The Daily COVID-19 Literature Surveillance Summary

February 22, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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EXECUTIVE SUMMARY

Transmission & Prevention

- N95 respirators and surgical/face masks are comparable in effectiveness of preventing airborne infections. Researchers from Poland and the Cleveland Clinic conducted a meta-analysis of six articles evaluating the effectiveness of N95 vs medical masks in reducing the risk of acute respiratory infections. They found that N95 masks did not significantly reduce infection risk for respiratory viruses over medical masks (RR=1.12, CI: 0.88-1.41, p=0.36; Fig 3) and that medical masks provide similar protection against respiratory viruses including coronaviruses (RR=0.74, CI:0.32-1.73, p=0.49). This suggests that the data to support the superiority of N95 masks over medical masks is insufficient.

Management

- SARS-CoV-2 infection can effect the lower urinary tract and male genital system. A group of Italian physicians review sixteen studies involving 575 patient (538 male, 37 female) to investigate the effects of SARS-CoV-2 on urinary tract and male genitals. They found that patients with COVID-19 may have de novo or worsening lower urinary tract symptoms, as well as testicular and epididymal discomfort or pain. They also found that spermatogenesis can be impaired in patients with moderate infection. This review is important in alerting healthcare professionals to focus attention on the lower urinary tract and male genital system in COVID-19 patients.

R&D: Diagnosis & Treatments

- Clinical stage molecule PT150 is a modulator of glucocorticoid and androgen receptors with antiviral activity against SARS-CoV-2. A multidisciplinary, multi-institutional team in the US examined the in vitro effects of PT150 (a glucocorticoid antagonist that downregulates the androgen receptor and acts as a minor glucocorticoid receptor agonist) by culturing MERS-positive and SARS-CoV-2-positive cells with PT150 and remdesivir. In the SARS-CoV-2 cells, PT150 had an effective 90% inhibitory antiviral concentration (EC90) of 5.55 μM compared to an EC90 of 0.0013 μM for remdesivir, and no cytotoxicity seen at the highest dose of either treatment. The authors postulate PT150 may have some benefit as an adjuvant therapy against the hypercortisolemia associated with more severe COVID-19.

TABLE OF CONTENTS

COMPARATIVE EFFECTIVENESS OF N95 RESPIRATORS AND SURGICAL/FACE MASKS IN PREVENTING AIRBORNE INFECTIONS IN THE ERA OF SARS-COV2 PANDEMIC: A META-ANALYSIS OF RANDOMIZED TRIALS

Barycka K, Szarpak L, Filipiak KJ, Jaguszewski M, Smereka J, Ladny JR, Turan O.. PLoS One. 2020 Dec 15;15(12):e0242901. doi: 10.1371/journal.pone.0242901. eCollection 2020.
Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

BLUF

Researchers from Poland and the Cleveland Clinic conducted a meta-analysis of six articles evaluating the effectiveness of N95 vs medical masks in reducing the risk of acute respiratory infections. They found that N95 masks did not significantly reduce infection risk for respiratory viruses over medical masks (RR=1.12, CI: 0.88-1.41, p=0.36; Fig 3) and that medical masks provide similar protection against respiratory viruses including coronaviruses (RR=0.74, CI:0.32-1.73, p=0.49; Table 2). This suggests that the data to support the superiority of N95 masks over medical masks is insufficient.

