The Pharmacist Activist

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The heart of the discerning acquires knowledge; the ears of the wise seek it out. Proverbs 18:15

Editorial

Coronavirus Conundrum

Science, Evidence, Knowledge, Reasoning, Opinion, Civility, and Lessons – All are necessary!

I am a pharmacist, scientist, and teacher with particular expertise regarding drug therapy. Not all pharmacists, scientists, and teachers will have the same opinions and beliefs regarding complex issues.

The coronavirus (COVID-19) experience has a very broad range of characteristics, risks, and implications, many of which I don't begin to understand. The only thing that is entirely clear at this time is that no one individual has the wisdom to make all of the best decisions and actions during this time of crisis. Accordingly, I have attempted to avoid criticizing and/or second-guessing the decisions and actions that have been made by the President, Governors, public health officials, and others in authority. They have a huge responsibility and I believe that, notwithstanding even strong differences of opinion, they are motivated to do what they consider to be in the best interests of both the public and our country. Many others have experience, knowledge, and perspectives that can be of value in attaining understanding of the scope and specifics of the challenge and in formulating plans and actions. It is in this context that I provide the following commentary.

Science

I marvel at and learn from the vast amount of information that has been acquired from research and other means of scientific discovery. This has resulted in exponential increases in knowledge and technology, much of which I don't comprehend, let alone learn and apply. However, one thing has become very clear – the more I learn, the more I recognize how much more remains to be discovered and learned. Each new fact or clue discovered is the next piece with multiple connections of an ever-expanding puzzle on a moving table. As one disease becomes better understood and more effectively treated, another previously unknown disease emerges (e.g., SARS, MERS, COVID-19). Research and scientific discovery must continue to be vigorously pursued but, in my view, will never provide the answers to every question. At this time, there are many more questions regarding COVID-19 than there are definitive answers, and both will continue to increase.

Evidence

I am a strong advocate for evidence-based medicine and drug therapy. With respect to my involvement in reviewing and writing about new drugs, I would like to see more comprehensive studies of effectiveness and safety than what the Food and Drug Administration requires for approving most new drugs. Specifically, in addition to studies comparing an investigational drug with placebo, I would like to see the drug directly

compared with at least one drug that is already on the market and considered a first-line treatment for the disease for which the new drug has been developed. When I review a new drug, I identify what I consider to be the advantages and disadvantages of a new drug when compared with previous drugs with which it is most similar in activity and use. If the new drug has only been evaluated in placebo-controlled studies, but also could have been compared directly with an older drug used for the same condition, I identify that as a "disadvantage" for the new drug.

There are, however, urgent situations such as COVID-19 in which actions must be taken before evidence can be acquired. At the time I write this, there is no treatment that has been demonstrated to be effective, or not effective, in adequate clinical trials for COVID-19. Although some currently available medications (e.g., hydroxychloroquine) have been suggested to be of potential benefit, some have been highly critical of suggestions that these drugs be considered for use before studies are conducted and evidence is provided. At best, these criticisms are excessive and inconsistent with previous experience.

Let's consider the experience with another important infectious disease – Lyme disease – and ask what medication is the treatment of choice for most patients with Lyme disease? Most health professionals would immediately respond that it is doxycycline. Now look at the labeling (i.e., package insert) for Vibramycin, the original and best known trade name for doxycycline products. There is absolutely no mention of Lyme disease or the microorganism that causes it. How can that be? The answer is that there have not been well-controlled clinical studies that have resulted in documentation (i.e., evidence) of effectiveness of the drug for Lyme disease and the resultant action to request FDA approval of the drug for this condition. It has been the sound clinical knowledge and reasoning that have resulted in the successful "anecdotal" use of doxycycline that are responsible for its widespread use for Lyme disease and its being viewed as the usual treatment of choice. When it is used for this condition, it is being prescribed "off-label." An analogous situation now exists with respect to the use of hydroxychloroquine for treating COVID-19.

