In the Fog of Coronavirus Disease (COVID)

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"*. . . factors on which war is based are wrapped in a fog of greater or lesser uncertainty. A sensitive and discriminating judgment is called for; a skilled intelligence to scent out the truth.*"
—Carl von Clausewitz, 1832

In the 19th century, the term "fog of war" was coined by a Prussian military analyst named Carl von Clausewitz to describe the uncertainty and limited situational awareness experienced by commanders during the heat of battle [1]. The term explains an inability to make informed decisions due to the lack of complete information when decisive action is necessary. Clearly, in the midst of the current pandemic, the fog of coronavirus disease (COVID) has influenced the clinical evaluation of antiviral therapies. We have seen the confusion surrounding the use of hydroxychloroquine and lopinavir/ritonavir, even as randomized controlled trials of these popular regimens eventually scored them noneffective for treating coronavirus disease 2019 (COVID-19) [2, 3]. In this issue of *Clinical Infectious Diseases*, Ivashchenko and colleagues report the use of favipiravir (FPV; Avifavir™) for treatment of patients with moderate COVID-19 disease [4], and one can only wonder how to judge whether this oral agent will become a part of COVID-19 management or whether it will be discarded. Clinicians are justifiably frustrated by the need to devise management plans for treating the thousands and thousands of COVID-19 patients while faced with early data that are promising but unproven.

In the United States, the Public Health Service Act allows the Secretary of the Department of Health and Human Services (HHS) the authority to declare a public health emergency when conditions indicate a significant potential effect on national security. Under these rules, the Secretary of HHS declared that such circumstances exist for the COVID-19 pandemic, and, thus, the Food and Drug Administration was permitted emergency use authorization (EUA) for COVID-19-related countermeasures to the pandemic [5]. EUAs have ranged from the many diagnostic tests, to widespread use of convalescent plasma, to specific antiviral therapy, and all are active only as long as the emergency is in effect. Among antiviral agents, on 1 May 2020, remdesivir (Veklury™, Gilead) was the first to receive an EUA as a therapeutic based on data from randomized, double-blind, placebo-controlled clinical trials [6]. Of note, remdesivir was associated with an improved time to recovery using the World Health Organization (WHO) ordinal criteria [7], but no virus clearance data were presented. A smaller underpowered study from China had previously reported no clinical benefit of remdesivir [8]. Currently, the drug is authorized in the United States only for the treatment of hospitalized patients with severe COVID-19 disease (ie, SpO2 ≤ 94% on room air, or requiring supplemental O2, or on mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

FPV is a purine nucleic acid analog, derived from pyrazine carboxamide (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) and is a prodrug that becomes ribosylated and phosphorylated to an active tri-phosphate that inhibits RNA-dependent RNA polymerase (RdRp). FPV is well known as a broad spectrum antiviral agent for RNA viruses such as influenza, arenavirus, bunyavirus, and flaviviruses, including Ebola [9–11]. It is orally bioavailable, peaks at ~2 hours post administration, has a half-life of 2.5.5 hours [10], and is approved for treatment of influenza in Japan. In regard to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), FPV has an in vitro 50% antiviral effective concentration (EC50) of 61.8 uM and a cytotoxic concentration of >400 uM [12]. In comparison, remdesivir has an EC50 of 0.77 uM and chloroquine an EC50 of 6.9 uM [12]. Yet FPV became a candidate antiviral for SARS-CoV-2 in open-label trials, usually combined with standard of care versus other agents [10]. For example, in trials of FPV versus lopinavir/ritonavir early in the first weeks of the pandemic in China, FPV was superior in terms of clearance of virus and clinical improvement [13].

In this issue, Ivashchenko et al. report on an unblinded randomized trial across multiple institutions in which ~20 moderately severe COVID-19 patients/arm received standard of care (SOC), FPV at 3200 mg loading dose followed by 1200 mg/day, or FPV at 3600 mg loading dose followed by 1600 mg/day. The

reported results are for the first stage of a 2-stage trial design and include the early assessment of safety and antiviral effect. An expanded phase 3 trial component is ongoing at the time of this writing. As with many other COVID-19 trials, other antiviral agents were allowed in this trial, for example, hydroxychloroquine (in 65% of patients), chloroquine (in 10%), and lopinavir/ritonavir (in 5%). Both FPV-treated groups showed significant time to clearance of virus from nasopharynx compared to SOC, for example, at 4 days of treatment 67.5% versus 30% ($P = .018$). Importantly, although there was no difference in antiviral effect or adverse events between FPV cohorts, at a dose of <43 mg/kg vs ≥43 mg/kg, early clearance of virus occurred in 47.3% versus 80% of patients, respectively ($P = .036$), suggesting a dose effect. In addition, the time to becoming afebrile and to improvement in chest X-ray was improved in the FPV groups.

For busy clinicians, what can be learned from this small trial? FPV appears easy to administer, with few side effects, and an antiviral effect seems to be a function of the dose/kg. This raises the question of whether a more granular analysis would yield the same outcome.

Of note, FPV is cleared in the liver by aldehyde oxidase and xanthine oxidase, enzymes that can be inhibited by a long list of drugs often used in patients with comorbidities [10]. Given the relatively high EC50 of FPV, careful attention to drug levels will likely be very important if this agent is to be widely effective. At this time, we must be cautious and await the results of phase 3 trials. There are currently 32 FPV-related COVID-19 trials listed on clinicaltrials.gov. Hopefully, the fog will soon lift, and we will have a clear understanding of the effectiveness of this agent for treatment of COVID-19.

Note

Potential conflicts of interest. The author: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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