ABSTRACT

BACKGROUND: Recently, several randomized controlled trials (RCTs) have evaluated the effect of N95 respirators compared with medical masks to protect against acute respiratory infections. However, these studies are limited by modest sample sizes and inconclusive results. Therefore, the goal of the present study was to review the relevant and available published RCTs with the aid of the increased power of meta-analytic methods in order to assess the effectiveness of medical masks and N95 respirators in reducing the risk of respiratory infections. METHODS: This meta-analysis follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting and reporting results. We searched PubMed, Web of Science, Embase, and Cochrane databases from inception through April 1, 2020 to identify potentially relevant studies. Two authors (LS and JS) independently searched the titles and abstracts of the potentially eligible articles. They independently retrieved required data from the eligible trials; the data were initially tabulated for statistical analysis. Two authors (JRL and LS) independently assessed the methodological quality of the included RCTs using the Cochrane Collaboration's tool for assessing risk of bias. RESULTS: Six articles met the inclusion criteria. The pooled analysis showed that N95 respirators did not reduce the risk of infection with respiratory viruses compared with medical/surgical masks (5.7% vs. 7.9%; RR = 1.12; 95% CI: 0.88-1.41; p = 0.36); however, there was no statistically significant difference in laboratory-confirmed influenza between N95 and medical masks (RR = 0.91; 95% CI: 0.77-1.07; p = 0.26). Medical masks provided similar protection against other viruses, including coronavirus (RR = 0.74; 95% CI: 0.32-1.73; p = 0.49). Respiratory illness, as well as influenza-like illness were less frequently observed with N95 respirators. CONCLUSIONS: Our meta-analysis suggests that there are insufficient data to definitively determine whether N95 respirators are superior to medical masks in protection against transmissible acute respiratory infections. Further randomized trials are necessary to compare the above methods of respiratory protection in the context of COVID-19 incidence.

FIGURES

Parameter	No. of studies	Number of cases		RR (95%CI)	P-value	I^2 statistic
		Medical masks	*N95*			
Respiratory syncytial virus	2	2/306 (0.7%)	1/302 (0.3%)	1.98 (0.18, 21.68)	0.58	NA
Metapneumovirus	2	4/306 (1.3%)	3/302 (1.0%)	1.32 (0.30, 5.83)	0.71	NA
Parainfluenza virus	2	2/306 (0.7%)	2/302 (0.7%)	0.99 (0.17, 5.67)	0.99	0%
Rhinovirus-enterovirus	2	11/306 (3.6%)	12/302 (4.0%)	0.91 (0.41, 2.02)	0.81	0%
Coronavirus	2	9/306 (2.9%)	12/302 (4.0%)	0.74 (0.32, 1.73)	0.49	NA
Adenoviruses	1	0/94 (0.0%)	2/92 (2.2%)	0.20 (0.01, 4.02)	0.29	NA
Picornoviruses	1	0/94 (0.0%)	1/92 (1.1%)	0.33 (0.01, 7.91)	0.49	NA

RR = Risk Ratio; CI = Confidence Interval; NA = Not applicable.

Table 2. Data of laboratory-confirmed other respiratory viruses in medical masks vs. N95 groups

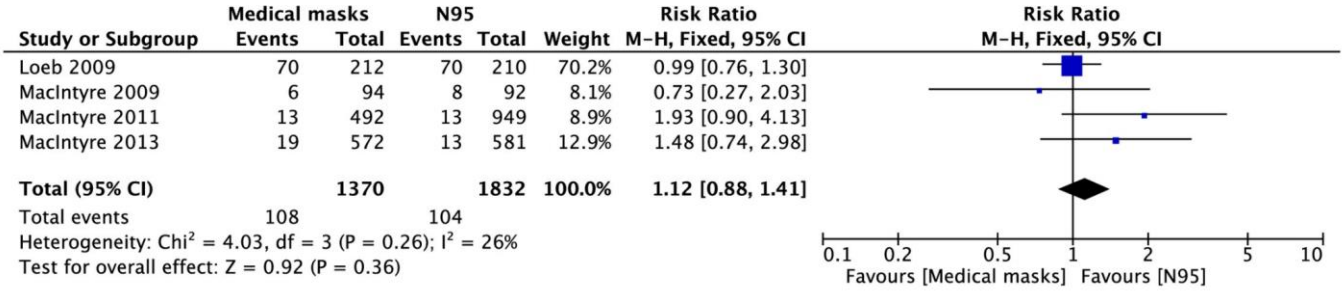

Fig 3. Forest plot of laboratory-confirmed infection with any respiratory viruses in medical masks vs. N95 groups. The center of each square represents the relative risk for individual trials, and the corresponding horizontal line stands for 95% confidence interval. The diamonds represent pooled results.

