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Preclinical efficacy of BIO101 on respiratory function in SARS-CoV-2-infected Syrian hamsters

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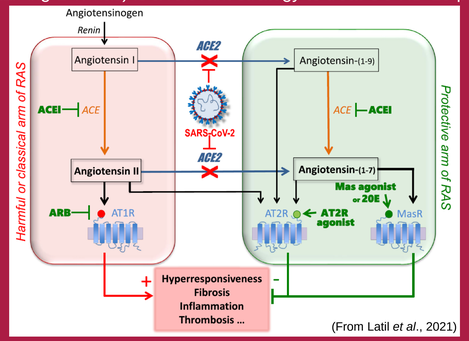
INTRODUCTION

- Interaction of SARS-CoV-2 with ACE2 impairs ACE2 activity and leads to the dysregulation of the renin angiotensin system (RAS).
- RAS balance restoration by stimulating the protective axis (ACE2/Ang-1-7/Mas) is a relevant strategy to treat COVID-19 patients.



(From Latil *et al.*, 2021)

- **Biophytis** develops **BIO101 (20-hydroxyecdysone)**, a Mas receptor activator downstream of ACE2. A phase 2/3 study (COVA) is ongoing in adults ≥ 45-year-old with confirmed COVID-19 pneumonia requiring hospitalization with evidence of respiratory decompensation.

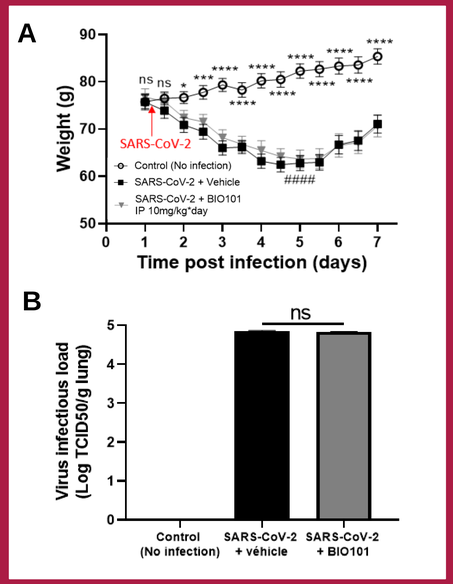
AIM

The aim of this study is to evaluate respiratory functions on SARS-CoV-2-infected golden Syrian hamsters after BIO101 treatment

