A mechanistic skin immunology model for the support of atopic dermatitis clinical trial design and biomarker programs

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Background

There are a variety of topical and systemic small-molecule and biologic treatments available against atopic dermatitis (AD), but the disease, patient and response heterogeneity impair consensus on clinical management [1]. The oral bacterial lysate OM-85, a non-specific immunomodulator, has potential application in patients with AD. A clinical trial to determine the potential of OM-85 in early AD (NCT05222516) is underway. Even though the current understanding of the drivers for disease severity and treatment response remains partial, further research needs to be conducted to reveal the relationships between intrinsic immunological features, extrinsic factors and disease severity to provide personalized treatment.

To achieve this, *in silico* exploration of best responders can be performed through the use of a knowledge-based mathematical model. Such models can complement data-driven biomarker research with a "totality of evidence" paradigm, in which severity or response emerges from piece-wise collection of quantitative functional relationships. Here, we show that this evidence-based methodology can be used to identify a reduced set of biomarkers which would predict the response accurately. Then, we assess whether such a predictive model for response would be useful to inform trial design in a clinical setting.

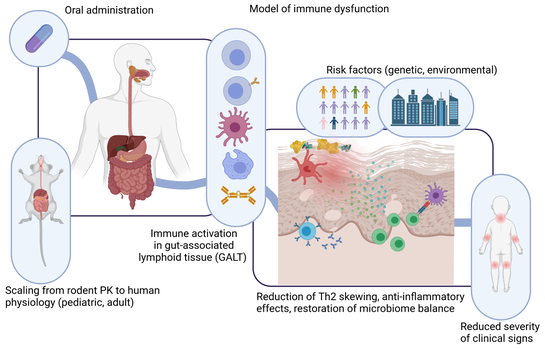

Figure 1: Schematic of atopic dermatitis mechanism implemented in the model including mechanism of action of OM-85, allergen/pathogen-induced inflammation, skin barrier dysregulation and regulatory immune responses. Oral administration of the bacterial lysate exposes the gut-associated mucosal immune system (GALT) to the antigenic stimulus of the product which activates the migration of circulating immune components to the skin barrier. Figure created with biorender.com

Methods

In order to couple biomarker identification and clinical response prediction, we developed an *in silico* clinical trial approach on top of a mechanistic model of AD in paediatric patients. This model describes the mechanisms driving the immune response dysregulation, the loss of skin barrier integrity, and the perturbation of the skin microbiome (Figure 1). The model incorporates knowledge about:

- the absorption, distribution, metabolism, and excretion properties and the mechanisms of action of OM-85;
- the human physiology involved in immune activation in mucosal tissues and the gut-lung and gut-skin axis;
- the skin immunologic system.

We calibrated this model using data measuring the main variables in paediatric patients with AD [2][3]. Then, we interfaced this model with three treatment models (emollients [4], topical corticosteroids and OM-85 [5]). We generated a virtual population of paediatric patients characterized by age, weight and 13 baseline levels of cytokines and alarmin signals. Then, we used this virtual population to determine the evolution of AD severity in both control and treated arms. We thereby conducted a responder identification analysis, selecting the best subset of predictive biomarkers, as well as an investigation of different regimen or trial design parameters (comparator arm, endpoint; results not shown here).

Results

The model can reproduce severity evolution for three different treatments acting on different time scales:

- SCORAD decrease after 3 month induction phase with topical corticosteroids in OM-85 treated vs placebo arms during a 9 month clinical trial (Figure 2 A);
- EASI improvement after topical corticosteroids application for 40 days (Figure 2 B);
- EASI improvement after daily administration of emollient for 6 months (Figure 2 C).

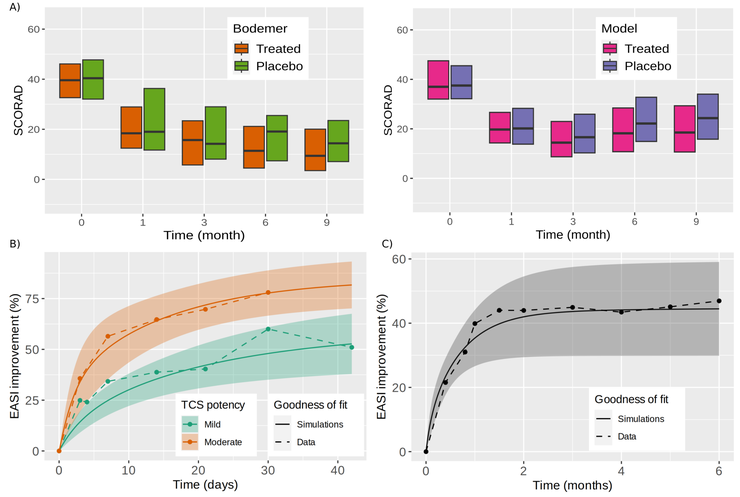

Figure 2: Goodness of fit of decrease of AD severity (SCORAD and EASI): A) following OM-85 administration of model simulations (right panel) compared to clinical dataset (Bodemer et al., left panel) [5]. The difference of median SCORAD between placebo and treated arms as well as the interquartile range are reproduced; B) following topical corticosteroids treatment (mild or moderate, meta-analysis of several clinical datasets); C) following emollients [4].

