The Pharmacist Activist

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I guide you in the way of wisdom and lead you along straight paths. Proverbs 4:11

Editorial

Coronavirus Conundrum: Part 2

WHO, HCQ, FDA, Remdesivir, Moving Forward!

I appreciate the many responses I received to my editorial in the May 1 issue of *The Pharmacist Activist*. Most were very supportive of the perspectives I voiced, some called my attention to information of which I was not aware, and two were critical of my statement that I would use hydroxychloroquine (HCQ) without evidence of effectiveness and safety if I experienced the misfortune of having moderate to severe COVID-19.

World Health Organization

One of the responses I received noted the following:

> "Regarding your opinion that using the names Wuhan or Chinese virus is not racist, I encourage you to read the 2015 World Health Organization (WHO) best practices for naming new infectious diseases (if you haven't already)."

I was not familiar with this statement and the reader was kind enough to include the link to the document that includes these statements: "The best practices state that a disease name should consist of generic descriptive terms, based on the symptoms that the disease causes (e.g., respiratory disease, neurologic syndrome, watery diarrhoea) and more specific descriptive terms when robust information is available on how the disease manifests, who it affects, its severity or seasonality (e.g., progressive, juvenile, severe, winter). If the pathogen that causes the disease is known, it should be part of the disease name (e.g., coronavirus, influenza virus, salmonella).

Terms that should be avoided in disease names include geographic locations (e.g., Middle East Respiratory Syndrome, Spanish Flu, Rift Valley fever), people's names (e.g., Creutzfeldt-Jakob disease, Chagas disease), species of animal or food (e.g., swine flu, bird flu, monkey pox), cultural, population, industry or occupational references (e.g., legionnaires), and terms that incite undue fear (unknown, fatal, epidemic)."

This is helpful guidance that I appreciate, but I consider it overly restrictive. It is also unfortunate that the WHO seems to ignore one of its best practices in characterizing COVID-19 as a pandemic, a designation that can incite fear. The WHO best practices apply to new diseases and not those that are already identified with commonly used names. However, it is interesting to speculate what Lyme disease should be called if it was identified now. The designation could not include Lyme, Connecticut, tick, deer or mice (the common animal hosts for the ticks), or even the name of the microorganism (although the latter escapes identification in the best practices, *Borrelia burgdorferi* includes the name of Dr. Burgdorfer). Perhaps Multi-system Spirochetal Disease would be an appropriate name for which the abbreviation MSSD would be adopted and the meaning of the specific letters soon forgotten. I recently asked several individuals who knew about SARS if they could identify the words represented by those letters, and no one identified all four.

And, in the news as I write this, is the Asian giant hornet, also known as the murder hornet! We must come up with a better designation.

Hydroxychloroquine

In my previous editorial I noted that the son-in-law of a friend of mine was in the ICU with serious COVID-19 and that hydroxychloroquine (HCQ) had been used for treatment. One reader inquired about this individual's outcome, and I am pleased to report that he recovered and has been discharged from the hospital. It is not known whether, or to what extent, HCQ contributed to his recovery, but it certainly did no harm.

Most of the responses I received voiced strong agreement with the circumstances that I described in which I would insist on being treated with HCQ if I was the patient afflicted with COVID-19. These can best be summarized in the following response:

> "My elderly mother is immunocompromised as a result of cancer chemotherapy. Using the 'what would I do' criteria, and if she

> was diagnosed with COVID-19, under the care of her physician and pharmacist, and might benefit from short-term treatment with HCQ, I would move heaven and earth to get her 20 tablets of HCQ if she chose to try it (which I would encourage)."

One of the critical responses I received concluded with the following statement:

> "So sure, if someone is at death's doorstep, let him/her try hydroxychloroquine. Let them try a witch doctor doing incantations. There is nothing to lose either way."

He included a link to a story in *Vanity Fair* that was published that day (April 24) that was critical of statements made by President Trump about HCQ, and also included statistics from a report of patients with COVID-19 at some Veterans Administration (VA) hospitals that identified a higher death rate among individuals who had been treated with HCQ compared with those who didn't receive it. I responded to him with the following:

> "I had not seen the *Vanity Fair* article and read it on the link you sent. I consider it flawed reporting motivated by a political bias. I acknowledge that HCQ may not be effective for COVID-19. However, there have been numerous experiences (not studies) that have suggested it to be of benefit. When the VA 'study' that is cited in the *Vanity Fair* article is examined, the two groups of patients for whom the results have been publicized are not comparable. However, this is ignored or not recognized by those who have viewed this report as evidence that HCQ is not effective and dangerous to the point of causing deaths."

