Mechanistic model based meta-analysis for paediatric respiratory tract infection prophylaxis trial design

Arsène S. [1] Chevalier A. [2] Couty C. [1] Faddeenkov I. [1] Go N. [1] Granjeon-Noriot S. [1] Kahoul R. [1] Kulesza A. [*1] Lehr L. [2] Pasquali C. [2] Sireau A. [1]

[*]Presenter [1]Novadiscovery, Lyon, France [2]OM Pharma, Meyrin, Switzerland

Background

Recurrent viral respiratory tract infections (RTIs) are associated with wheezing in pre-school children and the inception of asthma, but an efficient strategy to prevent or reduce the frequency of viral RTIs in patients at risk of recurrent infections remains an unmet need.

OM-85 (a bacterial lysate) is an oral immunomodulator proven to be efficacious for the prophylaxis of recurrent RTIs in children (Yin *et al.* [3]). Confirmation of the efficacy for wheezing is difficult due to patient and disease heterogeneity, especially in context of the COVID-19 pandemic. Model informed drug development (MIDD) can help trial design choices through conduction of *in silico* clinical trials [1] that systematically test the impact of trial design on the demonstrable efficacy and its magnitude.

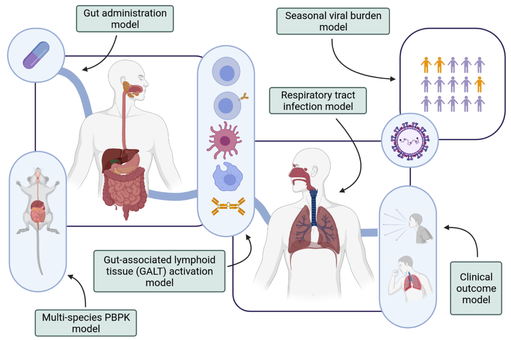

Figure 1: Recurrence of RTI and wheezing and mechanism of action of OM-85, implemented as ordinary differential equations in our model. Patient populations are exposed to viruses in line with RTI seasonal disease burden data (top right), modulating the probability of viral exposure. The individual (and fluctuating) immune competence determines (for each exposure) a) if a detectable infection develops and b) how severe and long the infection (viraemia, inflammation) proceeds. These factors, together with airway geometry, determine the probability of wheezing. Oral administration of OM-85 exposes the gut-associated mucosal immune system (GALT) to an antigenic stimulus leading to migration of activated immune components to the respiratory tract. The pro-type 1 profile of the response reinforces an antiviral pre-alert state and reduce excess inflammation. Figure created with biorender.com

Methods

We built a mechanistic, multi-scale RTI model and a virtual population for *in silico* RTI prophylaxis trials of OM-85 (Figure 1). It contains a physiologically based pharmacokinetics (PBPK) and pharmacodynamics (PD) model based on published ADME (absorption, distribution, metabolism, and excretion) properties of bacterial lysates and knowledge of its mechanism of action; calibrated to rodent PK data and human immune activation PD data. Further, it includes an immunological model based upon knowledge about resolution of viral RTIs in the respiratory tract mucosa by nonlytic and lytic immune effectors, calibrated against viraemia data in experimental infection. Additionally, it uses an epidemiological model of seasonal variations of viral disease burden, reproducing seasonal RTI data. Finally, it relies on a biophysical wheezing outcome model, integrating age-dependent airway geometry data. The combined model is calibrated with age-dependent RTI prevalence data and the clinical data (Yin *et al.* [3] about the effect of OM-85. *In silico* clinical trials are defined as two arm placebo-controlled trials with currently approved regimen in the intervention arm, patients being 1 to 5 year old children with varying risk for RTI (rate of RTI during a preceding observational period), varying follow-up period, and absolute benefit and rate ratio related endpoints.

Results

Simulations from the mucosal immune reaction model and variability are shown in Figure 2 a) as compared to our primary and secondary reference infection data. Good overlap with experimental data qualifies to represent realistic viral infection courses.

Simulated baseline 12-month RTI prevalence in a 1-2 and 3-4 year old subpopulation are compared to a negative binomial model fitted to data reported by Vissing *et al.* [2], Figure 2 b), ensuring that the virtual populations represents well a general population cohort with respect to RTI incidence.

Simulated and reported sum of upper and lower disease burden (scaled) are compared in Figure 2 c) for children < 3 years, indicating that overall seasonality of RTI incidence is well captured by the model.

