SARS-CoV-2 E-PROTEIN VIROPORIN INHIBITOR BIT225 ACTIVE IN hACE2 TRANSGENIC MICE

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BACKGROUND

The CoV-2 envelope (E) viroporin protein plays an important role in virus assembly, budding, immunopathogenesis and disease severity. E protein has ion channel activity, is located in Golgi and ER membranes of infected cells and is associated with inflammasome activation, apoptosis, increased immune-mediated pathogenicity and viral escape of host-mediated immune effectors.

Increases in proinflammatory cytokines are associated with the edema and acute respiratory distress syndrome (ARDS) observed with SARS-CoV infection.

Here we report that BIT225, an investigational HIV-1 clinical compound, targets the SARS-CoV-2 E protein, and in lethally-infected K18-hACE2 transgenic mice reduces inflammatory and viral markers and prevents body weight loss and mortality when dosing was initiated before or after infection.

BIT225

(N-[5-(1-methyl-1H-pyrazol-4-yl)-naphthalene-2- carboxyl]-guanidine) is an oral, broad-spectrum, first-in-class, viroporin inhibitor that uniquely combines immunomodulatory and direct-acting antiviral activities. It is an investigational HIV-1 clinical compound that reduces virus and inflammatory markers through its antagonism of the HIV-1 Vpu viroporin protein. The drug has a known clinical safety and PK profile with over 200 people dosed in clinical trials to date.

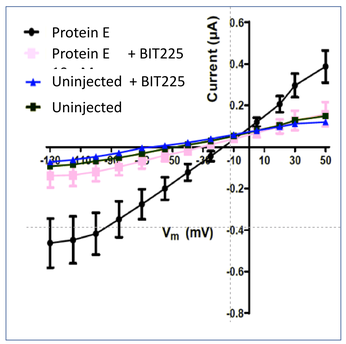

Figure 1. BIT225 inhibited ion channel activity of E protein, but not that of TMEM16A in Xenopus oocytes. SARS-CoV-2 E protein ion channel activity was measured in Xenopus oocytes in the presence and absence of BIT225 (10 μM).

RESULTS

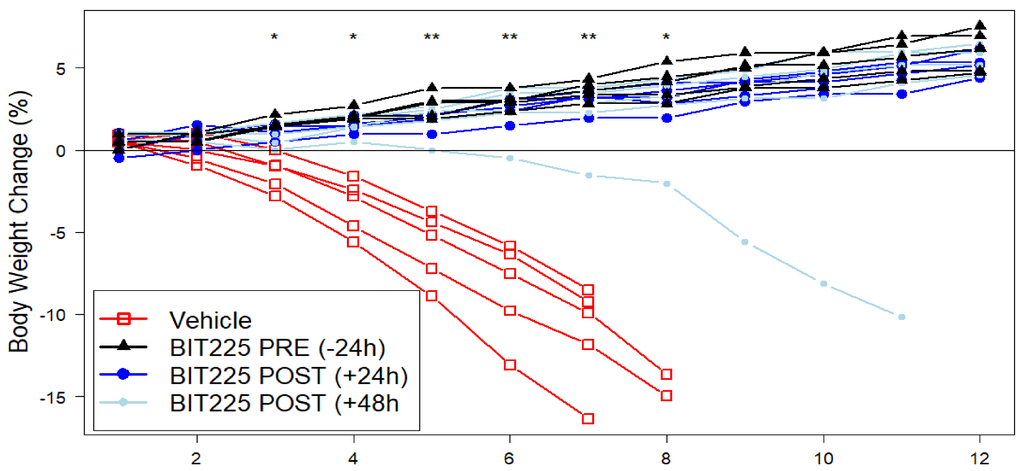

Figure 2. Pre- and Post-infection efficacy of BIT225 dosed at 300mg/kg BID for 12 days in SARS-CoV-2 infected K18 mice. BIT225 initiated 12 h pre-infection (n=12) or 24 h post-infection (n=5) completely prevented body weight loss and mortality. BIT225 initiated 48 h post-infection prevented body weight loss and mortality in 4/5 mice. All vehicle-dosed animals reached a mortality endpoint by day 9 (n=5). K18-hACE2 transgenic mice were infected intranasally with 10^4 pfu SARS-CoV-2 (US-WA1/2020) and dosed orally twice daily with BIT225 for up to 12 Days. * P < 0.05; ** P < 0.01; *** P < 0.001.