PREVENTION IN THE COMMUNITY

DELAYED SECOND DOSE VERSUS STANDARD REGIMEN FOR COVID-19 VACCINATION

Kadire SR, Wachter RM, Lurie N.. N Engl J Med. 2021 Feb 17. doi: 10.1056/NEJMclde2101987. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

Internists and health policy experts from Indiana University, University of California San Francisco, and the University of Pennsylvania debate the best allocation strategy for a limited COVID-19 vaccine supply. One author recommends delaying the second dose to vaccinate as many people as possible as quickly as possible, while the other recommends maintaining the current vaccination schedule due to the lack of data describing how delayed boosters would compromise vaccine effectiveness (see summary). The article suggests there is no current one correct solution to this question and open discourse must occur as decisions are made.

SUMMARY

The argument for delaying the second dose:
- By the time a second dose is required (3-4 weeks) the patient is effectively protected 80-90%
- The benefit of a second dose confers a 10% benefit of protection from 85-95%
- However, it appears to be more beneficial to take the would be second dose and instead initially vaccinate another to raise their protection from 0 to 85%
- The UK has already endorsed a delayed vaccination schedule
- The CDC has relaxed their guidelines, endorsing 6 weeks is acceptable for the second dose

The argument for maintaining current recommendations:
- There is no current evidence supporting a delay
- There exists no current data to infer the effectiveness of a delayed dose
- Frontline workers need assurance the vaccines are effective and skirting the guidelines cannot offer said reassurance
- Suboptimal vaccination could help promote antigenic variants of the virus, thus worsening the pandemic

UROLOGY

SARS-COV-2 INFECTION AFFECTS THE LOWER URINARY TRACT AND MALE GENITAL SYSTEM: A SYSTEMATIC REVIEW

Creta M, Sagnelli C, Celentano G, Napolitano L, La Rocca R, Capece M, Califano G, Calogero A, Sica A, Mangiapia F, Ciccozzi M, Fusco F, Mirone V, Sagnelli E, Longo N.. J Med Virol. 2021 Feb 17. doi: 10.1002/jmv.26883. Online ahead of print.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A group of Italian physicians review sixteen studies involving 575 patient (538 male, 37 female) to investigate the effects of SARS-CoV-2 on urinary tract and male genitals. They found that patients with COVID-19 may have de novo or worsening lower urinary tract symptoms, as well as testicular and epididymal discomfort or pain. They also found that spermatogenesis can be impaired in patients with moderate infection. This review is important in alerting healthcare professionals to focus attention on the lower urinary tract and male genital system in COVID-19 patients.

ABSTRACT

PubMed, Scopus, and ISI Web of Knowledge databases were searched to identify studies published up to December 2020 on the involvement of urinary and male genital systems in COVID-19. Sixteen studies involving a total of 575 patients (538 males and 37 females) were included in this systematic review. The COVID-19 phase was available for 479 patients: 426 in the acute and 53 in the recovery phase. De novo lower urinary tract symptoms (LUTS) were observed in 43 patients and deterioration of preexisting LUTS in 7. Bladder hemorrhage was observed in 3 patients and acute urinary retention in one. Regarding male genital system, scrotal discomfort was observed in 8 patients, swelling in 14, pain in 16, and erythema in one; low flow priapism was observed in 2 patients. Ultrasound examination identified acute orchitis in 10 patients, acute epididymitis in 7, and acute epididymo-orchitis in 16. A case-control study reported that patients with moderate COVID-19 show a significant reduction in sperm concertation, total number of sperms per ejaculate, progressive motility, and complete motility. Contrary to what known from the first studies on the subject, this review also including subsequent studies give evidence of an involvement of lower urinary tract and male genital system in COVID-19.

