The Prudent Prescriber

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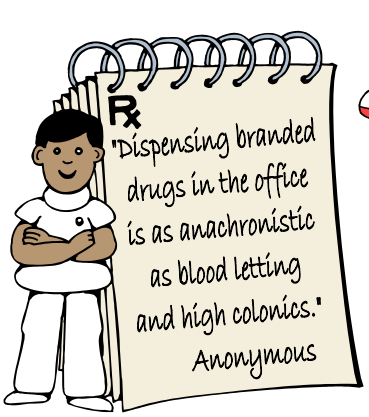
May 2020

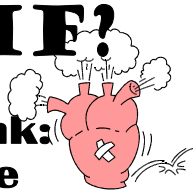


Steve Nolan, Pharm.D. follows through this month with further appraisal of potential pharmaceutical answers to COVID-19.

The search continues…
Last month we talked about the lack of good clinical evidence for using hydroxychloroquine for COVID-19, and things haven't gotten any for that drug in the interim. As we look to other drugs in the news, we're faced with evaluating similarly incomplete, premature clinical trial data. Remdesivir seems to be getting the lion's share of the limelight, so we'll take a look at the available data in this issue.

Continued "leaks" and "early peeks" dominate the lay press and even medical journals are publishing premature data. The three P's (p values, placebo groups, and peer review) are being edged out by "first to report" news, often based on overheard interviews and expert opinions rather than on evidence. Surely an ongoing pandemic requires much quicker turnaround by clinical investigators and the FDA than we would normally tolerate, but some modicum of scientific rigor and restraint must remain or we risk doing more harm than good with some of these treatments. Fish tank chloroquine, anyone?

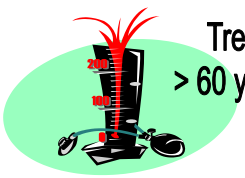
CHF?



Think:
Ace
Aldactone
B-blocker
Dig
Diuretic

Avoid these expensive "me-too" drugs:

Mydayis
Lucemyra
Xyzal
Gralise
Viibyrd
Lexette foam
Drizalma DR



Treat patients > 60 years to 150/90

Pharm Reps ≠ Rational Prescribing
(PR) **(RP)**

Antibiotics do NOT

help acute bronchitis

ß-blockers in post-MI save lives

Pill splitters save BIG

NOW AVAILABLE on the Generic Marquee

Advair→fluticasone/salmeterol or Wixela Inhub
Eliquis→apixaban
Lyrica→pregablin
Apriso→mesalamine ER capsules
Nuvaring→etonogestrel & EE ring

Here's an example report from major news outlets on April 17: "COVID-19 patients who are getting an experimental drug called remdesivir have been recovering quickly, with most going home in days, STAT News reported Thursday after it obtained a video of a conversation about the trial."
So, these were news outlets reporting a story from another news outlet that cited "a video of a conversation about the trial." The trial referenced here had no placebo group and no sample size calculation. Results from trials like these should never see the public light of day, but these are extraordinary times.

In the April issue of The Lancet, Dr. John Norrie effectively sums it up with "...the temptation to lower the threshold of convincing evidence must be resisted, because adopting ineffective and potentially unsafe interventions risks only harm without worthwhile benefit, while making it even harder to undertake trials to find truly effective and safe interventions." As Dr. Norrie notes, "we have already seen other drugs, repurposed for COVID-19, including hydroxychloroquine and lopinavir–ritonavir report disappointing findings so far in randomized trials after early promise."

Here's the scoop on remdesivir
Originally part of the search for hepatitis C drugs and then tested against Ebola, remdesivir stops viral replication by inhibiting viral RNA synthesis. Ebola didn't pan out and the drug is not currently FDA approved in the U.S. (sort of, more on that later). There is in-vitro and animal data showing activity against SARS-CoV-2, so now the drug is the subject of over 25 clinical trials. It's only given IV so it can't be evaluated as an early intervention to prevent mild disease from becoming serious and the manufacturer has stated it has no plans to spend money creating a pill form. That may be a telling sign of their confidence in the drug.

Clinical Studies

Clinicaltrials.gov lists exactly one completed study on remdesivir. That was a Chinese study, published in The Lancet on April 29. It was actually a pretty well-designed multi-center study with good adherence to protocol, double blinding, placebo control, with no patients lost to follow up. The studied population (n=236) had severe COVID-19 disease and received 10 days of remdesivir or placebo. The primary endpoint was time to clinical improvement, defined as 2- point improvement on a 6-point scale at 21 days. It was stopped early after showing no benefit for remdesivir on clinical improvement, mortality, or viral clearance. The explanation was an inadequate population size. (Wang Y, Zhang D, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicenter trial. Lancet. 2020; (published online April 29.)