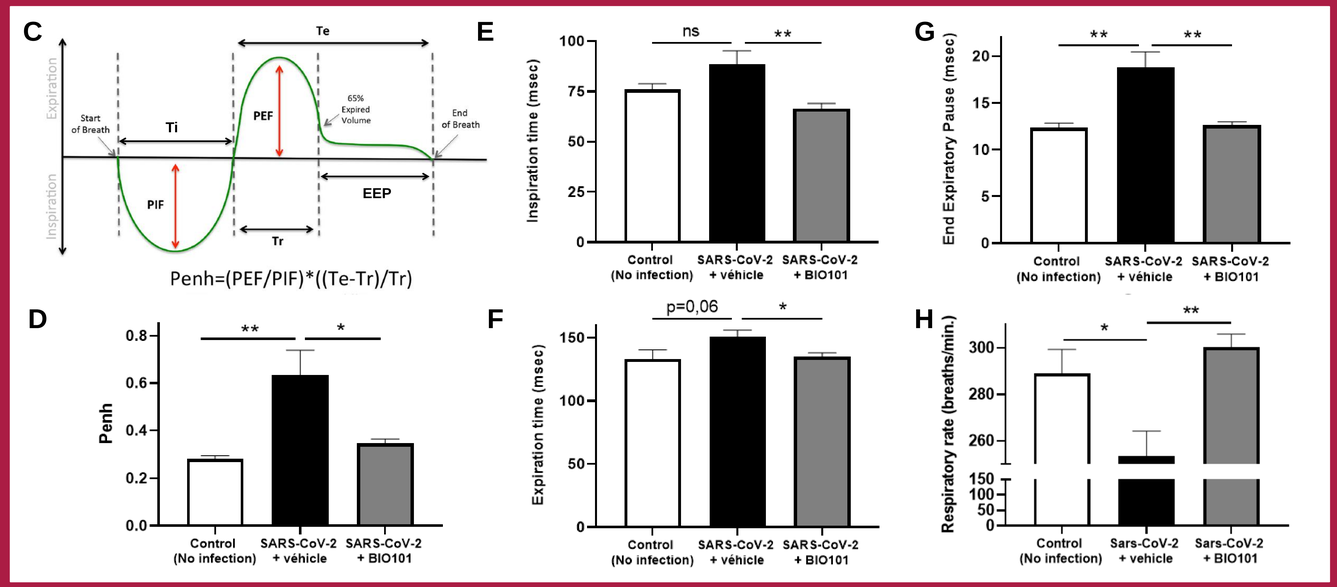
METHOD

Golden Syrian hamsters (*Mesocricetus auratus*) harbor a high degree of homology with humans within the region of ACE2, involved in interaction with the ACE2-binding domain of SARS-CoV-2 Spike (Chan *et al.*, 2020) and are susceptible to SARS-CoV-2 infection. They constitutes a model of interest for testing various therapeutic solutions (van der Lubbe *et al.*, 2021; Driouich *et al.*, 2021).
6-7-week-old female hamsters were inoculated intranasally with 10^6 $TCID_{50}$/mL inoculum of SARS-CoV-2. BIO101 was intraperitoneally administered daily (10 mg/kg*day) during 7 days. The weight of each hamster was evaluated daily during time course infection.
Pulmonary function was assessed by whole-body plethysmography, 5 days after infection. Breathing parameters were measured on the basis of the thoracoabdominal flow curve: the Enhanced Pause (Penh), a dimensionless index of calculated airway function (Hamelman *et al.*, 1997), End Expiratory Pause (EEP), expiration time (Te), inspiration time (Ti) and breathing frequency were evaluated.

RESULTS



(**A**) Hamsters **body weight evaluation** during SARS-CoV-2 time course infection and (**B**) **virus infection load in lungs** at the end of study (7 days *post* infection) in control (no infection), or SARS-CoV-2 infected hamsters treated with the vehicle, or SARS-CoV-2 infected hamsters treated with BIO101 (with *p<0.05, ****p<0.0001 (control group compared to SARS-CoV2+vehicle group) and ###p<0.001 compared to D0).



Respiratory function evaluation 5 days after SARS-CoV-2 infection in hamsters.
(**C**) Penh is a classically used, and derived measure of respiratory distress. Penh is derived by assessing several measures of the respiratory response curve (peak expiratory flow of breath (PEF), peak inspiratory flow of breath (PIF), time of expiratory portion of breath (Te) and time required to exhale 65% of breath volume (Tr). EEP: End expiratory Pressure (adapted from Menachery *et al.*, 2015). (**D**) Normalization of enhanced pause (Penh), (**E**) evaluation of Inspiration time, (**F**) expiration time, (**G**) End Expiratory Pause, and (**H**) respiratory rate after BIO101-treatment of SARS-CoV-2 infected hamsters. Histograms show values of control group (not infected with SARS-CoV-2), infected with SARS-CoV-2 and treated with the vehicle (SARS-CoV-2 + vehicle) or infected with the SARS-CoV-2 and treated with BIO101 (SARS-CoV-2 + BIO101) with * p <0.05, and ** p <0.01.

CONCLUSIONS

This study on respiratory function carried out by whole body plethysmography reveals that BIO101 significantly attenuates this dysfunction (Penh) but also decrease the prolongation of the expiration time during the disease, which is confirm by the decrease of EEP.

These results demonstrate significant beneficial effects of treatment with BIO101, on the respiratory parameters of hamsters infected with SARS-CoV-2 and provides a solid preclinical proof of concept for the ongoing phase 2/3 COVA clinical study.

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