FIGURES

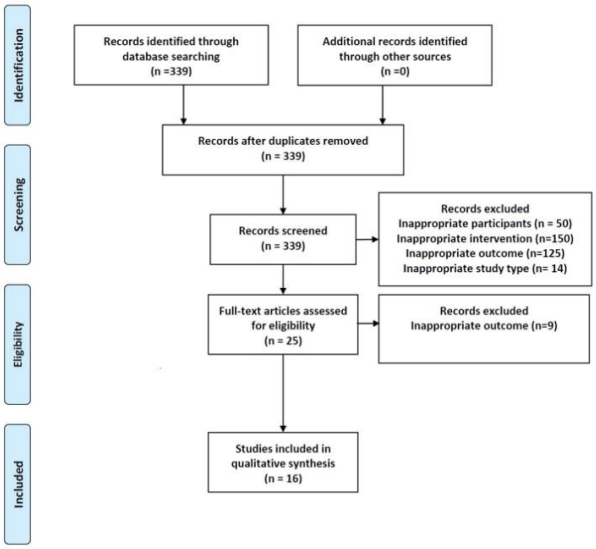

Figure 1: Flow diagram of the systematic review.

MACROPHAGE ACTIVATION AND CYTOKINE RELEASE SYNDROME IN COVID-19: CURRENT UPDATES AND ANALYSIS OF REPURPOSED AND INVESTIGATIONAL ANTI-CYTOKINE DRUGS

Iqubal A, Hoda F, Najmi AK, Haque SE.. Drug Res (Stuttg). 2021 Jan 12. doi: 10.1055/a-1291-7692. Online ahead of print.
Level of Evidence: 5 - Systematic review of randomized trials or n-of-1 trials

BLUF

Full Article unable to be accessed.

ABSTRACT

Coronavirus disease (COVID-19) emerged from Wuhan, has now become pandemic and the mortality rate is growing exponentially. Clinical complication and fatality rate is much higher for patients having co-morbid issues. Compromised immune response and hyper inflammation is hall mark of pathogenesis and major cause of mortality. Cytokine release syndrome (CRS) or cytokine storm is a term used to affiliate the situation of hyper inflammation and therefore use of anti-cytokine and anti-inflammatory drugs is used to take care of this situation. Looking into the clinical benefit of these anti-inflammatory drugs, many of them enter into clinical trials. However, understanding the immunopathology of COVID-19 is important otherwise, indiscriminate use of these drugs could be fetal as there exists a very fine line of difference between viral clearing cytokines and inflammatory cytokines. If any drug suppresses the viral clearing cytokines, it will worsen the situation and hence, the use of these drugs must be based on the clinical condition, viral load, co-existing disease condition and severity of the infection.

HYPOALBUMINEMIA IN COVID-19: ASSESSING THE HYPOTHESIS FOR UNDERLYING PULMONARY CAPILLARY LEAKAGE

Wu MA, Fossali T, Pandolfi L, Carsana L, Ottolina D, Frangipane V, Rech R, Tosoni A, Lopez G, Agarossi A, Cogliati C, Meloni F, Marchini B, Nebuloni M, Catena E, Colombo R.. J Intern Med. 2021 Jan 7. doi: 10.1111/joim.13208. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

A retrospective cohort study conducted at the Luigi Sacco Hospital in Milan by the Division of Internal Medicine found that between non-ICU and ICU patients, a greater deficiency in arterial oxygen, as well as significant hypoalbuminemia was observed in ICU patients (Figure 1). In addition, while bronchoalveolar lavage levels of interleukin 8 (IL-8) positively correlated to increased bronchoalveolar lavage protein levels and worse health outcomes, IL-10 levels were negatively correlated (Figure 4), suggesting these immune markers can be used to assess disease severity and prognosis in COVID-19 patients.

SUMMARY

Methodology

The Luigi Sacco Hospital, which serves as a referral centre for the COVID-19 epidemic surge in Northern Italy, was the site of study for the period from 21 February to 15 April 2020. All patients older than 18 within this time period were screened, excluding those without serum albumin measurements within 3 days of admission. Screening included Chest X-rays to assign a quantitative score regarding the degree of pulmonary involvement based on lung infiltrates, according to the Brixia Score. SimpleStep ELISA kits were utilized to quantify IL-8 and IL-10 levels, and proteins quantifications were performed using Pierce BCA Protein Assay Kits. For the ten patients who died in this window, lung tissues were collected and examined in greater detail using lead citrate stains.