Some things we know

I was initially surprised when I learned that some had suggested that chloroquine (e.g., Aralen and generics) and hydroxychloroquine (e.g,, Plaquenil and generics) might be of benefit in treating COVID-19. I think first of these agents as antiparasitic drugs that are effective for the treatment and prophylaxis of malaria. However, they also have an effect on the body's immune system, and have been approved for the treatment of immunologically-mediated disorders such as lupus and rheumatoid arthritis. The topics of parasitic infections (e.g., malaria), lupus, and rheumatoid arthritis are among those that I have taught, and I am very familiar with the characteristics, actions, and risks of these drugs. Of the two drugs I consider hydroxychloroquine to be safer than chloroquine, partly because of the extent to which it has often been used in the treatment of lupus for extended periods of time, with most patients tolerating it well. As with all drugs, the use of hydroxychloroquine is associated with certain adverse events and risks, but I consider the risk of serious adverse events to be low and disagree with those who have stated or implied that there is a high risk of cardiac and other potentially fatal complications. Careful assessment and monitoring of both drug and patient risk factors should enable avoidance of serious drug-related problems in most patients.

Other medications that are currently available for other indications have also been suggested to be of potential benefit for treating patients with COVID-19. Protease enzymes are thought to have a role with respect to the activity of the virus, and lopinavir/ritonavir (Kaletra), a combination of HIV protease inhibitors, has been evaluated on a limited basis. Some patients with serious COVID-19 may experience further damage from a "cytokine storm" that is thought to be associated with excessive activity of interleukin-6 (IL-6). Tocilizumab (Actemra) and sarilumab (Kevzara) are IL-6 receptor antagonists that were initially approved for the treatment of patients with moderately to severely active rheumatoid arthritis. Tocilizumab has been subsequently approved for other uses including patients with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

Numerous investigational medications are being evaluated for potential benefit in treating COVID-19, with the antiviral agent remdesivir among the most promising.

Reasoning and opinion

On March 27 I was asked by the coordinator of the COVID-19 response in the county in which I reside to respond to a ques-

tion she had received about hydroxychloroquine. I responded with some of the information discussed above and noted that there are no clinical studies with sufficient controls and size to demonstrate the effectiveness, or lack of effectiveness, of the drug in the treatment of COVID-19 (i.e., no evidence). I concluded my response with the following statements:

> Because of my age and medical issues, I am an individual who would be considered at high risk of serious complications from COVID-19. If I was to have the misfortune of contracting COVID-19 and experienced moderate to severe symptoms, I would *insist* on being treated with hydroxychloroquine.

I arrived at that opinion based on my limited knowledge of COVID-19, anecdotal experience, my knowledge of the risks of hydroxychloroquine, as well as my age and medical issues, and applied my reasoning and judgment to reach that conclusion for myself. Indeed, I made that decision very quickly. As an individual who is at high risk, serious complications from COVID-19 can be fatal. I consider the risk of my experiencing a serious adverse event with hydroxychloroquine to be much lower than the risk of death caused by COVID-19. I accept that risk. I have not concluded at this time that I would use it if I tested positive for COVID-19 or experienced mild symptoms, nor would I use it for prophylaxis to reduce the risk of infection in my current experience of relative isolation and social distancing. And I do *not* have a supply of hydroxychloroquine just in case I would need it.

Some health professionals who are on the front-lines in treating patients with COVID-19, and are placing themselves at high risk, are using hydroxychloroquine for prophylaxis to reduce their risk of contracting the infection. They have made this decision based on their knowledge and judgment in the context of assessing their personal risks, and I understand and support their decision for themselves that is made in the absence of evidence.

For health professionals and others who are in a better position to exercise knowledge and clinical judgment, what responsibility do we have to share our perspectives and provide guidance for others? Recently a high official at the Centers for Disease Control and Prevention (CDC) responded to a question about hydroxychloroquine: "I'm not going to recommend it and not going to not recommend it. We're not an opinion organization, we're a science-based data-driven organization…" In my opinion, it is unacceptable that at a time when thousands of people are dying, some very capable officials who are supposed to be protecting us are so obsessed with a need for evidence that they refuse to identify options based on what is being explored or guidance that could be life-saving.

