ACES/ARBS, NSAIDS, REMDESIVIR & UPDATES FROM THE FRONT LINES

APRIL 1, 2020
WEBINAR SERIES PARTNERS

<table>
<thead>
<tr>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Clinical Toxicology (AACT)</td>
</tr>
<tr>
<td>American Academy of Emergency Medicine (AAEM)</td>
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<tr>
<td>American Association of Poison Control Centers (AAPCC)</td>
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<tr>
<td>American College of Medical Toxicology (ACMT)</td>
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<td>Asia Pacific Association of Medical Toxicologists (APAMT)</td>
</tr>
<tr>
<td>European Association of Poison Centers and Clinical Toxicologists (EAPCCT)</td>
</tr>
<tr>
<td>Middle East &amp; North Africa Clinical Toxicology Association (MENATOX)</td>
</tr>
</tbody>
</table>
Outbreak evolution for the current 10 most affected countries
NONE OF OUR SPEAKERS HAVE ANY CONFLICTS OF INTEREST TO DISCLOSE
NSAIDS AND ACES/ARBS
MEDICAL & PUBLIC HEALTH CONSIDERATIONS DURING THE COVID-19 PANDEMIC
April 1, 2020

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OBJECTIVES

- Understand role of ACE2 in SARS-CoV2 (nCoV19) viral entry
- Understand the impact of NSAIDS on ACE2
- Discuss the roles NSAIDS may play in COVID19 severity
Discovery of Angiotensin Converting Enzyme 2 (ACE2) protein

Counter part to ACE1
- Creates angiotensin II (AII)
- Pro-inflammatory, vasoconstrictor

ACE2
- Degrades pro inflammatory AII to A1-7
- Anti-inflammatory, vasodilatory
ACE2 determined to be docking site SARS-CoV spike protein (cellular attachment protein)

Binding site for corona virus cell entry

ACE2 docking for SARS-CoV2 highly likely
Observed fatal cases of COVID frequently had conditions treated with drugs that increase ACE2.

Despite large confounding by age.

Concern that drugs that increase ACE2 may increase disease burden.

- ACE inhibitor/ARB
- "Ibuprofen"

Zhou. Lancet. 2020
ACE2 MODULATORS

Decrease ACE2

Angiotensin II
Diabetes
Inflammation

Increase ACE2

NSAID
Thiazolidinediones
ACE/ARB
Mineralocorticoid antagonists
Pressure overloaded disease (heart failure)
MARCH 14-18
FRENCH MINISTER OF HEALTH, WHO, NHS, FDA, BMI

#COVID-19 | Taking anti-inflammatory drugs (ibuprofen, cortisone, ...) could be an aggravating factor of the infection. If you have a fever, take paracetamol. If you are already on anti-inflammatory drugs or in doubt, ask your doctor for advice.

At this time, FDA is not aware of scientific evidence connecting the use of NSAIDs, like ibuprofen, with worsening COVID-19 symptoms. The agency is investigating this issue further and will communicate publicly when more information is available. However, all prescription NSAID labels warn that “the pharmacological activity of NSAIDs in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.”

There is currently no strong evidence that ibuprofen can make coronavirus (COVID-19) worse.

But until we have more information, take paracetamol to treat the symptoms of coronavirus, unless your doctor has told you paracetamol is not suitable for you.

If you are already taking ibuprofen or another non-steroidal anti-inflammatory (NSAID) on the advice of a doctor, do not stop taking it without checking first.
Viral Misinformation

Hi all- just passing along info... I figured I would share what I got from a friend whose sister is a nurse at NYU...

Information from Vienna’s laboratory studying COVID-19 say vast majority of people who died had ibuprofen/Advil in their system so do not take it!! Those who recovered did not take ibuprofen so if you have symptoms, take Paracetamol only!!! Looks like this virus thrives on ibuprofen so don’t do it and tell everyone you know.

