Assessing immunomodulators in human challenge studies

insights from wild-type influenza infections in healthy adults and rhinovirus infections in patients with asthma

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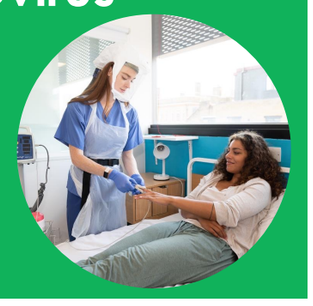


Background

Human challenge studies using wild-type viruses replicate what is seen in the field in the same populations, and as such they have been used to aid vaccine and drug development for decades. Viral load and symptom reduction are typical key endpoints for direct acting antivirals. However, more recently immunomodulators have been developed that treat the disease processes and they look to establish mechanism of action in a human infection, with a focus on achieving reduction of both symptoms and disease biomarkers. Defining relevant endpoints and study designs can be important in establishing confidence of mechanism of action of immunomodulators in infected humans.

Methods

A total of 27 healthy adults and 20 individuals with asthma, all with low or absent antibodies to the challenge viruses (≤20 HAI or ≤4 neutralisation titre respectively), were inoculated with either wild-type Influenza A virus (27 healthy subjects) or rhinovirus (13 asthmatic subjects, with 7 receiving a diluent). Participants were quarantined and monitored for safety, viral shedding, and disease progression. Symptom severity, febrile illness, asthma exacerbations, and immune response markers were assessed using daily symptom diaries, temperature recordings, blood cell counts, and biomarker assays. Key clinical and laboratory endpoints were evaluated to investigate the effects of immunomodulators on disease processes.

Influenza in healthy participants results

Of the biomarker subgroup (n=25), fourteen of twenty-five subjects became infected (56%) with 21% of infected subjects having a lab-confirmed febrile illness. The microarray and cytokine/chemokine biomarker data were assessed in relation to established phenotype groups (e.g., febrile infected vs afebrile infected, and uninfected) as well as with data driven grouping (tertile groupings of sum of maximum VAS symptom levels) are presented, in particular in relation to biomarker/inflammatory responses to infection and related to severity of disease (Figure 2). Individual time-course data is further presented (Figure 1) showing subjects with a febrile infected phenotype associated with high virology, symptoms, mucous discharge, blood immune cell changes and upregulation in blood cytokines and chemokines as measured in proteins (CCL8, CXCL10) and microarray expression (CCL2, CCL8, CXCL10, IL1beta).

Figure 1: Influenza infected "febrile" examples of clinical, blood immune cell and cytokine/chemokine time-course. Top Row: PCR, viral culture, total symptom score, temperature. Middle row: blood immune cell count change and cytokines/chemokines log 2 change from baseline; Bottom row: temperature change over time normalised as to whether recorded in am, middle of day or evening. Subject 1 left column, Subject 2 right column.

