Coupling a QSP model with a simple statistical layer to predict asthma exacerbation rate reduction from allergen challenge results

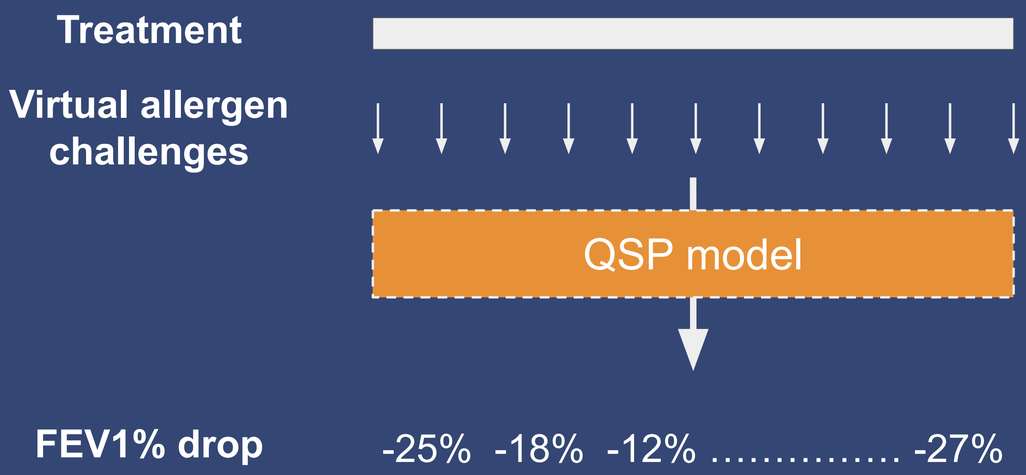
Théo Galland[1], Cristhyne Leon[1], Caterina Sansone[2], Anne Vaslin Chessex[2], Christian Pasquali[2], Lorenz Lehr[2], Alexander Kulesza[1], **Simon Arsène**[1]

[1] Nova In Silico, Lyon, France [2] OM Pharma, Meyrin, Switzerland

BACKGROUND

Allergen challenge studies experimentally mimic triggers of asthma exacerbations by challenging sensitized animals or patients with an allergen, resulting in lung function alteration [1]. Effects of treatments have been tested in this setting as proof-of-concept, however, the gold standard in asthma is assessed in another context: in clinical trials that measure the reduction in the number of exacerbations over a long period of time (exacerbation trial). To bridge these two contexts, here we propose a computational tool which builds upon existing early preclinical and clinical data from allergen challenge studies to predict reduction in asthma exacerbation rate.

We explored how **a QSP model, coupled with a statistical layer**, could help **bridge the gap** between **allergen challenge studies and clinical asthma outcomes**.



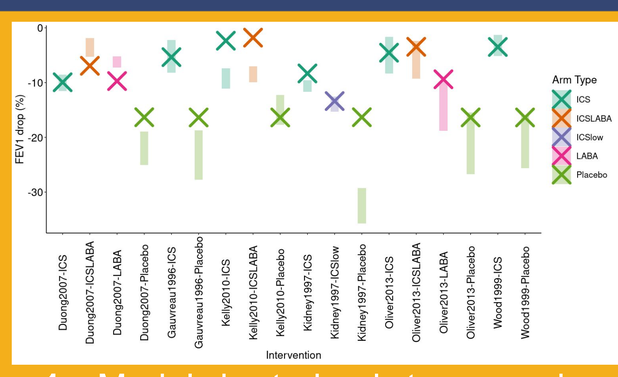


Fig 1. Model is trained to reproduced FEV1% drop after allergen challenge with ICS and LABA treatments.

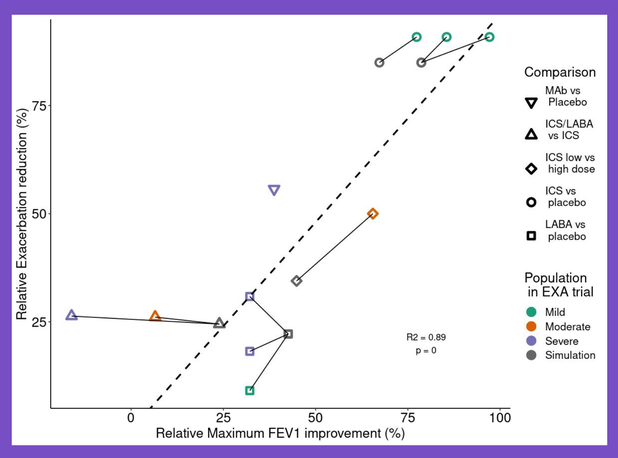


Fig 2. Model can reproduce interventions effect sizes in the two contexts (allergen challenge and exacerbation trial)

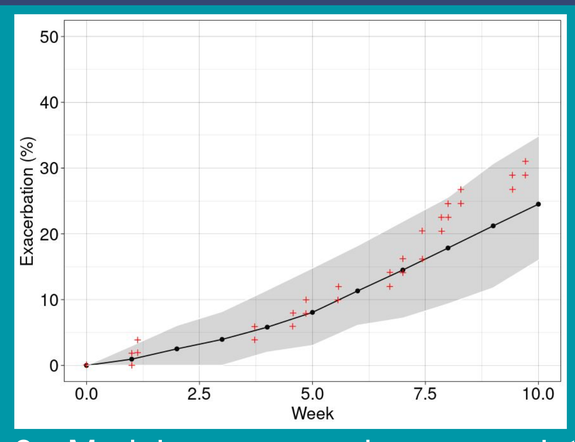


Fig 3. Model can reproduce cumulative percentage of exacerbation (in %) in the placebo arm of the Wenzel trial [2].

METHODS

We collected, for a number of different interventions and matching target populations, inhaled corticosteroids (ICS) vs long-acting beta-agonists (LABA) for example, the reported effect size in the two contexts: allergen challenge and exacerbation trial. We then assessed the correlation between reduction of FEV1%, relative to placebo, following allergen challenge and reduction of exacerbation rate, relative to placebo, for each type of intervention. Using this, we established a translational relationship between relative effect size in allergen challenge and in exacerbation trial. We then incorporated this into a statistical layer which outputs exacerbation rate and which is built on top of an already developed QSP model of allergen challenge (preclinical and clinical). For this, we integrated into this QSP model the effect of ICS and LABA in asthma (Fig 1).

RESULTS

We found a high correlation between relative reduction of exacerbation rate and relative FEV1% drop improvement following allergen challenge (Fig 2, $r^2 = 0.89$). We used this relationship for the development of the exacerbation statistical layer built on top of our QSP allergen challenge model.

This set up yielded a computational tool which, for a given intervention (type of treatment, dosing regimen etc), can simulate the effect in both contexts. Finally, we verified the approach by comparing the simulation outputs with the collected data (Fig 2, Fig 3).

CONCLUSION

- Here, we show how a computational approach based on a QSP model coupled with a simple statistical layer can bridge results obtained in the two main settings in asthma development: allergen challenges and clinical trials measuring exacerbation rates.
- This work paves the way towards an asthma computational platform with the potential for becoming a powerful tool for supporting trial design in asthma, by enabling the continuous integration of data produced throughout the entire development cycle.

REFERENCES

[1] G. M. Gauvreau, M. Y. Evans, Allergen Inhalation Challenge: A Human Model of Asthma Exacerbation. Contributions to Microbiology (2007), pp. 21–32.
[2] S. Wenzel et al., The Lancet. 388 (2016), pp. 31–44.