J&J's Tylenol production at maximum capacity as coronavirus boosts demand

NEW YORK (Reuters) - Johnson & Johnson is running its Tylenol

SO, WHAT EXACTLY IS GOING?
BIOLOGIC PLAUSABILITY

- NSAID Mechanism
  - COX 1 and 2 inhibition
  - ↑ACE2

- NSAID
  - ↓ Renal PGE synthesis
  - Inhibit renin secretion
  - ↓ angiotensin II
  - ↑ ACE2

- Acetaminophen
  - Decrease ↓ PGE in brain
  - No ACE2 modulation
Rofecoxib, Celecoxib, Meloxicam, Flubiprofen

Inflammatory arthritis

7 days

Rofecoxib, Celecoxib, Meloxicam, Flubiprofen

Control

Inflammatory arthritis

Nothing

Control

Inflammatory arthritis

ACE2

ACE2/ACE

Asghar. Inflammopharmacology. 2017
Ibuprofen
Diabetes
Control
8 weeks

Control

Pioglitazone
8 weeks

Diabetes

Qiao. Cardiology. 2015
HOW DOES ACE2 UPREGULATION IMPACT COVID-19?
ACE2 UPREGULATION INCREASED INFECTIVITY?

Your cell

Less ACE2
ACE2 UPREGULATION INCREASED INFECTIVITY?

Less ACE2

More ACE2
DOWN REGULATION, GOOD FOR VIRUS?

- HIV- secretes a downregulating nef protein
  - Aid in endocytosis
  - May prevent HIV secondary strain super infection
- SARS-CoV2 also down regulates ACE2
  - May lead to worse COVID19 disease
ACE2-DOWN REGULATION PATHOGENESIS

nCOV 19

ACE2

Your cell

All

More inflammation
ACE2-DOWN REGULATION PATHOGENESIS

More inflammation

Less inflammation
ACE2 knock out worsens pathogenesis in animal model of influenza.

ACE2 knockout > control lung injury

Ameliorated by administration of soluble ACE2

Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics

David Gurwitz

Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

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Email: gurwitz@post.tau.ac.il

Abstract
At the time of writing this commentary (February 2020), the coronavirus COVID-19 epidemic has already resulted in more fatalities compared with the SARS and MERS coronavirus epidemics combined. Therapeutics that may assist to contain its rapid spread and reduce its high mortality rates are urgently needed. Developing vaccines against the SARS-CoV-2 virus may take many months. Moreover, vaccines based on viral-encoded peptides may not be effective against future coronavirus epidemics, as virus mutations could make them futile. Indeed, new Influenza virus strains emerge every year, requiring new immunizations. A tentative suggestion based on existing therapeutics, which would likely be resistant to new coronavirus mutations, is to use available angiotensin receptor 1 (AT1R) blockers, such as losartan, as therapeutics for reducing the aggressiveness and mortality from SARS-CoV-2 virus infections. This idea is based on observations that the angiotensin-converting enzyme 2 (ACE2) gene

Soluble angiotensin-converting enzyme 2; a potential approach for coronavirus infection therapy?

Daniel Battle; Jan Wysocki; Karla Satchell

https://doi.org/10.1042/CS20200163

THERAPEUTIC ACE2
**ACE2-NSAIDS**

**Known Knowns**
- Theoretically plausible
  - NSAIDS increase ACE2
- Animal experimental data supports this
  - Animal studies > 7 days exposure
  - Confounded by ACE2 diseases (arthritis diabetes)
  - Impact on healthy individual not clear
- Animal data does not equal human experimental data
  - No human ACE2/NSAID literature
  - Some drugs like ACE/ARB show variable impact on human ACE2 (Vaduganathan et al.)

**Known unknowns**
- Does ACE2 regulation modify disease severity?
- Are clinical outcomes different among patients taking NSAID and have COVID19?

