$rate_{ij} = \exp\{E0_{ij} + E_{TOT,ij}\} \quad Ne_{ij} \sim \text{Poisson}(rate_{ij})$$

$E0_{ij}$ = placebo response; Ne_{ij} = total number of exacerbation events assumed to be Poisson distributed; $rate_{ij}$ = number of exacerbation events per patient year

Joint drug effect model

$$E_{TOT,ij} = (Dose_{ij} \cdot E_{MAX,ij} / (ED_{50,ij} + Dose_{ij})) \cdot (1 + SCL)$$

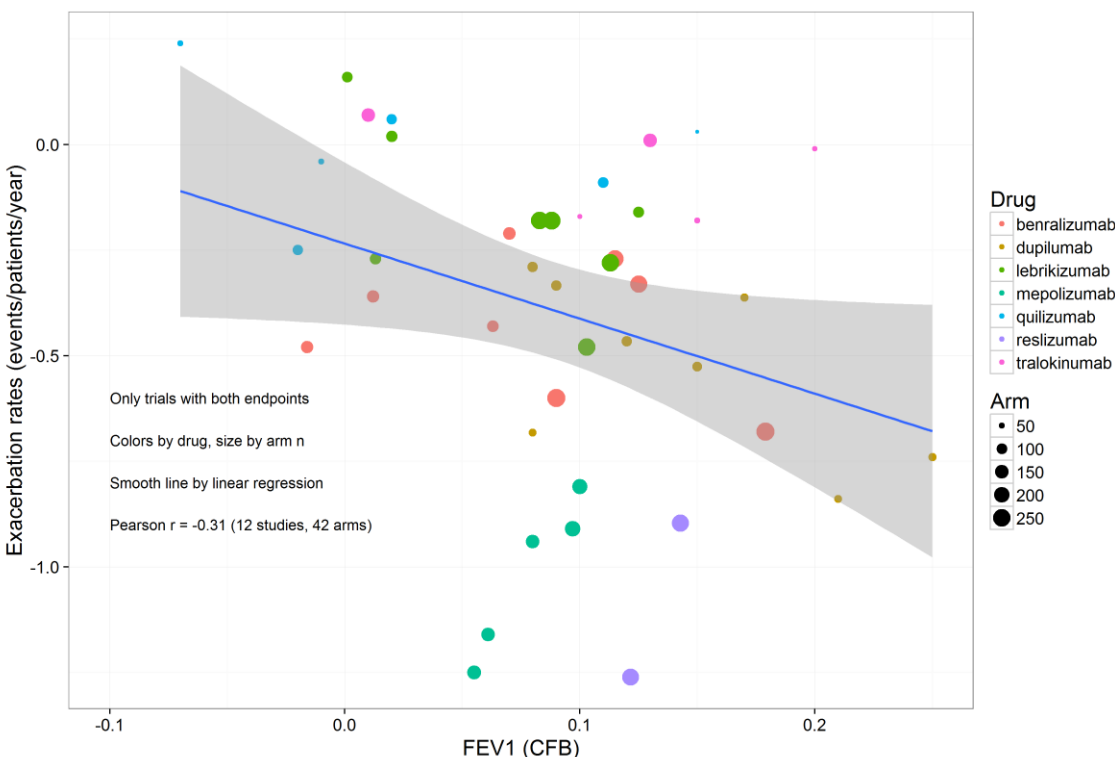
E_{TOT} = total drug effect as a function of drug and dose; SCL = scaling factor between endpoints; E_{max} = maximum drug effect; ED_{50} = dose that induces 50% of response

The MBMA was based on a comprehensive database of summary clinical outcome efficacy data from randomized controlled trials with biologics in moderate to severe asthma [1]. FEV1 and exacerbation rate data were modelled simultaneously; differences in variances of mean endpoint values between studies were accounted for using appropriate weighing schemes. Different variance structures were used for FEV1 (Gaussian) and exacerbation rate (Poisson) endpoints. The treatment effect on both endpoints was modelled as a function of drug and dose, where the two endpoints effects were related using a scaling factor. Given presumed non-Gaussian distribution of the placebo effect across studies, this was modelled non-parametrically by estimating study-, time- and endpoint-specific fixed effects. The effect of continuous covariates on endpoints was tested using power functions. All analyses were performed using R (version 3.4.2), typically applying functions `gnls()` and `nlme()`.