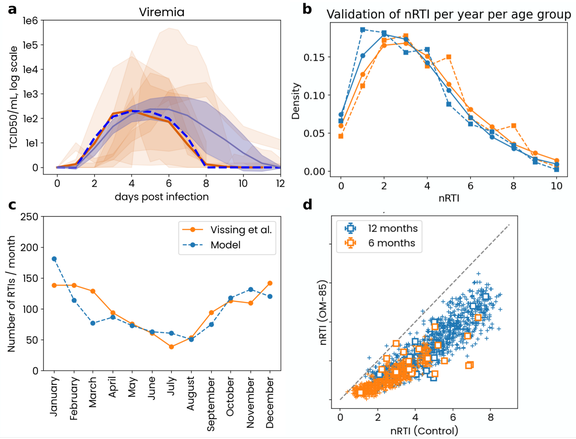

Figure 2: Goodness of fit for model vs. reference data a) Viral load during a experimental viral infections b) RTI prevalence distribution in the pediatric population for two age groups c) Instantaneous RTI incidence seasonality compared to data, b and c from Vissing *et al.* [2] d) Meta-analyzed efficacy of OM-85 with two durations of follow-up (crosses: *in silico* trial, boxes: cumulative incidence of RTI from Yin *et al.* [3]), follow up (blue: 12 months, orange: 6 months).

Absolute benefit (number of prevented RTI episodes) for 12 and 6 months follow up from Yin *et al.* [3] is faced to pooled simulated data, for 10 subpopulations with at least 1 to 10 RTIs in the observational period. Good overlap with 12-month follow up confirms that simulated risk-stratified efficacy is in line with clinical data and indicates that shorter studies tend to include populations at higher risk.

The impact of trial design aspects other than the included patients is highlighted on the example of varying follow-up Figure 3 a) on a metric related to clinical effectiveness (absolute benefit, AB) and on an estimated sample size based on event rate ratios and negative binomial regression (R package MKmisc).

Longer follow-up can capture more prevented RTIs as shown in Figure 3 b)—difference of AB is 0.5 with 12 months of follow-up if compared to 6 months. The same trend is observed for wheezing episodes (not shown). With longer follow up, AB variability increases, but the number of prevented episodes saturates (attenuation of the response, being dependent on the treatment period; not shown). This behavior is in line with sample sizes estimates based on the rate ratio. Twice the sample size is required for 12 months of follow-up compared to 6 months, as shown in Figure 3 c), with a minimum at 5 month follow up (including 3 months treatment period). Note that the maximum AB is achieved with 12 months follow up (see above).

Patient age and baseline risk also modified mean effect and its variability (-0.2 prevented RTIs for 3-6 years old range compared to 1-6 range; +0.3 prevented RTIs for inclusion of patients with at least 5 vs 3 RTIs in preceding year; data not shown).

In silico trials with varying treatment period duration indicate potential for optimization regarding the dosing-regimen as longer exposure seems to increase the effect size without affecting the response heterogeneity (+1.7 prevented RTIs with 12 months of treatment compared to 3 months with 12-month follow-up in both cases). Indeed, there is a timescale separation between the PK (days) and the PD (weeks) response which suggests that immunomodulation can increase over time with increasing exposure (data not shown).

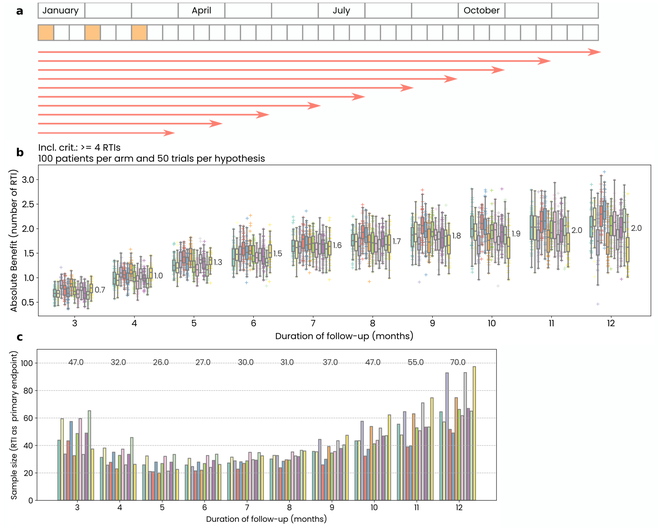

Figure 3: Simulated impact of follow-up duration on the efficacy of OM-85. a) Exploration plan: follow-up periods (red arrows) ranging from 3 to 12 months with a 3-month treatment (orange boxes, 10 day/month, 3.5 mg) (patients have ≥ 4 RTIs during 12 prior months). For each follow-up duration, 100 virtual trials with 50 patients per arm are simulated. b) Number of prevented RTIs during follow-up (median, boxplots represents [Q1, Q3]) as a function of follow-up duration. c) Sample size to show superiority over placebo as a function of follow-up duration. The 12 bars per follow-up indicate the sensitivity of the model to parameters representing major mechanistic uncertainty.

Conclusion

We developed a mechanistic model which can be used in a similar way as model-based meta-analysis to inform and optimize clinical trials. Here in the context of prophylaxis of RTIs and wheezing, and in particular in a setting where data is heterogeneous and individual patient data hard to access, our mechanistic modeling approach allows to systematically assess the impact of a significant number of various trial parameters (dosing regimen, included at-risk population, duration of follow-up, starting treatment month etc.). Our model indicates eligibility criteria should be adapted to the follow-up, and that endpoint selection should balance power and clinical benefit considerations and should be based on regimen-adjusted and population adjusted effect size calculations to maximize success and impact of an RTI prophylaxis trial.

References

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