- No randomized control trials on use of NSAID in COVID19
- No studies registered with clinicaltrials.gov evaluating NSAID use
- No COVID19 cohort or interventional studies have on NSAID use
### OLD RISKS, NEW DISEASE

- **NSAID Mechanism**
  - COX 1 and 2 inhibition
  - Thrombosis - ↑ TxA2 (Black Box Warning) (COX2>COX1)
    - Increased risk of CVA/AMI with NSAID use alone, URI alone, and further increase with both (Wen et al.)
  - Increased complications? - Leukotriene ↑
    - NSAID induced bronchospasm (Sturtevant et al.)
    - Increased empyema in children with URI reported (Le Bourgeois et al.)
- ↓ PGE Gastric/Renal
  - Increased risk of GI bleed (decreased GI mucosal secretions)
  - Pre-renalin acute kidney injury
- **Efficacy**
  - 899 URI patients, no significant difference between APAP and IBU for URI symptoms (Little et al.)
- Change in NSAID prescribing due to COVID19 premature
  - More clinical outcome data needed
  - Continue long term NSAID (aspirin, gout, osteoarthritis)
- Be aware of their current risk profile
- Additional resources
  - Oxford Center for Evidence Based Medicine (CEBM)
    - [https://www.cebm.net/covid-19/nsaids-in-acute-respiratory-infection/](https://www.cebm.net/covid-19/nsaids-in-acute-respiratory-infection/)
  - Perspective-

### NSAID Candidates vs. Consider avoiding

<table>
<thead>
<tr>
<th>NSAID Candidates</th>
<th>Consider avoiding</th>
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</thead>
<tbody>
<tr>
<td>• Patients with low risk for adverse effect</td>
<td></td>
</tr>
<tr>
<td>• Unable to tolerate acetaminophen</td>
<td></td>
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<tr>
<td>• Break through analgesia/anti pyretic</td>
<td></td>
</tr>
<tr>
<td>• Advanced age</td>
<td></td>
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<tr>
<td>• History of thrombosis</td>
<td></td>
</tr>
<tr>
<td>• History of peptic ulcer of gastrointestinal bleed</td>
<td></td>
</tr>
<tr>
<td>• Asthma</td>
<td></td>
</tr>
<tr>
<td>• Renal disease</td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


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Figure 1. New and existing drugs interfering with the renin-angiotensin (Ang) system cascade.
Interaction between SARS-CoV-2 and the Renin–Angiotensin–Aldosterone System.

Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy?
• Ang II → lung injury
• Unclear upregulation of ACE2 in humans
• ARB → more ACE2 on cells → less lung injury in animal models
• ACEI improve pneumonia outcomes
• SARS-CoV2 downregulates ACE2, decreasing levels

Hypothesis: More ACE2 could be good

• Ang II ↓ in shock
• Upregulation of ACE2 → more viral entry?
• ARBs increase ACE2 in the gut → fecal-oral spread of SARS-CoV2
• Ang II → decreased ACE2 on cells → less viral entry?
• Anecdotal benefit of Ang II used as a pressor in COVID