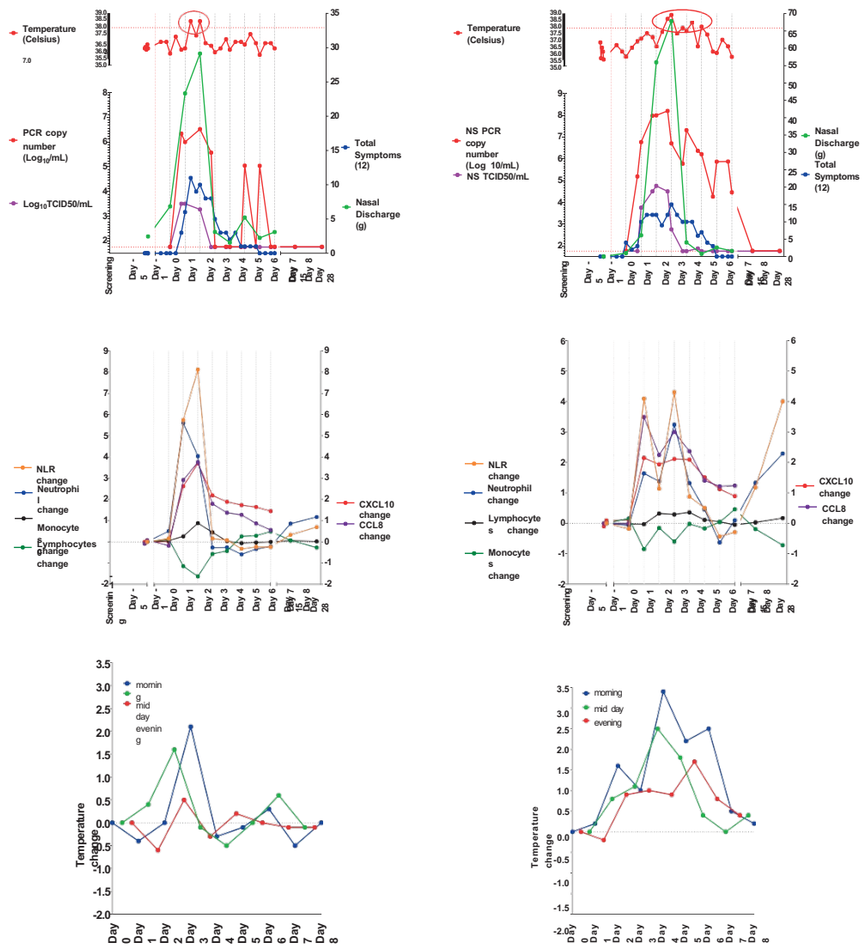
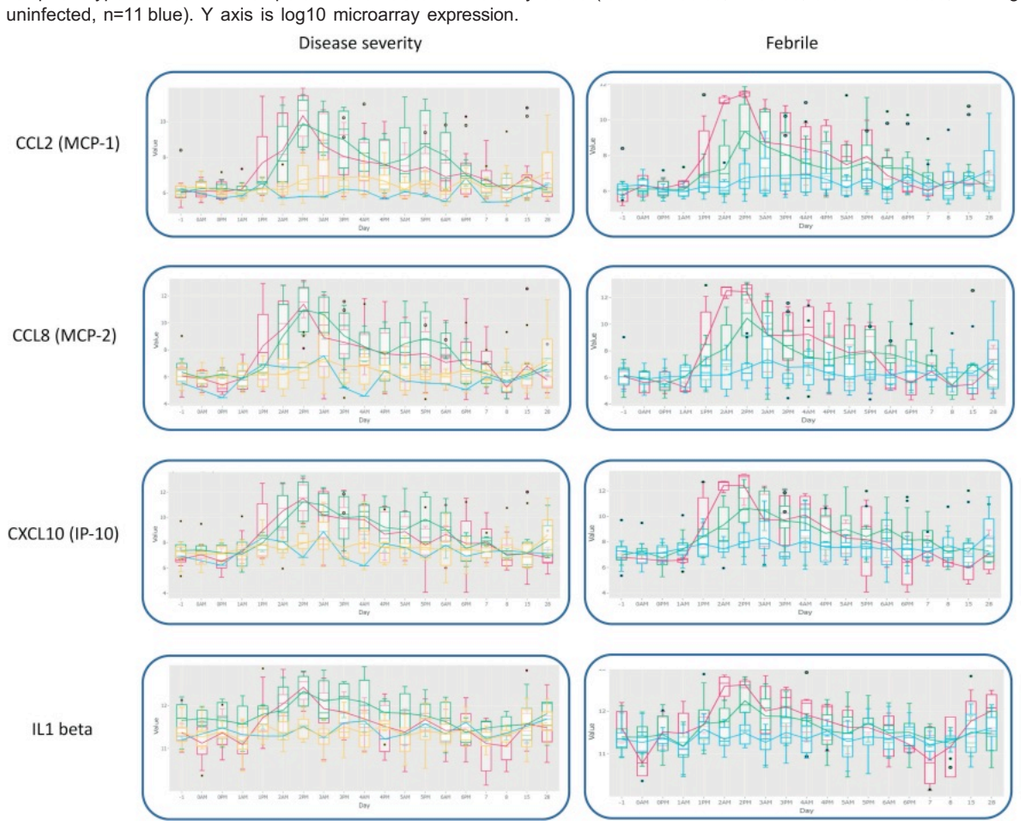


