A Key Endpoint in Viral Challenge Models of Asthma Exacerbations

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RATIONALE

Human Rhinovirus (HRV) is reported to be a leading cause of up to 80% of asthma exacerbations[1]. The viral pathway and associated immune responses represent a potential key therapeutic target for new and novel asthma treatments. The use of a human viral challenge model has been widely explored over the last few decades and there is interest in its use to enhance early clinical development. The safety and conduct of this model have been repeatedly demonstrated, however, to date the endpoints that can be used are yet to be validated. The present study investigated the robustness of lower respiratory tract symptoms (LRTS) as a key endpoint to assess severity of asthma exacerbations in an HRV-16 human challenge model.

METHODS

Twenty male and female mild asthma (GINA 1) subjects, aged 20-46 years old were recruited (REC Ref:14/LO/0485). Key Inclusion criteria included an $FEV_1 \geq 70\%$, reversibility $\geq 12\%$ and 200 mL, PC20 < 16mg/mL, a positive skin prick test, and low levels of HRV serum neutralising antibodies. Subjects were excluded if they had a smoking history > 10 pack years or an exacerbation within the last 4 weeks. The double-blind study consisted of a screening period and 2-week run-in where PEF was measured morning and evening before a 10-day in-patient quarantine. Subjects were admitted to the quarantine clinic on day -1 and randomized to receive HRV-16 (n=13) or placebo (n=7). Administration occurred on day 0, via a pipette which delivered 2 x 250 µL per nostril followed by 24 hours monitoring and time-pointed assessments until discharge on the am of day 8. LRTS was recorded three times daily throughout quarantine, on self-reported subject diary cards that graded each symptom between 0 (none) and 3 (severe). ACQ's were completed at day 0 prior to inoculation and on day 7. PEF and FEV_1 were measured four times daily and twice daily respectively throughout the quarantine period. Quantification of virus by Polymerase Chain Reaction (qPCR) was performed on nasopharyngeal swabs. Predictive power of LRTS against PEF, FEV_1 and ACQ was determined. Reproducibility of LRTS was assessed in uninfected subjects in stable state. Differentiation of acute worsening following infection from stable state using LRTS was evaluated.

Statistical Analysis

Robustness of LRTS (max change) as a potential endpoint was evaluated using several statistical approaches. Firstly, LRTS change correlations with ACQ and PEF changes were assessed using univariate linear regression. Secondly, the reproducibility of LRTS during quarantine in non-infected subjects was assessed using a linear mix model and the interclass correlation (ICC) was estimated. Finally, the differential/predictive power of LRTS for infected and non-infected was assessed using logistic regression, and the corresponding sensitivity and specificity was calculated.

RESULTS

From the 13 asthma subjects inoculated with virus, 11 (85%) were infected (confirmed by qPCR), and 4 of the infected (36%) had significant asthma worsening (ACQ score rise of $\geq$ 0.5 and measurable reductions in PEF).

Temporal Relationships of Lung function and symptoms

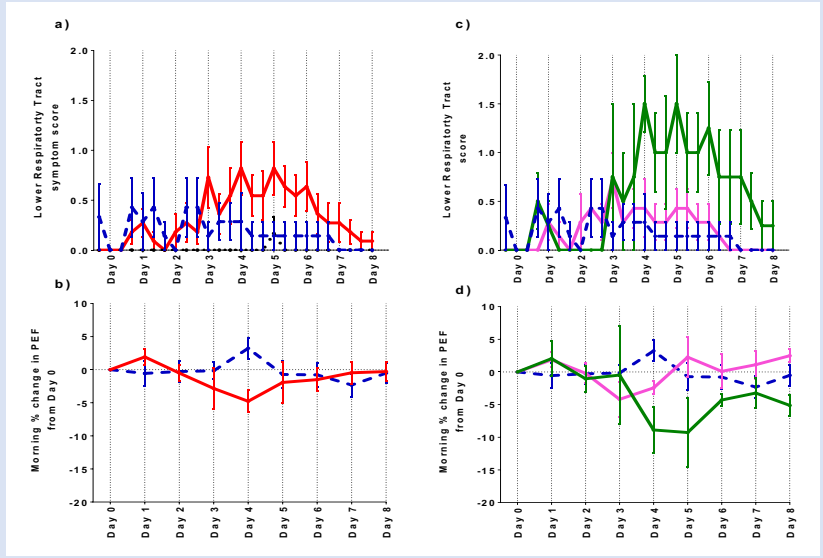

Figure 1. Changes in LRT symptoms and lung function after challenge: subjects with mild atopic asthma given either HRV. a) and b) Time course plots respectively: lower respiratory tract (LRT) composite symptoms change from baseline Day 0 morning; morning % change in PEF from baseline Day 0. Asthma subjects infected (***red***, n=11) or given placebo (***blue***, n=7). c) and d) Time course plots showing subgroups of infected subjects with asthma based on ACQ rise from baseline to Day 7, respectively: lower respiratory tract (LRT) composite symptoms change from baseline Day 0 morning; morning % change in PEF from baseline Day 0. Subset of subjects with asthma that were infected and maintained control (***pink***, n=7), subset of subjects with asthma that were infected and had reduced control (***green***, n=4), or subjects with asthma that were given placebo (***blue***, n=7).