Hypothesis: Less ACE2 is good

ACEI/ARB: Beneficial

ACEI/ARB: Harmful
<table>
<thead>
<tr>
<th>Society</th>
<th>Summary of recommendations</th>
<th>Last Statement Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Society of Hypertension</td>
<td>Recommend continuing ACEis/ARBs due to lack of evidence to support differential use in COVID-19 patients. In those with severe symptoms or sepsis, antihypertensive decisions should be made on a case-by-case basis taking into account current guidelines</td>
<td>March 12, 2020</td>
</tr>
<tr>
<td>European Society of Cardiology Council on Hypertension</td>
<td>Strongly encourage continuing ACEis/ARBs due to lack of evidence to support discontinuing</td>
<td>March 13, 2020</td>
</tr>
<tr>
<td>Hypertension Canada</td>
<td>Recommend continuing ACEis/ARBs due to lack of evidence that patients with hypertension or those treated with ACEis/ARBs are at higher risk of adverse outcomes from COVID-19 infection</td>
<td>March 13, 2020</td>
</tr>
<tr>
<td>Canadian Cardiovascular Society</td>
<td>Strongly encourage continuing ACEis/ARBs and Angiotensin Receptor Nephilysin Inhibitors due to a lack of clinical evidence to support withdrawal of these agents</td>
<td>March 15, 2020</td>
</tr>
<tr>
<td>The Renal Association, United Kingdom</td>
<td>Strongly encourage continuing ACEis/ARBs due to unconvincing evidence that these medications increase risk</td>
<td>March 15, 2020</td>
</tr>
<tr>
<td>International Society of Hypertension</td>
<td>Strongly recommend that the routine use of ACEis/ARBs to treat hypertension should not be influenced by concerns about COVID-19 in the absence of compelling data that ACEis/ARBs either improve or worsen susceptibility to COVID-19 infection nor do they affect the outcomes of those infected</td>
<td>March 16, 2020</td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>Encourage continuing ACEis/ARBs because there is no evidence linking them to COVID-19 disease severity, and discontinuation of antihypertensive therapy without medical indication could in some circumstances result in harm</td>
<td>March 16, 2020</td>
</tr>
<tr>
<td>Spanish Society of Hypertension</td>
<td>Recommend that ACEis/ARBs should not be empirically stopped in patients who are already taking them; in seriously ill patients, changes should be made on a case-by-case basis</td>
<td>March 16, 2020</td>
</tr>
<tr>
<td>American Heart Association, Heart Failure Society of America, American College of Cardiology</td>
<td>Recommend continuing ACEis/ARBs for all patients already prescribed them</td>
<td>March 17, 2020</td>
</tr>
<tr>
<td>European Renal Association - European Dialysis and Transplant Association</td>
<td>Recommend continuing ACEis/ARBs in COVID-19 infection patients due to a lack of evidence to support differential use and the discontinuation of ACEis/ARBs in COVID-19 patients</td>
<td>March 17, 2020</td>
</tr>
<tr>
<td>American Society of Pediatric Nephrology</td>
<td>Strongly recommend continuing ACEis/ARBs until new evidence to the contrary becomes available</td>
<td>March 17, 2020</td>
</tr>
<tr>
<td>High Blood Pressure Research Council of Australia</td>
<td>Recommend continuing routine use of ACEis/ARBs. Patients should not cease blood pressure lowering medications unless advised to do so by their physician</td>
<td>March 18, 2020</td>
</tr>
<tr>
<td>Australian Diabetes Society</td>
<td>Recommend that usual antihypertensive therapy is continued given that speculation about risk of ACE inhibitors and ARBs is purely theoretical</td>
<td>March 29, 2020</td>
</tr>
</tbody>
</table>

ONGOING TRIALS

- Observational
  - Italy: Retrospective, ACEI or ARB use (CODIV-ACE)
  - UK: Matched prospective case-control ACEI vs not
  - Wuhan, China: Case-control ACEI vs not

- Investigational
  - Minnesota: outpatient losartan 25 mg vs placebo
  - Minnesota: inpatient losartan 25 mg vs placebo
Angiotensin II for the Treatment of COVID-19–Related Vasodilatory Shock

Jonathan H. Chow, MD, Michael A. Mazzeffi, MD, MPH, and Michael T. McCurdy, MD

Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients

Yingxia Liu, Fengming Huang, Jun Xu, Penghui Yang, Yuhao Qin, Mengli Cao, Zhaqin Wang, Xiaohe Li, Shaogeng Zhang, Lu Ye, Jingjun Lv, Jie Wei, Tuxiu Xie, Hong Gao, Kai-Feng Xu, Fusheng Wang, Lei Liu, Chengyu Jiang
doi: https://doi.org/10.1183/09506202.122020.20039586
ACEI AND ARB RETROSPECTIVE DATA

- 78 patients in China with COVID-19 and HTN
- For age > 65 with HTN (46 pts), severe disease was greatly reduced in those who took ARBs prior to hospitalization
- …based on 10 patients on ARBs
Figure 1

Cohort A (n=333) COVID-19 patients in the Shenzhen Third People’s Hospital (Shenzhen, China)