Results
- In comparison to the general patient population, ICU patients displayed more significant hypoalbuminemia and greater disparity in arterial oxygen, suggesting impaired immunity and worse lung involvement

- There was a significant positive correlation between concentration of IL-8 and protein concentrations, and an inverse correlation between IL-10 and protein concentrations, respectively.

-Ultrastructural analysis in post-mortem patients revealed decreases in amount of surfactants, as well as extensive opening of junctional complexes. Opening of these junctions suggest that macromolecules and proteins are able to cross into pulmonary tissue.

ABSTRACT

BACKGROUND: Since the first observations of patients with COVID-19, significant hypoalbuminaemia was detected. Its causes have not been investigated yet. OBJECTIVE: We hypothesized that pulmonary capillary leakage affects the severity of respiratory failure, causing a shift of fluids and proteins through the epithelial-endothelial barrier. METHODS: One hundred seventy-four COVID-19 patients with respiratory symptoms, 92 admitted to the intermediate medicine ward (IMW) and 82 to the intensive care unit (ICU) at Luigi Sacco Hospital in Milan, were studied. RESULTS: Baseline characteristics at admission were considered. Proteins, interleukin 8 (IL-8) and interleukin 10 (IL-10) in bronchoalveolar lavage fluid (BALF) were analysed in 26 ICU patients. In addition, ten autopsy ultrastructural lung studies were performed in patients with COVID-19 and compared with postmortem findings in a control group (bacterial pneumonia-ARDS and H1N1-ARDS). ICU patients had lower serum albumin than IMW patients [20 (18-23) vs 28 (24-33) g L-1 , P < 0.001]. Serum albumin was lower in more compromised groups (lower PaO2 -to-FiO2 ratio and worst chest X-ray findings) and was associated with 30 days of probability of survival. Protein concentration was correlated with IL-8 and IL-10 levels in BALF. Electron microscopy examinations of eight out of ten COVID-19 lung tissues showed loosening of junctional complexes, quantitatively more pronounced than in controls, and direct viral infection of type 2 pneumocytes and endothelial cells. CONCLUSION:

Hypoalbuminaemia may serve as severity marker of epithelial-endothelial damage in patients with COVID-19. There are clues that pulmonary capillary leak syndrome plays a key role in the pathogenesis of COVID-19 and might be a potential therapeutic target.

FIGURES

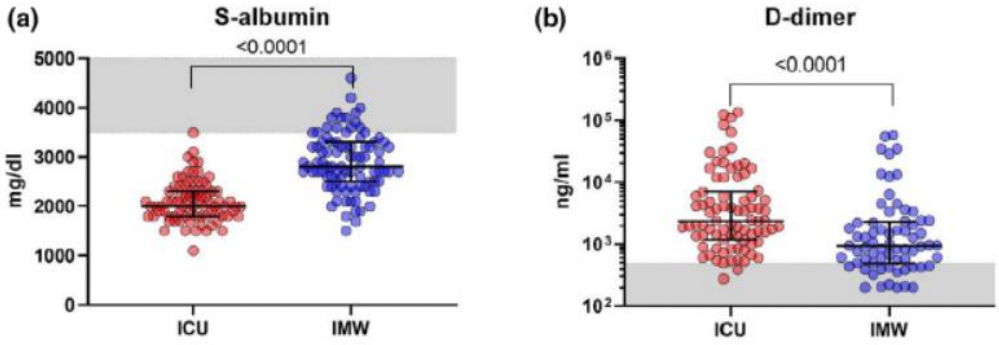

Figure 1. Dot plots of serum albumin (panel a) and D-dimer (panel b) at admission. Grey bands represent reference ranges for healthy populations. Most of patients had out-of-range values.