Figure 2: Blood transcriptomic inflammatory levels over time for influenza inoculated subjects (n=25), based on disease severity phenotypes and individual expression: Left column "disease severity" phenotype derived from a total of 58 subjects using peak symptom VAS (sum of max levels of: runny nose, stuffy nose, sore throat, sneezing, cough) within the infected and uninfected (infected tertiles: upper n=8 red; mid n=4 green; lower, n=2 yellow, and uninfected = blue). Right column "febrile" phenotype derived from temperature ≥37.9C and infectivity status (febrile infected, n=3 red, afebrile infected, n=11 green; and uninfected, n=11 blue). Y axis is log10 microarray expression.



HRV-16 in patients with mild asthma results

Of the 13 inoculated with HRV-16, 11 were infected and evaluable (85%). Of those 11 infected, 4 had reduced control and 7 remained well controlled (according to ACQ change ≥0.5 from Day 0 to Day 7). Reduced control was associated with a fall in peak flow (PEF) alongside LRT symptoms, blood cell and biomarker changes.

Figure 3: HRV-16 infected with asthma showing an acute worsening of asthma.
Left: Viral load over time for infected patients that have reduced control (green, n=4) vs those that remain well controlled (pink, n=7). Right: An Infected participant with viral shedding (red)) and upper respiratory tract symptoms (green, n=4) initiate within 36hrs and move to peak by 60hrs post inoculation. Lower respiratory tract symptoms (blue) initiate after 72/80hrs, lasting for several days. Llung function falls (PEF in purple) occurred from 72hrs and lasted for several days with maximal trough at 96hrs.

