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Pharma Conference 2020: Volatileisothiocyanates and bioactivity in Physorhynchuschamaerapistrum – Neelam Sherwani - Sultan Qaboos University, Sultanate of Oman

Neelam Shrwani

Sultan Qaboos University, Sultanate of Oman, Oman

Coronavirus disease 2019 (COVID-19) is overshadowing society across the world, and it will redefine many aspects of how we live and work in the future. In a crisis, people are rightly looking for solutions from their leaders and experts, and their response and actions will define them for years to come. COVID-19 may also be such a defining moment for clinical pharmacology in terms of its role in drug development and therapy. Though most drug development takes years from discovery to approval, for the COVID-19 pandemic, drug development is on a fundamentally different timeline. Broadly speaking, there are three horizons for development of COVID-19 therapies, which include treatments for infection-induced morbidities such as acute respiratory distress syndrome (ARDS) or concomitant bacterial superinfections. It is clear that clinical pharmacologists will play a key role in all of these development horizons. However, the overall expectations related to horizons 2 and 3 are arguably not radically different from the time before the crisis, albeit there will most likely be considerably more investment in infectious diseases in general and specifically in coronavirus therapies. The speed at which horizon 1 is developing on a day-to-day basis is unprecedented, and we believe that this is where the most urgent and critical need for clinical pharmacology leadership is required. The list of approved drugs that may be repurposed to provide benefit in COVID-19–infected patients has been growing rapidly,1 and many are currently being tested or indeed used clinically in critically ill patients. At present, there are more than 200 registered clinical trials involving COVID-19 patients. Conventional drug development paradigms and trial designs do not fit well with the urgency and limited window of opportunity at the individual patient level and scale of the crisis. The clinical pharmacology remit to get the right drug and indeed “the right dose in every patient” has never been clearer,4 but in the context of the COVID-19 pandemic we need to add “as soon as possible.” Patients in greatest need may not have the time to benefit from an overly cautious approach, whereas they may also be at highest risk of experiencing exaggerated and previously unknown adverse events. A major challenge at present is, of course, that the evidence for clinical efficacy in COVID-19 is very sparse for any pharmacological treatment. However, clinical pharmacologists have a wealth of knowledge about approved drugs, many of which are currently in clinical trials for repurposing. This knowledge can be harnessed and translated immediately to optimize dosing and treatment regimens. The recent reviews published in this journal of the clinical pharmacology of azithromycin and favipiravir as potential COVID-19 therapies are examples of how *Clinical Pharmacology & Therapeutics* (*CPT*) aims to contribute to the rapid dissemination of such critical information and knowledge. In addition, rational dosing regimens developed for other infectious diseases may inform best clinical practice for repurposing in COVID-19 research.

As a next step, knowledge gained about potentially effective COVID-19 therapies can be integrated very rapidly in quantitative pharmacology models, which in turn can be used to simulate and optimize trials (including guiding selection and timing of informative biomarkers) and to rationalize and personalize dosing in patients. New data can be integrated immediately to update and improve the model in a rapid-turnaround version of Sheiner’s “learn-and-confirm” cycle. One of the first examples of such an approach published in *CPT* is the work by Garcia-Cremades who developed a model integrating historical and emerging preclinical and clinical pharmacokinetic, virologic, and safety data to optimize hydroxychloroquine dosing in COVID-19 patients. As pointed out by the authors, there are obvious limitations associated with their work, in particular that at the time of publication the evidence for the actual efficacy of hydroxychloroquine or any other pharmacological treatment against COVID-19 was limited at best. However, clinical pharmacologists are very well positioned to handle this inevitable uncertainty in the best possible scientific and transparent manner. The use of models allows for

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integration of all available information from various sources, makes all assumptions transparent and explicit, and provides a framework to quantify uncertainty. The key conclusion that can be made from the work by Garcia-Cremades and coworkers is that dosing regimens for hydroxychloroquine used in other indications are unlikely to work in COVID-19. Therefore, we believe that reports such as the recent one from Magagnoli about the apparent lack of efficacy of repurposed drugs need to be interpreted with caution and with expert clinical pharmacology input.

As illustrated by the work of Garcia-Cremades, not only has the COVID-19 pandemic drawn the attention of the scientific community to research in clinical pharmacology, the pandemic has presented new opportunities to advance research in all aspects of our discipline. For example, clinical pharmacologists have been leaders in clinical trial design, including use of Bayesian methods and most recently the incorporation of multiple data types, such as real-world data in drug development and approval. The pandemic presents a unique opportunity to advance the sciences of clinical trial design with a focus, as noted above, on trials for rapidly progressing infections and for which real-world data should be integrated into the trial design. Discovery and use of novel biomarkers and other surrogate end points are needed in the case of a new infectious agent such as COVID-19, which has a distinct clinical presentation and is associated with unique clinical sequalae, such as ARDS. Indeed, the need for continued biomarker discovery, validation, and use has been highlighted in several recent manuscripts in the journal. Moreover, complications associated with COVID-19, such as microbial superinfections, ARDS, and renal failure occur quickly, progress rapidly, and are associated with high mortality rates. These comorbidities require rapid evaluation and treatment, presenting further opportunities to advance clinical trial design, biomarker discovery, and the use of surrogate end points.

Real-world data from the electronic health record (EHR) have increasingly been used in pharmacoepidemiology and pharmacovigilance to monitor drug utilization patterns, as well as the efficacy and safety of drugs in large patient populations. Importantly, a recent commentary in *CPT* from European regulators describes the tremendous opportunities for learning about drug efficacy and toxicity from data in the EHR and highlights various initiatives that are focused on bringing real-world data to a level of acceptability by regulatory authorities, provide a timely review of current status, challenges, and future directions for EHRs in drug repurposing. New resources and databases such as the Johns Hopkins Center for Systems Science and Engineering are being developed and made available to researchers. These resources and others present unprecedented opportunities for using real-world data in pharmacoepidemiologic studies, for drug repurposing, and to discover and probe the mechanisms of adverse drug reactions, drug–drug interactions, and many aspects of therapeutic drug use in a real-world setting.

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