The individual who made this comment is a friend who is very knowledgeable about healthcare issues and pharmaceutical companies, and with whom I can have cordial and respectful discussions regarding matters on which we have differing opinions. I called him (April 24) to discuss the HCQ issues, and reiterated that I would insist on being treated with it if I was diagnosed with moderate or severe COVID-19. I asked if I was correct in understanding that he would decline to be treated with it if he was in that situation. He responded that he would not use it and I inquired as to whether that meant that he would expect no treatment except supportive care that might include use of a ventilator. He noted that he would request to be treated with remdesivir on a compassionate use basis, even though he recognized that it was an investigational drug for which effectiveness, safety, and dosage for treating COVID-19 had not been determined. I agreed that I would also want to be treated with remdesivir but, even with his connections, I noted that I considered it very unlikely that either of us would be among those selected on a timely basis from among the tens of thousands of individuals who would want to be included in a clinical trial or compassionate use program for the drug. (On May 1, the FDA issued an emergency use authorization for remdesivir that is discussed later in this commentary).

This response, as well as the other one that I received that challenged my decision to use HCQ for myself, were made in the context of comments that were highly critical of President Trump. A substantial amount of media coverage begins discussions of HCQ with the observation that it has been identified/recommended by the President as a medication that may be of benefit in treating COVID-19. It is very unfortunate that much of the consideration of the potential benefits, limitations, and risks of HCQ for COVID-19 has deteriorated to politically-charged discussions in which information, data, and commentary appear to be selected to fit a particular political point of view. In sharp contrast, it is experienced-informed clinical reasoning and judgment that are necessary while we wait for the results of studies that can provide evidence.

Some HCQ experience

HCQ has been approved and marketed in the U.S. for approximately 70 years, and is most commonly identified as an antimalarial drug. A short course of treatment is indicated for patients with active malaria infection, and it is used on a weekly basis before, during, and following travel for prophylaxis in individuals visiting areas in which chloroquine/HCQ-susceptible malaria infections are endemic. In the U.S., lupus is the condition for which HCQ is most commonly prescribed, for which it is administered on a daily basis and thousands of patients have taken it for many decades. The vast majority of these patients have tolerated it well, and ocular/retinal toxicity has been the greatest concern with its use for which patients should be monitored.

There are many medications marketed in the U.S. that are known to cause prolongation of the QT interval of the electrocardiogram that is associated with an increased risk of arrhythmias for which there are prominent warnings in the product labeling. To my knowledge, confirmed by my review of drug therapy and medical references, these complications have not been identified as risks with the use of HCQ for more than 60 years of the period of time in which it has been available. However, during the last several weeks there has been extensive publicity about the alleged danger of using HCQ in treating COVID-19 because of this risk.

I am very familiar with, and have great concern about the risks of using drugs that are known to prolong the QT interval. I have participated as an expert witness in a lawsuit pertaining to the death of a patient that was attributed to the additive QT-prolonging actions resulting from the concurrent use of ziprasidone (e.g., Geodon) and moxifloxacin (e.g., Avelox), two drugs that are well documented as having this risk (another story for a future issue). Indeed, this action of moxifloxacin is so consistent and well known that it has been used as an active comparator drug in studies in healthy volunteers in which the cardiovascular safety of investigational drugs is assessed to determine if a drug has a QT-prolonging action.

It would appear that a QT-prolonging risk of HCQ has only been identified within the last several years. A warning appears in the current product labeling but, to date, I have not been able to determine when the warning was added and whether the concern was communicated to health professionals. Plaquenil is the original trade name for HCQ and I have tried to track, without success, the revisions in the package insert that have been made for this product, that is made even more difficult by the fact that the product has been sold multiple times to another company just within the last seven years. I have not yet received a response from the FDA to my request to learn when the product labeling was last revised. From what I have been able to learn from online searching, it could be that a warning regarding the risk of QT interval prolongation has only been added to the labeling sometime within the last four years. How could a risk that is this serious

escape attention for more than 60 years when so many patients are using it on a daily basis in multiple-drug regimens, unless the action is relatively weak and/or occurs rarely?