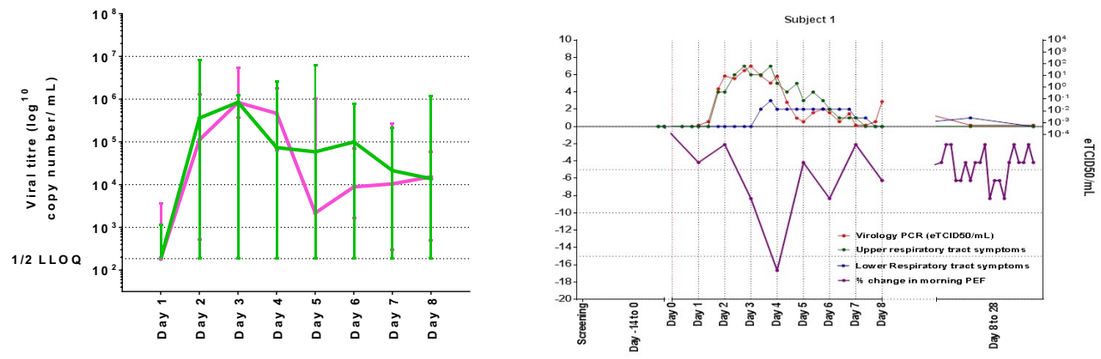
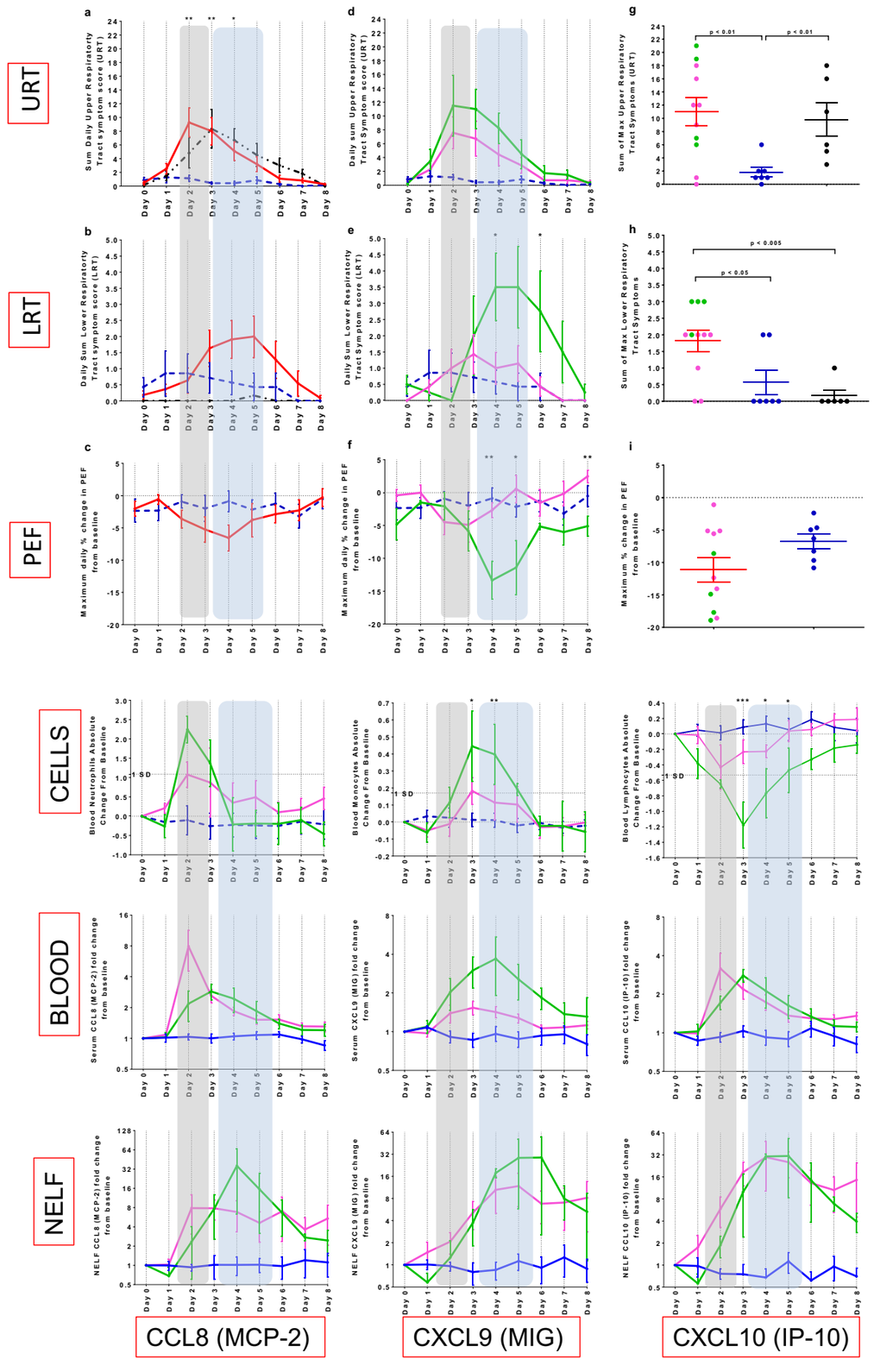


Figure 4: HRV-16 inoculated participants with asthma with URT, LRT, PEF, Blood cell, blood biomarker and nasal biomarker changes over time by level of control of their asthma.
Participants infected with asthma and reduced control (green, n=4), Infected with asthma and no reduced control (pink, n=7), uninfected (blue, n=7), healthy infected (black, n=6). Lung function (PEF), blood cells, and biomarkers were corrected to baseline.



Conclusions

- Inoculation with Influenza in healthy participants or HRV-16 in asthma induces robust viral curves associated with URT symptoms as well as LRT symptoms in asthma
- Significant upregulation of inflammatory markers associate with viral replication and URT symptoms. In asthma this precedes subsequent LRT and lung function changes and nasal inflammatory biomarker changes.
- As a consequence of the timing of viral curves, symptoms and inflammatory markers there are opportunities for prophylactics and post exposure prophylactic treatments to be evaluated in influenza challenge studies. In asthma there is additional opportunity to treat upon URT onset prior to LRT and lung function changes.

Acknowledgements

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