Covid-19, Hydroxychloroquine-Friend or Foe?

Katie Rubino, Caldwell Intellectual Property, NESACS Board of Publications

This article with its full set of references can be found at covid-19-hydroxychloroquine-friend-or-foe

Around the world, there are presently 1,696,588 confirmed cases of COVID-19 in 213 countries and territories.[i] Further, some experts predict a second wave of the COVID-19 resurfacing at some point later this year. Under these pressures, scientists are racing against the clock to develop and test a vaccine for the novel coronavirus.

To date, the World Health Organization (WHO) has announced that 3 candidate vaccines are in the clinical evaluation stage and 67 candidate vaccines are in the preclinical evaluation stage of testing.[ii] Candidate vaccines in the clinical evaluation stage are the furthest along in development and are currently being studied in humans to demonstrate safety and efficacy.[iii]

To start, testing of a candidate vaccine begins with preclinical testing. Preclinical testing includes the initial testing of the candidate vaccine in animal models to determine safety and toxicity.[iv] Next, a clinical vaccine enters the clinical evaluation stage which is generally broken down into three distinct phases. The first phase usually involves a small number of participants, generally around 100, to determine if a vaccine is safe for humans. The second phase enrolls several hundred participants and aims to evaluate the efficacy of a vaccine against the disease for which it is intended. Typically, phase two can last anywhere from a couple of months to a couple of years. Phase three enrolls the largest number of participants, frequently thousands of people spread over multiple

geographical locations. Phase three aims to determine the effectiveness of a vaccine over a certain period of time, generally a couple of years. Currently, Moderna Therapeutics has a candidate vaccine in phase 1 clinical trials and predicts that a commercially available vaccine will not be available for another 12–18 months.[v]

While waiting for the clinical trials of these candidate vaccines to be conducted, several already existing drug therapies have begun to be touted as gamechangers in the fight against COVID-19. Perhaps the most widely spoken of, hydroxychloroquine, has been proclaimed as a miracle pill. But, what exactly is this compound and are there any intellectual property rights that might affect access and manufacture of this medication?

Hydroxychloroquine was originally developed during World War II to treat malaria and was granted FDA approval in April of 1955.[vi] It was first synthesized in 1946, by adding a hydroxyl group to the anti-malarial drug chloroquine, a derivative of the compound quinine.[vii] After its development, hydroxychloroquine was found to be superior to chloroquine in treating malaria, producing less toxicity and side effects.

Currently, the Food and Drug Administration (FDA) has approved hydroxychloroquine to treat malaria and malaria prophylaxis as well as auto-immune conditions that include lupus erythematosus and rheumatoid arthritis.[viii] Recently, the FDA announced an Emergency Use Authorization (EUA), permitting the use of hydroxychloroquine to treat adults and adolescents who are hospitalized with COVID-19.[ix]

The exact mechanism as to how hydroxychloroquine works against COVID-19 and its FDA approved indications are not precisely known. Chemically, hydroxychloroquine is a weak base and may be effective against the Plasmodium parasites that cause malaria. Hydroxychloroquine may combat these parasites by concentrating in the acid vesicles of the parasites and inhibiting certain enzymes, thus paralyzing the parasite.[x] In the treatment of rheumatoid arthritis, hydroxychloroquine acts as a mild immunosuppressant

by inhibiting production of a rheumatoid factor—the autoantibody that causes rheumatoid arthritis within the body.[xi] Side effects from hydroxychloroquine can include hearing loss, retinal disorders, anemia, and cardiac complications. However, the side effect highlighted most heavily in the news is the possibility of a prolonged QT interval, particularly when hydroxychloroquine is administered in combination with the antibiotic azithromycin.[xii]

But, many antimicrobials other than hydroxychloroquine can cause prolonged QT intervals, such as, for example, the antibiotic ciprofloxacin which is commonly administered to patients to take at home for acute urinary tract infections.[xiii] When such antimicrobial agents are given in combination with agents that can prolong a QT interval, there is an additive risk and extra caution and monitoring are recommended.

Nonpharmacologic risk factors can also cause a prolonged QT interval. For example, being of the female gender may increase the risk for a prolonged QT factor, as females have QT intervals on average that are 20 milliseconds greater than males. [xiv] Frequently, doctors and pharmacists help mitigate risk factors for QT interval prolongation by ensuring that drug doses of agents causing QT prolongation do not exceed dosing ranges. For example, drug induced arrhythmias often occur at high drug concentrations.[xv] In addition, such medications are frequently prescribed with caution in patients who have underlying cardiac conditions.[xvi]

Currently, there are 440 clinical trials around the world currently studying various agents for the treatment of COVID-19.[xvii] Of those 440 clinical studies, 68 of them are

studying the use of hydroxychloroquine.[xviii] Study sites investigating hydroxychloroquine are at various locations, including Germany, South Korea, Canada, Spain, France, Pakistan, Utah, New Jersey, Pennsylvania, and California to name a few.[xix] Many of these studies are evaluating the effectiveness of hydroxychloroquine against other agents including placebo tablets, azithromycin, Tamiflu, zinc, Vitamin D, and Vitamin C, and many other various compounds.[xx]

From an intellectual property perspective, hydroxychloroquine is sold under the brand name Plaquenil, produced by Sanofi.[xxi] Sanofi has pledged to provide millions of doses of Plaquenil for a study of 300,000 patients in France.[xxii] The original patent on the compound is expired, allowing other companies to manufacture generic forms of Plaquenil. Generic manufacturers of generic hydroxychloroquine include Novartis, Teva, and Mylan.[xxiii]

Innovation and interest in hydroxychloroquine has remained high. A search of the USPTO's patent database reveals that over 4,177 patents have issued that include hydroxychloroquine and 8,048 patent applications have published that include hydroxychloroquine.[xxiv][xxv] Through the process of drug repositioning, new methods of treatments can be discovered, utilized, and patented. When a drug is first discovered for its initial use, a patent is generally obtained to cover the chemical compound of the drug. Further, patents that cover methods of treating a disease state with the chemical compound may also be filed. After these patents concerning the original compound have expired, new filings pertaining to new methods of treatment or use for the chemical compound can be obtained by others. For example, a search of recent aspirin filings shows patents obtained in the past 5 years that disclose unique methods for preparing aspirin, combining aspirin together in dosage forms with other medications, and stable aspirin preparations.[xxvi] These filings come almost 120 years after the original patent for acetylsalicylic aspirin was first obtained.

While many unanswered questions remain, hydroxychloroquine remains a viable option to help tackle the COVID-19 pandemic. As clinical trials continue to study its effectiveness and place in treatment, use of the medication in larger populations can help resolve lingering issues. We will stay tuned to see how recommended treatments evolve over the coming months as clinical trials continue to tackle some of the most challenging public health questions of our lifetime.