Several days ago I learned that the son-in-law of a friend was diagnosed with COVID-19 and was in the ICU of our local hospital. That night I awakened from my sleep thinking about this situation and debating with myself whether I should contact my friend the next day and ask about his family member's status and treatment. I do not personally know the patient, was not involved with his care, and some might view my question as curiosity or as none of my business. I decided I needed to call and was able to return to sleep. The next morning I called my friend and, after voicing concern and inquiring about his son-in-law's current status, I inquired whether he was being treated with hydroxychloroquine. I was encouraged to learn that he was being treated with it and that his condition was considered stable. It is too soon to know the results of this individual's treatment. However, if I failed to make that call and he died, even with the best supportive care provided in the ICU but not treated with hydroxychloroquine, I would have been haunted by knowing that I could have provided a suggestion for consideration that might have prevented a fatal outcome.

As of April 15 approximately 26,000 Americans have died from COVID-19. There are no treatments that have been evaluated in clinical trials with sufficient controls and size that have provided evidence of effectiveness. Health professionals and others who are in a position to integrate anecdotal information with sound reasoning and judgment have a responsibility to provide their observations/suggestions that may be of benefit in averting potentially fatal consequences. Deaths will not stay "on hold" while we conduct the research necessary for evidence.

Civility

Long before the arrival of COVID-19, there has been a sharp decline in civility of comments and discussion of individuals with differing opinions. Particularly evident in but not limited to politics, too often there can't just be disagreements,

but rather there are many examples of ridicule/condemnation of the views and character of others. In numerous situations, the reaction appears to be based not on the merits of the idea or recommendation, but rather on the individual who made the statement. Every political party and organization that is a strong advocate for a particular cause/issue has participated in this harmful rhetoric. It is nonpartisan and the consequence is gridlock rather than collaboration and progress on important matters.

As one example, some have alleged that certain individuals who have designated COVID-19 as the Wuhan virus or China virus are racist. This allegation ignores the many previous situations in which the designation for a disease has identified the community or country in which the disease was first identified. There is another respiratory illness that comes to mind. In 1976 members of the American Legion convened in Philadelphia to celebrate our nation's bicentennial. Many were afflicted with a mysterious, pneumonia-like disease that was previously unknown and fatal for some. The condition was designated as Legionnaires' disease and, when the causative organism was subsequently identified, it was designated as *Legionella pneumophila*. Not only is the community (i.e., phila) identified, but so is the specific group/organization of individuals who had the misfortune of being the first who were known to be afflicted with this disease. Using these designations is not viewed as being critical of patriotic members of the American Legion or the city of brotherly love.

Lessons

Science, evidence, knowledge, reasoning, opinion, and civility must all be viewed as important components of strategies and plans to move forward. So are the lessons that are learned from experience, including the following:

1. Pharmacists and other health professionals who are providing the front-line expertise, care, and services for patients in need are HEROES, as are their staff colleagues and other workers who place themselves at risk for the benefit of those at greater risk. Their professional roles and authority must be further enhanced in anticipation of future healthcare challenges.

2. Because of the recent books Bottle of Lies (Katherine Eban) and China Rx (Rosemary Gibson), there has been an increased awareness of the dependence of the United States on China and India for most commonly used medications including antibiotics. The COVID-19 experience must be cause to motivate actions to assure the availability and safeguards that can be provided by manufacturing drug products in this country.

3. The specific worst-case scenario for COVID-19 that I have heard in this country is that as many as 240,000 Americans may die. Fortunately, the numbers and curves of the graph are now suggesting that the number of deaths will be much less. Our country has been shut down and we might think that nothing worse could happen. However, there are even greater threats that many individuals, families, and homes are experiencing right now. Approximately 480,000 American die each year as a result of complications associated with smoking. Tens of thousands of Americans have died in the last several years as a consequence of opioid overdosage. The highest priority must be given now to COVID-19, the patients afflicted with the virus and their family members, the protection of health care workers and other essential employees, the needs of the unemployed, and the restoration of our economy. However, when we recover from COVID-19, will we devote even a small fraction of attention, publicity, and action to these other plagues of our society?

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