Clinical Correlations

Validity of LRTS (max change) as an optimal endpoint was supported by several significant clinical correlations.

- ACQ-5, ACQ-6 and ACQ-7 correlated with changes in LRTS (ACQ-5: r = 0.59, p<0.05) (fig. 2-4)
- ACQ-5, ACQ-6 and ACQ-7 correlated with changes in PEF (ACQ-5: r = -0.65, p<0.01) (fig. 2-4)
- LRTS correlated with changes in PEF (r = -0.5, p<0.05) (fig. 5)

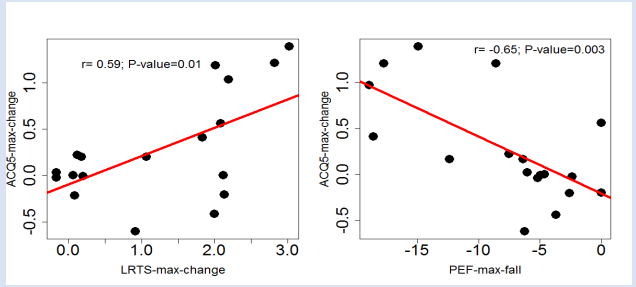

Figure 2. Linear regression analysis of the relationship between ACQ-5 vs. LRTS maximum change form baseline and ACQ-5 vs. maximum fall in PEF.

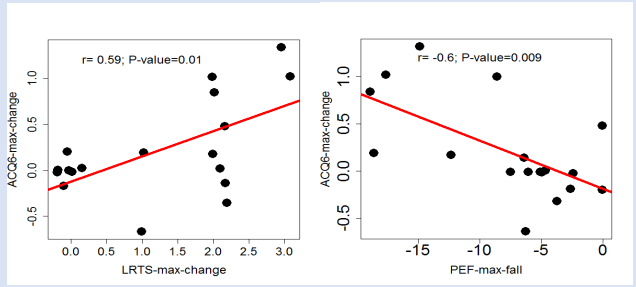

Figure 3. Linear regression analysis of the relationship between ACQ-6 vs. LRTS maximum change form baseline and ACQ-6 vs. maximum fall in PEF.

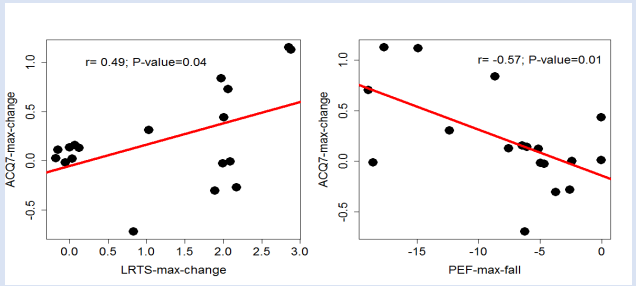

Figure 4. Linear regression analysis of the relationship between ACQ-7 vs. LRTS maximum change form baseline and ACQ-7 vs. maximum fall in PEF.

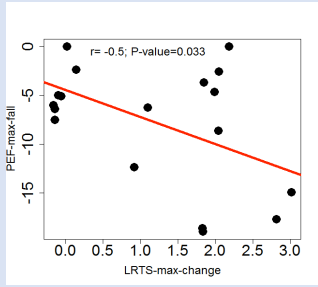

Figure 5. Linear regression analysis of the relationship between maximum fall in PEF vs. LRTS maximum change form baseline.

LRTS as a Key Endpoint

Predictive power of LRTS was demonstrated in which a clinically significant increase in LRTS (i.e. ≥50%[2]) was associated with a clinically significant decrease in PEF of ≥5%[3].

Clinically significant increases in LRTS (i.e. ≥50%) were more likely to be associated with clinically significant increases in ACQ of ≥0.5.

Moderate reproducibility of LRTS in uninfected subjects was confirmed during quarantine (ICC = 0.544).

Differentiation of acute worsening after infection vs. stable state was demonstrated for LRTS with sensitivity = 0.82, specificity = 0.71 and a true classification of 77.7%.

CONCLUSIONS

- The data supports robustness of LRTS as a key endpoint in assessing exacerbation severity of HRV induced asthma exacerbations.
- This is demonstrated by good predictive power, differentiation of acute vs stable state, and reproducibility in stable state.
- The findings encourage further evaluation of LRTS to define clinically important changes and powering studies.

References:
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