Antiviral activity against SARS-CoV-2

Molecule tested: ondansetron

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Introduction

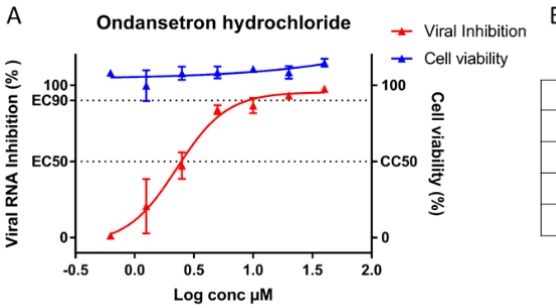
In response to the recent emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, the Unité des Virus Émergents performed preclinical evaluation of drug candidates against SARS-COV-2. **This interim report has not been peer-reviewed.** The data of this report are available upon request.

The molecule tested here is the ondansetron, a competitive serotonin type 3 receptor antagonist marketed for the treatment of nausea/vomiting.

In vitro evaluation of efficacy of ondansetron

Ondansetron was identified as a potential hit by an antiviral screen based on the SARS-CoV-2 cytopathic effect inhibition (Touret et al., 2020).

Then, the antiviral activity was further characterized from 40 µM to 0.6 µM in Vero-E6 cells using a viral RNA yield reduction assay as previously described (Touret et al., 2019, Touret et al., 2020). Dose-response curves are presented in figure 1A. Ondansetron showed half maximal effective concentration (EC50) and 90% effective concentration (EC90) of 2.5µM and 9µM respectively, without any cytotoxicity at these concentrations (Figure 1B). As ondansetron was found to be effective against SARS-CoV-2 with a selectivity index (SI) of 16.2, its antiviral activity was evaluated *in vivo*.



B

µM	Ondansetron
EC50	2,47
EC90	9,00
CC50	>40
SI	16,19

Figure 1: *In vitro* evaluation of Ondansetron in VeroE6 cells. A: Dose response and cytotoxicity evaluation. B Ondansetron interpolated antiviral activity values. All assay were performed as previously described (Touret et al., 2020).

In vivo evaluation of efficacy of ondansetron

Experiments were approved by the local ethical committee (C2EA—14) and French authorities (APAFIS#23975). Four-week-old female Syrian hamsters were intranasally infected with 10^4 TCID50 of the BavPat1 SARS-CoV2 strain as described previously (Driouich et al., 2020). To assess the efficacy of ondansetron, a group of 6 hamsters received the drug, orally, two times a day (BID). We used one dose of 4 mg/day (around 75 mg/kg/day). Treatment was initiated at day of infection, ended at 2 day post infection (dpi) and animals were sacrificed at 3 dpi. A control group of 6 infected/untreated animals received, orally, 0.9% Sodium Chloride solution. Viral replication was measured in lungs (infectious titres and viral RNA yields) and in plasma (viral RNA yields).

Results showed no significant reduction of viral replication in lungs and plasma compared to control group (**Figure 2**).

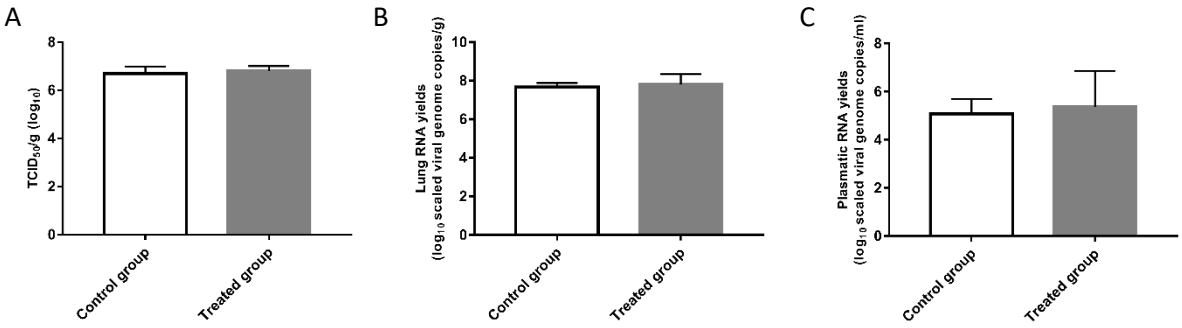


Figure 2: Viral replication in lungs (A-B) and in plasma (C). Lung infectious titers were measured using a $TCID_{50}$ assay and viral RNA yields were using an RT-qPCR assay as previously described (Driouich et al., 2020).

Conclusion

Ondansetron was found to inhibit SARS-CoV-2 replication *in vitro* using Vero-E6 cells. However, results obtained using a hamster model suggest that this molecule is a poor inhibitor of SARS-CoV-2 replication *in vivo.*

References

DRIOUICH, J.-S., COCHIN, M., LINGAS, G., MOUREAU, G., TOURET, F., PETIT, P. R., PIORKOWSKI, G., BARTHÉLÉMY, K., COUTARD, B., GUEDJ, J., DE LAMBALLERIE, X., SOLAS, C. & NOUGAIRÈDE, A. 2020. Favipiravir antiviral efficacy against SARS-CoV-2 in a hamster model. *bioRxiv***,** 2020.07.07.191775.

TOURET, F., BARONTI, C., GOETHALS, O., VAN LOOCK, M., DE LAMBALLERIE, X. & QUERAT, G. 2019. Phylogenetically based establishment of a dengue virus panel, representing all available genotypes, as a tool in dengue drug discovery. *Antiviral Res,* 168**,** 109-113.

TOURET, F., GILLES, M., BARRAL, K., NOUGAIREDE, A., VAN HELDEN, J., DECROLY, E., DE LAMBALLERIE, X. & COUTARD, B. 2020. In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. *Sci Rep,* 10**,** 13093.