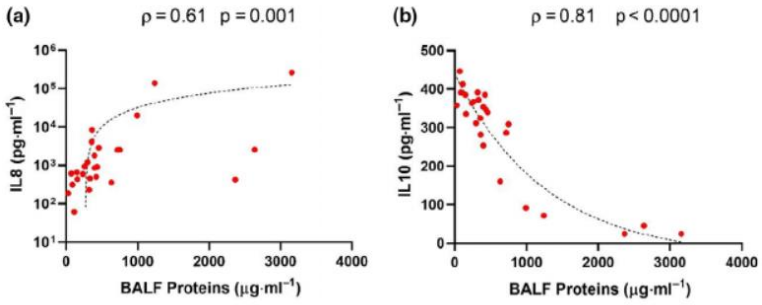

Figure 4. Correlation between concentrations of pro‐inflammatory interleukin 8 (IL‐8) and proteins in the bronchoalveolar lavage fluid. (b) Correlation between concentrations of anti‐inflammatory interleukin 10 (IL‐10) and proteins in the bronchoalveolar lavage fluid (BALF).

DEVELOPMENTS IN TREATMENTS

CLINICAL STAGE MOLECULE PT150 IS A MODULATOR OF GLUCOCORTICOID AND ANDROGEN RECEPTORS WITH ANTIVIRAL ACTIVITY AGAINST SARS-COV-2

Theise ND, Arment AR, Chakravarty D, Gregg JMH, Jacobson IM, Jung KH, Nair SS, Tewari AK, Thurston AW, Van Drie J, Westover JB.. Cell Cycle. 2020 Dec 11:1-7. doi: 10.1080/15384101.2020.1859752. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A multidisciplinary, multi-institutional team in the US examined the in vitro effects of PT150 (a glucocorticoid antagonist that downregulates the androgen receptor and acts as a minor glucocorticoid receptor agonist) by culturing MERS-positive and SARS-CoV-2-positive cells with PT150 and remdesivir. In the SARS-CoV-2 cells, PT150 had an effective 90% inhibitory antiviral concentration (EC90) of 5.55 μM compared to an EC90 of 0.0013 μM for remdesivir, and no cytotoxicity seen at the highest dose of either treatment (Table 1). The authors postulate PT150 may have some benefit as an adjuvant therapy against the hypercortisolemia associated with more severe COVID-19.

ABSTRACT

PT150 is a clinical-stage molecule, taken orally, with a strong safety profile having completed Phase 1 and Phase 2 clinical trials for its original use as an antidepressant. It has an active IND for COVID-19. Antiviral activities have been found for PT150 and other members of its class in a variety of virus families; thus, it was now tested against SARS-CoV-2 in human bronchial epithelial lining cells and showed effective 90% inhibitory antiviral concentration (EC90) of 5.55 microM. PT150 is a member of an extended platform of novel glucocorticoid receptor (GR) and androgen receptor (AR) modulating molecules. In vivo, their predominant net effect is one of systemic glucocorticoid antagonism, but they also show direct downregulation of AR and minor GR agonism at the cellular level. We hypothesize that anti-SARS-CoV-2 activity depends in part on this AR downregulation through diminished TMPRSS2 expression and modulation of ACE2 activity. Given that hypercortisolemia is now suggested to be a significant co-factor for COVID-19 progression, we also postulate an additive role for its potent immunomodulatory effects through systemic antagonism of cortisol.

FIGURES

Table 1. Antiviral efficacy: EC_{90} for POP test compound PT-150 against SARS-CoV-2 (Table view)

Test Compounds	Concentration (μM)	[a] Log_{10} $CCID_{50}$ virus per 0.2 mL	[a] Log_{10} $CCID_{50}$ virus per 0.2 mL	[b] EC_{90} (μM)
PT-150	30	3.00	3.00	5.55
	10	3.00	3.30	
	3	4.00	4.30	
	1	4.67	4.50	
Remdesivir	1.66	2.00		0.0013
	0.17	2.50		
	0.017	3.30		
	0.002	3.67		
Virus Control		4.30		
		4.67		
		5.00		

Table 1. Antiviral efficacy: EC90 for POP test compound PT-150 against SARS-CoV-2. Each well was scored positive for virus if any CPE was observed as compared with the uninfected control. Vero 76 cells were scored on day 5 and confirmed on days 6 & 7. a.Titer results from the virus yield reduction assay. b.EC90 = 90% effective concentration (concentration to reduce virus yield by 1 log10) determined by regression analysis.

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