44 patients with hypertension

unknown medication 3 patients

41 patients with hypertension

Total 78 COVID-19 patients with hypertension included

Cohort B (n=111) COVID-19 patients in the Renmin Hospital of Wuhan University (Wuhan, China)

29 patients with hypertension

unknown medication 6 patients

23 patients with hypertension

Cohort C (n=67) COVID-19 patients in the Fifth Medical Center of PLA General Hospital (Beijing, China)

14 patients with hypertension

Liu et al. Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. medRxiv preprint: https://www.medrxiv.org/content/10.1101/2020.03.20.20039586v1
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total patients (n=46)</th>
<th>Severe patients (n=28)</th>
<th>Mild patients (n=18)</th>
<th>Unadjusted</th>
<th>Adjusted</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI p value</td>
<td>OR 95% CI p value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td></td>
<td></td>
<td></td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>CCB</td>
<td>28 (56.5)</td>
<td>18 (64.3)</td>
<td>8 (44.4)</td>
<td>0.791</td>
<td>0.548-1.141 0.403</td>
</tr>
<tr>
<td>ARB</td>
<td>10 (21.7)</td>
<td>3 (10.7)</td>
<td>7 (38.9)</td>
<td>0.343</td>
<td>0.128-0.916 0.025</td>
</tr>
<tr>
<td>ACEI</td>
<td>2 (4.3)</td>
<td>1 (3.6)</td>
<td>1 (5.6)</td>
<td>0.571</td>
<td>0.139-2.342 0.378</td>
</tr>
<tr>
<td>Thiazide</td>
<td>3 (6.5)</td>
<td>0 (0)</td>
<td>3 (16.7)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>BB</td>
<td>7 (15.2)</td>
<td>3 (10.7)</td>
<td>4 (22.2)</td>
<td>0.49</td>
<td>0.2-1.198 0.119</td>
</tr>
</tbody>
</table>

ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor; CCB, calcium channel blocker; BB, beta blocker.

Adjustment was by multivariable logistic regression modeling with sex variable.

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Liu et al. Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. medRxiv preprint: https://www.medrxiv.org/content/10.1101/2020.03.20.20039586v1
WHAT CAN BE SAID CONFIDENTLY?

- **It is uncertain** if ACEIs and ARBs worsen or improve outcomes of COVID-19.
- Patients chronically taking ACEIs or ARBs **should not stop therapy** pending trials given **clear benefit in heart failure, HTN, and CKD**, plus the **uncertain risk-benefit ratio in COVID**.
- **It is uncertain** if angiotensin II is of additional benefit or detriment in treatment of COVID-19.
THANK YOU
PLEASE REACH OUT WITH ANY QUESTIONS

Many researchers (work shown and not)
Matt Sparks, Swapnil Hiremath, and the rest of the
Nephrology / Hypertension online community

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Poison Center; Associate Program
Director, Nephrology Fellowship,
University of Maryland
JDKing@som.umaryland.edu
@nephrotox
REMDESIVIR (GS-5734)
A REVIEW OF PERTINENT DRUG INFORMATION FOR SARS-COV-2
April 1, 2020

Matt Davis, PharmD
Infectious Diseases Pharmacist
UCLA Ronald Reagan Medical Center
Mrdavis@mednet.ucla.edu
@mattdavis138
MECHANISM OF ACTION: Interference with viral RNA-dependent RNA polymerase; premature termination of viral RNA transcription

STATUS: Investigational, COVID-19 Phase III trials ongoing

FORMULATION: Intravenous only

DOsing: 200 mg IV loading dose, then 100 mg IV daily for 5-10 days
Pediatric Dosing: 5 mg/kg IV loading dose (max 200 mg), then 2.5 mg/kg IV daily (max 100 mg)

MANUFACTURER: Gilead Sciences

*Optimal duration currently under investigation
REMDESVIR STRUCTURE ACTIVITY RELATIONSHIP

Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog

Siegel; ACS 2017.
Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog

Siegel; ACS 2017.
REMDESIVIR STRUCTURE ACTIVITY RELATIONSHIP

C-Adenosine Analog
Rate limiting phosphorylation

Monophosphate Form
Charge reduces permeability

Remdesivir
Neutral charge, bypasses rate limiting step

Siegel; ACS 2017.
REMDESVIR STRUCTURE ACTIVITY RELATIONSHIP

Monophosphoramide 1’Cyano
C-adenosine Nucleoside Analog

Siegel; ACS 2017.
REMDESIVIR STRUCTURE ACTIVITY RELATIONSHIP

C-Adenosine Analog

Poor selectivity, highly cytotoxic

Remdesivir

1’Cyanone modification confers selectivity

Siegel; ACS 2017.
REMDESIVIR (GS-5734) PHARMACOKINETICS

- **Distribution**: Unbound 12.1%; Widely distributed
  - Bladder, kidneys, liver, prostate gland, salivary gland (mandibular), pancreas
  - Seminal vesicle, epididymis, testes
  - Poorly crosses blood-brain barrier

- **Metabolism**: Phosphoramidate prodrug activated by esterases; CYP3A4 substrate

- **Elimination**: Rats - Urine 63%, feces 27.8%

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Remdesivir (GS-5734)</th>
<th>Nucleoside Metabolite (GS-441524)</th>
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<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>2.6 µg/mL</td>
<td>0.14-0.15 µg/mL</td>
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<tr>
<td>$T_{\text{max}}$</td>
<td>-</td>
<td>2.75-4 hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>0.84-1.04 hr</td>
<td>20.4-25.3 hr</td>
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</table>

SAFETY

- **Multiple-dose, 5-14 days**
  - Any TEAE - 56-72%; All Grade 1-2
  - **ALT/AST increase**
    - Onset 5-25 days; resolution 3-47 days
  - Phlebitis
  - Constipation
  - Dyspepsia
  - Extremity pain
  - Headache
  - Nausea

- **Ebola RCT**
  - Single patient experienced hypotension and cardiac arrest after RDV initiation; cannot be distinguished from fulminant Ebola
SAFETY

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---

**Sulfobutylether-ß Cyclodextrin (SBECD)**

- Remdesivir 150 mg solution - 9 g
- Remdesivir 150 mg lyophilized powder - 4.5 g
- Voriconazole 400 mg - 6.4 g

- Does **NOT** meet NIOSH/ASHP criteria for a hazardous compound

Consult updated pharmacy instructions from Gilead for additional information

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### IN VITRO ACTIVITY

<table>
<thead>
<tr>
<th>Filoviridae</th>
<th>Paramyxoviridae</th>
<th>Pneumoviridae</th>
<th>Orthocoronaviridae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola</td>
<td>Measles</td>
<td>Respiratory Syncytial Virus</td>
<td>HCoV-NL63</td>
</tr>
<tr>
<td>Marburg</td>
<td>Mumps</td>
<td>Human Metapneumovirus</td>
<td>HCoV-OC43</td>
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<tr>
<td></td>
<td>Nipah</td>
<td></td>
<td>HCoV-229E</td>
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<tr>
<td></td>
<td>Hendra</td>
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<td>HCoV-HKU1</td>
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<td>SARS-CoV-1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>SARS-CoV-2</td>
</tr>
</tbody>
</table>

HCoV = Human Coronavirus; MERS = Middle East Respiratory Syndrome; SARS = Severe Acute Respiratory Syndrome
## IN VITRO ACTIVITY

<table>
<thead>
<tr>
<th>Virus</th>
<th>EC50 (cells)</th>
<th>CC50 (cells)</th>
<th>Selectivity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2</td>
<td>0.77 µM (Vero E6)</td>
<td>&gt;100 µM (Vero E6)</td>
<td>&gt;130</td>
</tr>
<tr>
<td>SARS-CoV-1</td>
<td>0.069 µM (HAE)</td>
<td>&gt; 10 µM (HAE)</td>
<td>&gt;144</td>
</tr>
<tr>
<td>MERS</td>
<td>0.074 µM (HAE)</td>
<td>&gt; 10 µM (HAE)</td>
<td>&gt;135</td>
</tr>
<tr>
<td>Ebola</td>
<td>0.086 µM (MCr)</td>
<td>6.1 (Hep-2)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