I am not minimizing the potentially fatal risk of a drug prolonging the QT interval or the need to observe important precautions when it is used. However, it is also very important to learn the degree of the risk that was only recently identified after so many decades of use.

The FDA

The Food and Drug Administration (FDA) has issued an emergency use authorization (EUA) to permit the emergency unapproved use of hydroxychloroquine sulfate supplied from the strategic national stockpile (SNS) to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible. The suggested dosage is 800 mg orally on the first day of treatment and then 400 mg daily for 4 to 7 days of total treatment based on clinical evaluation. The issuance of this EUA followed numerous observations/suggestions (not to be interpreted as studies or evidence) that HCQ might be of benefit in patients with COVID-19. The EUA provided very helpful guidance and helped assure the availability of the drug by making it available from the SNS.

On April 24 the FDA issued a statement that "cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems." The statement includes the following comments:

> "Hydroxychloroquine and chloroquine have not been shown to be safe and effective for treating or preventing COVID-19.
>
> The FDA is aware of reports of serious heart rhythm problems in patients with COVID-19 treated with hydroxychloroquine or chloroquine, often in combination with azithromycin and other QT prolonging medicines.
>
> Hydroxychloroquine and chloroquine can cause abnormal heart rhythms such as QT interval prolongation and a dangerously rapid heart rate called ventricular tachycardia. These risks may increase when these medicines are combined with other medicines known to prolong the QT interval, including the antibiotic azithromycin, which is also being used in some COVID-19 patients without FDA approval for this condition. Patients who also have other health issues such as heart and kidney disease are likely to be at increased risk of these heart problems when receiving these medicines."

This information provided by the FDA is important and of value. However, I take strong exception to the FDA cautioning against use of HCQ outside of the hospital setting or a clinical trial. I recognize that the FDA is stating a "caution" and not a restriction or mandate. However, I consider this caution to be excessive, unnecessary, and alarming to the point that some are concluding that the use of HCQ outside of the hospital setting is inappropriate and/or dangerous. In our litigious society, can allegations of negligence or malpractice be far behind if a "caution" stated by the FDA is not observed and a patient is alleged to have experienced negative consequences whether or not it is known if they resulted from COVID-19, a particular medication, or other factor? Observing the FDA "caution" would preclude physicians from prescribing it "off-label" for patients with COVID-19 who are not hospitalized but for whom they consider it to be of potential benefit in avoiding more serious complications, or prescribing it for themselves or other healthcare providers as prophylaxis to reduce the risk of contracting COVID-19.

The FDA does *not* have the authority to regulate the practice of medicine or pharmacy; it is the state boards of medicine and pharmacy that have this authority. Off-label prescribing, dispensing, and pertinent counseling is common with many medications and, indeed, has been of value in identifying potential additional benefits and uses of approved medications and that have provided the impetus for subsequent clinical trials and evidence. It is important, and to be expected, that the FDA should communicate concerns about reports of potentially serious adverse events of available medications. However, to "caution against the use of HCQ outside of the hospital setting or a clinical trial" is an unacceptable intrusion by the FDA into the professional roles and judgment of physicians and pharmacists with respect to the off-label use of approved medications. In addition, the FDA "caution" could be alarming to the many patients with lupus who have been treated with HCQ effectively and safely for years, with the result that they stop using the medication and be at risk of exacerbation of the disease. The national medical and pharmacy organizations should be challenging the FDA regarding such statements/actions, but they have been silent regarding this.

The FDA statement notes that it "is aware of reports of serious heart rhythm problems," and that HCQ "can cause abnormal heart rhythms such as QT interval prolongation." However, "reports" must not be interpreted as "studies" or "evidence." In addition to communicating a concern, the FDA should also accept the responsibility for sharing the pertinent information that is the basis for the concern. For example:

How many reports of serious heart rhythm problems are known to the FDA?

Did the patients who experienced heart rhythm problems have other risk factors for heart rhythm problems?

What consequences did the patients experience? (e.g., Were deaths attributable, at least in part, to the use of HCQ? If so, how many?).

What is the approximate number of patients who were treated with HCQ for COVID-19, or other conditions (e.g.,, lupus), during the relevant time period (i.e., to provide the denominator as part of the basis for determining the level of risk)?

What is the estimated degree of risk? (e.g., every patient treated with HCQ? 1 in 10? 1 in 100?, 1 in 1000?, 1 in 100,000?).