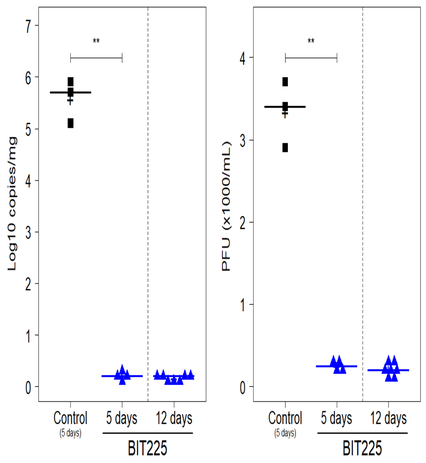

Figure 3A, B. BIT225 was associated with significant reduction in lung viral load (>5 log_{10}), virus titre (~3500 pfu/ml) ** P < 0.01

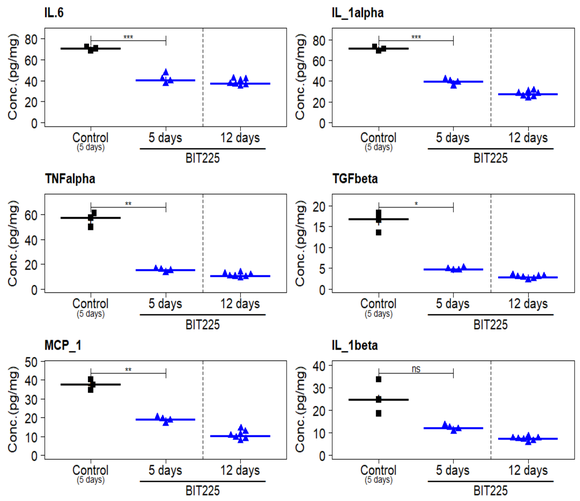

Figure 4. BIT225 was associated with significant reductions in lung pro-inflammatory cytokine levels. Similar results were seen in serum samples (not shown). ns – P>0.05; * P < 0.05; ** P < 0.01; *** P < 0.001.

CONCLUSIONS

The investigational HIV-1 drug BIT225 is an inhibitor of SARS-CoV-2 E protein viroporin activity. In the K18-hACE2 transgenic mouse model of COVID-19 disease, BIT225 protected mice from weight loss and death, inhibited virus replication and reduced inflammation. These effects were noted when treatment with BIT225 was initiated before or 24-48 hours after infection.

Despite the clinical and public health advances afforded by SARS-CoV-2 vaccines and therapeutics, compounds targeting additional aspects of the viral life cycle and pathobiology are needed. Agents that combine direct antiviral activity with immunomodulation are required to address the dual pathophysiology of infection. To date, approved therapeutic agents have focused on antiviral activity, but have left unaffected the profound immune dysregulation that may occur in consequent coronavirus infection.

Like numerous other viruses, SARS-CoV-2 utilizes a viroporin to enhance viral progeny release from infected cells, and to enable viral escape from host immune effectors. Whether used as monotherapy, or in combination with other agents, viroporin antagonists such as BIT225 may play an important role in corona virus therapeutics.

BIT225 was originally developed as an inhibitor of virus-encoded viroporins, which form ion conductive pores in membranes of infected cells that facilitate viral infection, replication and/or release and modulate immune function leading to viral escape from immune effectors. BIT225 has shown antiviral activity against both HIV-1 and HCV in the clinic, as well as potential to reverse adverse viral-induced immunopathogenesis.

The data reported here validate SARS-CoV-2 E protein as a viable antiviral target and support the clinical study of BIT225 in treatment of SARS-CoV-2.

ADDITIONAL KEY INFORMATION

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