Exploratory analysis

A total of 24 and 21 trials (all placebo controlled) and 660 and 108 observations were included for FEV1 and exacerbation rate, respectively. Exploratory data analysis indicated that an increased FEV1 (change from baseline, CFB) effect was related to a lower exacerbation rate (Figure 1).

Figure 1. Correlation between placebo-corrected FEV1 (CFB) and exacerbation rate



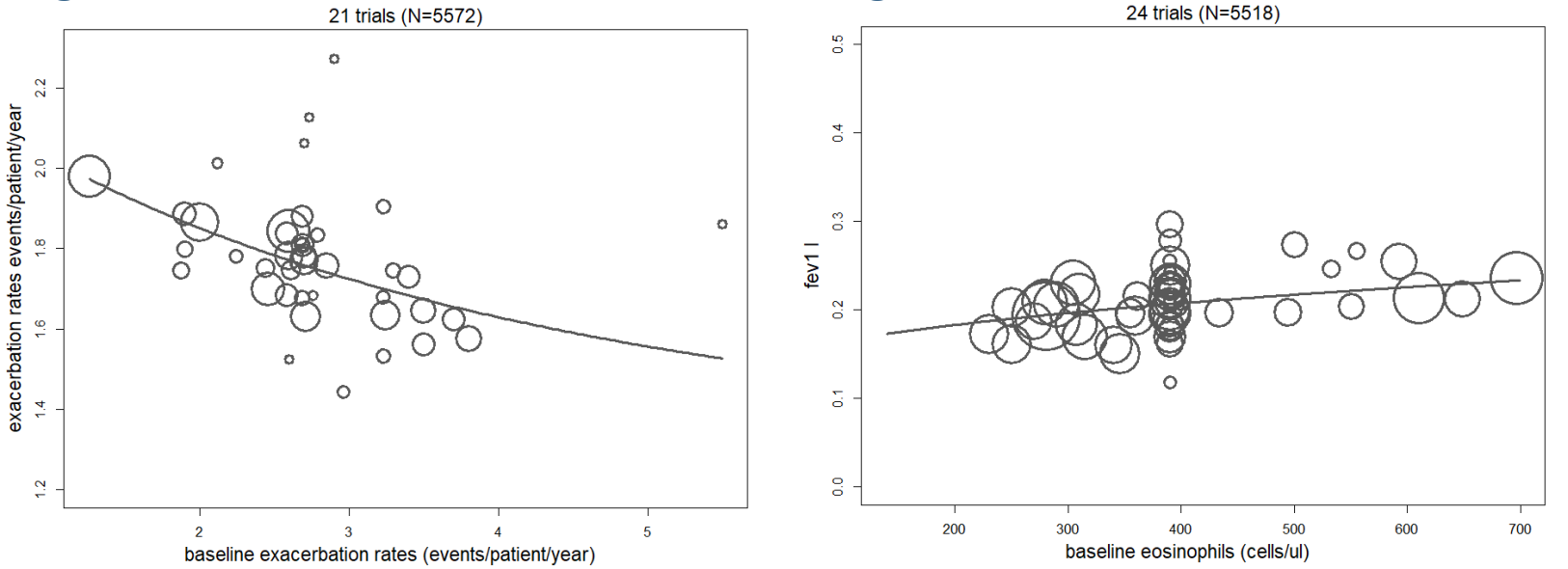
Joint FEV1 and exacerbation rate model

A joint MBMA model of FEV1 and exacerbation rate was developed based on the observed correlation (Figure 1). The developed model provided a good and unbiased description of the data (Figure 2).

Drug-specific effects were shared between endpoints, and the scaling factor correlating the drug effect of FEV1 and exacerbation rate was estimated to be -0.872 (RSE of 2%).

Baseline exacerbation rate and baseline eosinophil levels were found to significantly affect drug effect, with estimated exponents of 0.902 (RSE of 43.6%) and 0.419 (RSE of 26.9%), respectively. Partial residual plots confirmed the estimated covariate effects on both endpoints. Effects of baseline exacerbation rate on drug effect of exacerbation rate (Figure 3 - left panel) and baseline eosinophils on drug effect of FEV1 (Figure 3 - right panel) are both well captured across drugs.