EC50 = 50% effective concentration; CC50 = 50% cytotoxic concentration; Selectivity Index = CC50/EC50; Vero E6 = African monkey kidney cells; HAE = human airway epithelial cells; MCr = macrophages; Hep-2 = human epithelial type 2 cells.
<table>
<thead>
<tr>
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<th>CC50 (cells)</th>
<th>Selectivity Index</th>
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<td>SARS-CoV-1</td>
<td></td>
<td>&gt; 10 µM (HAE)</td>
<td>&gt;144</td>
</tr>
<tr>
<td>MERS</td>
<td></td>
<td>&gt; 10 µM (HAE)</td>
<td>&gt;135</td>
</tr>
<tr>
<td>Ebola</td>
<td></td>
<td>6.1 (Hep-2)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**SARS-CoV-2 EC_{50}**

- Ribavirin 109.5 µM
- Penciclovir 95.96 µM
- Favipiravir 61.9 µM
- Hydroxychloroquine 0.77 µM
- Chloroquine 1.13-5.47 µM
CORONAVIRUSES AND PROOFREADING

Ribavirin

Penciclovir

Favipiravir

Removed by proofreading

Maintains activity; high fitness cost

Remdesivir

Agostini; mBio 2018.
Jordan; AAC 2018.
**IN VIVO ANIMAL PROPHYLAXIS**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virologic</th>
<th>Clinical/Pathologic</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-1</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MERS</td>
<td>✓</td>
<td>✓</td>
<td>✓*</td>
</tr>
</tbody>
</table>

*MERS-infected mice showed improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir

De wit E; Proc Natl Acad Sci 2020.  
Sheahan; Nat Comm 2020.  
Sheahan; Sci Transl Med 2017.
### IN VIVO ANIMAL TREATMENT

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virologic</th>
<th>Clinical/Pathologic</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-1</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️ (Day 1) † (Day 2)</td>
</tr>
<tr>
<td>MERS</td>
<td>✔️</td>
<td>✔️</td>
<td>✖️ *</td>
</tr>
<tr>
<td>Ebola</td>
<td>✔️</td>
<td>✔️</td>
<td>---</td>
</tr>
</tbody>
</table>

*MERS-infected mice did not show improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir; Macaques in Ebola model were euthanized if deemed clinically moribund

---

Agostini; mBio 2018.  
Jordan; AAC 2018.
“A drug that inhibits viral replication may be of little use once virus replication has reached its peak...”
RANDOMIZED, CONTROLLED EBOLA TRIAL

Standard of Care + 1:1:1:1
Stratified on cycle-threshold (i.e. viral load)
I° Outcome: 28 day mortality

- **ZMapp (Control)**
  - Triple monoclonal antibody

- **Remdesivir (RDV)**
  - 200 mg load
  - 100 mg daily x9-13d

- **REGN-EB3**
  - Triple monoclonal antibody

- **MAb114**
  - Single Ebola survivor monoclonal

Mulangu; NEJM 2019.
RANDOMIZED, CONTROLLED EBOLA TRIAL

- Similar duration of symptoms (~5.5 days)/viral load
  - Per day OR 1.12 (1.00-1.24)
- Baseline characteristics generally well matched
  - Higher SCr/LFTs in ZMapp/RDV (sicker?)
- ZMapp and RDV arms halted; mortality signal

Mulangu; NEJM 2019.
RANDOMIZED, CONTROLLED EBOLA TRIAL

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- Baseline characteristics generally well matched
  - Higher SCr/LFTs in ZMapp/RDV (sicker?)
- ZMapp and RDV arms halted; mortality signal