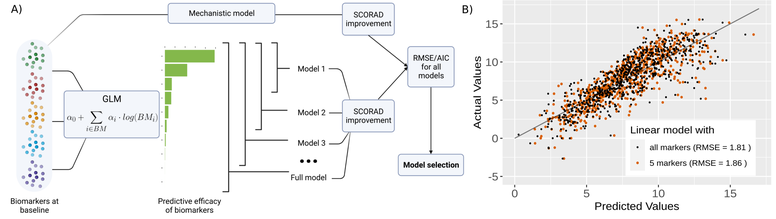

Figure 3: A) Schematic of biomarker selection. We used a GLM to identify significant biomarker. Then, we used GLM on subsets of biomarkers, enabling comparison with data obtained with our mechanistic model. BM: biomarker; GLM: generalized linear model; AIC: Akaike information criterion; RMSE: root-mean-square error B) Treatment response predicted by the general linear model (either all thirteen or reduced to the five most important variables) compare to actual values from the model simulations. Selecting the 5 most significant biomarkers based on efficacy prediction leads to a similar RMSE with less parameter needed.

Then, we used our model to simulate a paediatric virtual population in order to link severity outcome to baseline biomarkers. We found seven variables to be influential, notably associated with the pathogen entry or the immune regulatory response, the predicted severity of which is equivalent to the prediction of all 13 baseline biomarkers (Figure 3 A). Stratifying it further to the five most important ones leads to an even more optimal prediction, containing less parameters (Figure 3 B). The model predictions therefore highlighted that:

- absolute benefit (mean SCORAD difference between placebo and treatment arms) is 48.8% higher when the best 50% predicted patients are selected based on their biomarker baseline levels (Figure 4 A);
- selecting only the 25% best responders leads to an 72.0% increase in absolute benefit (Figure 4 A);
- the selection of only the best 25% responders does not seem to majorly impact sample size or statistical power (71% severity decrease) to demonstrate treatment efficacy compared to selecting only the best 50% (52% severity decrease, Figure 4 B).

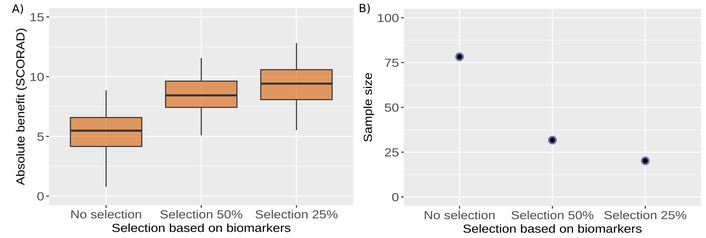

Figure 4: A) Absolute benefit distribution (median and interquartile range) without any selection, selecting the top 50% or the top 25% predicted best responders. B) Sample size to demonstrate efficacy of the treatment in *in silico* clinical trials without any patient selection, selection of the top 50% or the top 25% predicted best responders.

We also found that the minimum treatment duration to achieve good chances of success (statistical power above 0.75) with a reasonable sample size (less than 100 patients per arm) is four months (results not shown here). The model indicated that care should be taken when selecting the corticosteroid used: in two hypothetical scenarios with very mild and moderate potency, a 30% difference in control-group EASI change was predicted; which may impact the sample size needed to detect between-arm differences.

Conclusion

We performed a best responder analysis within an *in silico* clinical trials framework on the back of a mechanistic model which may lead to the identification of novel therapeutic pathways and prospects for personalized medicine. We found a subset of biomarkers that predict the best responders to the bacterial lysate OM-85 and we showed that patient selection based on this subset may lead to a bigger size of the effect demonstrated in a trial. Thus, we proposed an *in silico* approach that - together with the existing preclinical and upcoming data from a running clinical trial (NCT05222516) - can be used to confirm future (e.g. Phase IIb and III) clinical trial design choices, thereby improving success of the development program as a whole chances and create opportunities for more personalized medicine to a tailored group of patients.

References

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