Figure 3. Effect of baseline covariates on drug effect

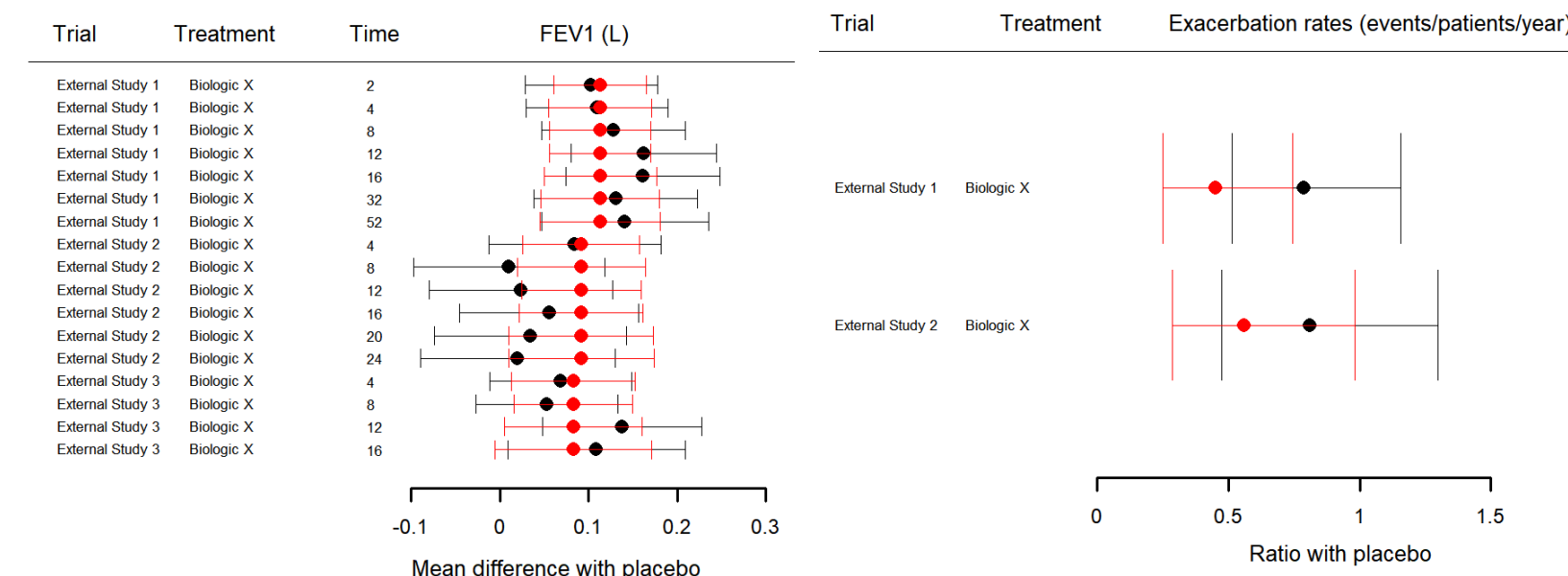


Open circles represent individual observations across all drugs normalized by simulated covariate range and by reference drug effect; size is by arm N. Solid line represents the model prediction. Left panel is exacerbation rate and right panel FEV1.

Model validation

The joint MBMA model was externally validated using additional biologic data that were not part of the analysis data set (Figure 4). The results confirmed robustness and predictive ability of the developed framework.

Figure 4. External Validation of the Joint Model



Red points are the model predictions; black points are the observations. Horizontal bars show the 95% CIs (1000 replicates).

Conclusions

- A joint MBMA model of drug effect on FEV1 and exacerbation rate was successfully developed using summary clinical outcome data from randomized controlled trials in moderate to severe asthma
- This joint model may be used to provide early insights on expected late stage clinical response (exacerbation rate) for new drugs based on FEV1 response in early Phase I/IIa studies
- This predictive framework can support timely decisions (e.g. Go/noGo criteria, dose/regimen selection, and study design optimization) in the clinical development programs of biologics for the treatment of moderate to severe asthma

References

- [1] https://www.certara.com/wp-content/uploads/Resources/Brochures/BR_ClinicalTrialOutcomeDatabases.pdf