Started too late? (latest start day 3)
Flaw in animal model?
Standard of care/resources?
FIRST U.S. COVID-19 CASE REPORT

35M, PMH (-)
Cough/fever
Travel from Wuhan

0

5

SARS-CoV-2 (+)
Admitted

4

Urgent Care

10

SpO₂ 90%
LLL opacity
Abx started

11

Streaky opacities/rales
Supplemental O₂
SARS-CoV-2 (+)
RDV (evening)

12

O₂ Stopped
Rales resolve

Febrile

Cough

Cough

Mulangu; NEJM 2019.
FIRST U.S. COMMUNITY TRANSMITTED CASE REPORT

40s F, Flu-like Illness x3 days to OSH No known RFs

SARS-CoV-2 testing request denied
SARS-CoV-2 (+) off paralytics RDV requested
SARS-CoV-2 (-) x2 24 hr apart

Days 11-20 RDV x 10 days prone stopped/extubated floor transfer

ARDS = Acute respiratory distress syndrome; ECLS = extracorporeal life support; RVP = Respiratory viral panel

Sanville; CID 2020.
CONCLUDING REMARKS

• Current data insufficient to draw definitive conclusions
• Seemingly well tolerated in published COVID-19 cases
• Clinical trials and compassionate use ongoing

“[...] scientists are **patiently waiting** for the final results of these ongoing trials.”
## CURRENT INVESTIGATIONS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Population</th>
<th>Intervention</th>
<th>Renal</th>
<th>Completion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive</td>
<td>NIAID</td>
<td>n = 440</td>
<td>RDV vs. PCB; Adaptive</td>
<td>eGFR &lt; 50 mL/min</td>
<td>4/1/2023</td>
</tr>
<tr>
<td>Moderate</td>
<td>Gilead</td>
<td>SpO₂ ≥ 94%; n = 600</td>
<td>5 vs. 10 days RDV vs. SOC</td>
<td>CrCl &lt; 50 mL/min</td>
<td>5/2020</td>
</tr>
<tr>
<td>Severe*</td>
<td>Gilead</td>
<td>SpO₂ &lt; 94%; n = 400</td>
<td>5 vs. 10 days RDV</td>
<td>CrCl &lt; 50 mL/min</td>
<td>5/2020</td>
</tr>
<tr>
<td>Expanded</td>
<td>USAMR</td>
<td>U.S. DoD-Affiliates; All age</td>
<td>RDV</td>
<td>eGFR &lt; 30 mL/min</td>
<td>--</td>
</tr>
<tr>
<td>Mild/Mod (Ch)</td>
<td>CMU</td>
<td>SpO₂ &gt; 94%; n = 308</td>
<td>RDV vs. PCB</td>
<td>eGFR &lt; 30 mL/min</td>
<td>4/27/2020</td>
</tr>
<tr>
<td>Severe (Ch)</td>
<td>CMU</td>
<td>SpO₂ &lt; 94%; n = 453</td>
<td>RDV vs. PCB</td>
<td>eGFR &lt; 30 mL/min</td>
<td>5/1/2020</td>
</tr>
</tbody>
</table>

RDV = remdesivir; PCB = placebo; USAMR = U.S. Army Medical R&D Command; CMU = Capital Medical University, Beijing

*All data current as of 3/31/2020, subject to change
REFERENCES

THANK YOU
PLEASE REACH OUT WITH ANY QUESTIONS

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UPDATES FROM THE FRONT LINE

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- IRCCS Maugeri Hospital and University of Pavia (Italy)

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- The Icahn School of Medicine at Mount Sinai
  Elmhurst Hospital Center

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Q&A
ON-DEMAND RESOURCES

- All webinars are recorded and posted to the ACMT website
- PDFs of webinar slides are also available on the website
- Questions? Email: info@acmt.net

www.acmt.net/COVID-19_Webinars
NEXT WEBINAR

Topic To Be Announced on Monday 4/6

Wednesday, April 8, 2020
@ 3:00 PM EDT