How does the prolongation of the QT interval with HCQ compare with that experienced with moxifloxacin and placebo? This is a study that could be conducted quickly in healthy volunteers *if* there was sufficient interest in doing so for the purpose of providing clarifying and useful information for assessing the level of risk.

It is noteworthy that many of those who demand science and/or

evidence for every decision or opinion are not asking questions such as the above, but rather appear to accept the statement of a risk that is not accompanied with any data.

It is also of interest that the FDA statement identifies azithromycin as a medication that can prolong the QT interval. For a number of years, the labeling for this agent has included a warning regarding this possibility. However, it is probably impossible to estimate the number of millions of Z-Paks that have been prescribed, in large part as a result of its high level of effectiveness, safety, and convenience of use. Although appropriate precautions should be observed, I consider the risk of serious complications from prolongation of the QT interval with azithromycin to be extremely low.

Remdesivir

On May 1 the FDA issued an EUA for the investigational antiviral drug remdesivir (Gilead Sciences) for intravenous treatment of suspected or confirmed COVID-19 in adults and children hospitalized with severe disease. Severe disease is defined as patients with low blood oxygen levels or needing oxygen therapy or more intensive breathing support such as a mechanical ventilator. In a preliminary analysis of 468 recovered patients, remdesivir was shown to shorten the time to recovery (to a median time of 11 days compared with 15 days for those receiving placebo), and it is the first drug to be demonstrated to provide benefit in patients with COVID-19 in an adequate and controlled clinical trial. More than 1,000 patients were enrolled in the study but the outcome for many of the patients was not yet known as of May 1. There was also a numerical reduction in the death rate in the patients treated with remdesivir (8.0%), compared with 11.6% in those receiving placebo; however, this difference was not determined to be statistically significant.

Although the issuance of the EUA is different than FDA approval of remdesivir, the preliminary results of this study are very encouraging, and additional experience is being acquired in this study as well as other clinical trials. As studies of other medications are also being conducted, it appears likely that remdesivir will be one component of a multi-drug regimen that will be determined to be most effective for the management of severe COVID-19.

Moving forward

We must continue to move forward in conducting clinical studies and acquiring experience with treatments that have the potential for effectiveness in treating COVID-19 in a manner that includes sound clinical reasoning and judgment. Components of a forward path also include, but are not limited to the following:

1. Sufficient protective equipment and workplace environments that are as safe as possible must be provided for pharmacists, physicians, nurses, and other essential workers who have the responsibility of providing care and services for patients afflicted with COVID-19.
2. Individuals who are at greater risk of contracting COVID-19 (e.g., the elderly, immunocompromised) must avoid/minimize to the extent possible activities and socialization that might increase their risk of infection, while concurrently assuring and protecting their personal rights and civil liberties
3. We must accelerate the pace at which restrictions are reduced and individuals, society, and our country return to life, work, and school. I recognize that the removal of current restrictions will result in an initial increase in the number of cases and deaths from COVID-19. Every COVID-19 death is a tragedy but the consequences of the restrictions imposed must not be underestimated, and include massive unemployment and delays in needed elective surgeries and treatments, as well as increased experiences of depression, domestic violence, suicide, and drug misuse/overdoses too numerous to count.
4. Partisan politics and criticisms pertaining to COVID-19 and related issues must stop! COVID-19 does not discriminate with respect to its victims and the scope and consequences of the current tragedies demand a collaborative and united fight against the viral enemy. Those who politicize these events should be called out and their comments should be rejected! There must be respectful dialogue among those with differing opinions.
5. Colleges of pharmacy and other health professional schools should provide leadership in restoring campus-based instruction and activities. Some universities are actively considering not resuming on-campus instruction and events until 2021. I want to think that colleges of pharmacy and other health professions can provide the creative thinking, strategies, and leadership that will enable the safe resumption of campus-based instruction and events this fall, and provide the educational experiences that will best assure the preparation of competent and dedicated health professionals who will soon have the responsibilities of responding to COVID-19 and future challenges.

No observations in this commentary should be misinterpreted to suggest that I am minimizing the level of risk and tragedy that exists from COVID-19 now or into the future. On the day that I write this (May 4), the number of COVID-19 deaths predicted to occur by August in the U.S. has been substantially increased to 134,000. We must continue to comply with appropriate precautions, but we also must not permit the crisis to cripple our lives, society, or economy. We must not live in fear!.

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