Other notable studies:

ACTT (Adaptive COVID-19 Treatment Trial) is being run by the National Institute of Allergy and Infectious Diseases (NIAID). This is a multi-part trial with an "adaptive" format allowing interim evaluation of the study to modify the treatment cohorts. It's a double blinded, placebo controlled, global study in over 100 sites. Ten days of remdesivir are being compared to 10 days of placebo infusion. Aiming to enroll 800 participants, the study will finalize results once 400 subjects reach "recovered" status. To be eligible, participants must be hospitalized with severe disease and require ventilator support, supplemental oxygen, or have radiographic infiltrates.

The primary outcome was originally mortality rate and rate of patients requiring ventilator support, but this was changed 8 weeks into the study. Preliminary results of the new primary outcome, time to improvement, showed a reduction of 4 days in recovery time in surviving patients, from 15 to 11 days.

These results prompted the investigators to stop the placebo arm and convert those patients to active treatment with remdesivir, halting the ability to ever definitively prove a mortality benefit. This, much to the chagrin of Dr. Steve Nissen, who argued a few more weeks of placebo comparison might have allowed for determination of this vital study question. You might remember Dr. Nissen, the Cleveland Clinic cardiologist that blew the whistle on the cardiovascular safety of Vioxx and years later, with Avandia. While somewhat unusual to change the primary endpoint ***during*** a trial, it's not unheard of and it may have made ethical sense to stop the placebo group early even if that meant losing an opportunity to see if the drug could save lives.

This was the study cited by NIAID Director Dr. Anthony Fauci on national TV. The preliminary results were described as "highly significant" and received widespread media coverage. Dr. Clifford Lane, the clinical director at NIAID, said the results of the ACTT trial so far show remdesivir is "not a home run, but is probably better than nothing." Well, there's that.

Two "SIMPLE" trials

Gilead Sciences, the manufacturer of remdesivir, has started two open label trials termed SIMPLE, one in severe disease (n=6,000) and one in moderate disease (n=1,600). Both compare either 5 or 10 days of remdesivir to placebo infusion in a non-blinded fashion. Both trials are slated for completion by the end of May.

The SOLIDARITY trial is being run by the World Health Organization. It's a randomized, open label, global study with multiple treatment arms. To be studied are lopinavir/ritonavir, interferon beta 1a, hydroxychloroquine, and remdesivir. The primary outcome is all cause mortality. This trial is slated for completion on May 18, 2022.

FDA gives the nod

A failed Ebola drug, remdesivir got new life on May 1 when the FDA granted an Emergency Use Authorization (EUA) approval in response to a request by Gilead Sciences (interesting side note: Gilead had previously applied for "orphan drug status" approval, which would have given considerable latitude for pricing and marketing. They later rescinded the application since "pandemic" and "orphan" don't belong in the same sentence). According to the letter sent to Gilead, the emergency use approval was based on "topline" data from the NIAID ACTT study and an open label trial conducted by Gilead. The FDA said "it is reasonable to believe that the known and potential benefits of RDV outweigh the known and potential risks of the drug for the treatment of patients hospitalized with severe COVID-19." The letter can be viewed here, www.gilead.com/remdesivir.
The FDA rules for an Emergency Use Authorization require an immediately life-threatening disease to gain access to an investigational drug outside of clinical trials. There must be no comparable or satisfactory alternative therapy, enrollment in a clinical trial not possible, and providing it must not interfere with investigational trials that could support product's development or marketing approval.

What's it worth?

The actual cost of producing enough remdesivir for a ten day course is estimated at $10 according to an analysis published in the Journal of Virus Eradication (Hill, Wang, et al. Minimum costs to manufacture new treatments for COVID-19. J Virus Eradication. April, 2020). The Institute for Clinical and Economic Review (ICER) proposes that a cost of $4,460 per patient would be cost effective. They arrived at that number disregarding R&D costs, citing recoupment has already occurred since

the drug was developed as part of the search for hepatitis C candidates. (You might recall Gilead as the owner of Sovaldi, the $84,000 per patient Hep C treatment). Analysts predict the drug could generate $5 - $10 billion in revenue. For now, Gilead is donating the drug until current supplies are used up, but they're keeping mum on what happens after that.
Hopefully remdesivir won't appear in a future "pharmaceutical outrage of the month" column.

Perspective

In an attempt to put the current evidence for remdesivir into perspective, it's useful to consider Gilead's other two anti-RNA virus drugs, Tamiflu and Sovaldi. Sovaldi was indeed a game changer, curing hepatitis C. Tamiflu knocks one day off influenza if you start it on day one (7 days to 6 days). My take: Remdesivir is more like Tamiflu than Sovaldi.

Parting shot: One last trial to not overlook is registered with the FDA: Coronavirus 2019 (COVID-19)-Using Ascorbic Acid and Zinc Supplementation (COVIDAtoZ). It's a single center, open label (n=520) trial comparing vitamin C and zinc to standard of care in mild, outpatient confirmed COVID-19 cases. Is it possible we'll have a Z drug for COVID-19? This trial is due for completion on April 30, 2021.