Pharmacovigilance and assessment of drug safety reports during COVID-19

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Abstract
The speed and volume of clinical research to discover effective drug against novel corona virus has been remarkable. To address the unmet medical need, the regulations are made flexible and convenient without any relaxation in drug safety reporting. The pharmacovigilance activities, especially adverse event reporting regardless of clinical trials or clinical practice should continue as usual because patient safety is the priority. The exposure to experimental drugs with limited evidence of risk-benefit makes it more crucial to adapt robust safety monitoring, accuracy in adverse event reporting, and timely assessment. With the current restriction on physical contact, travel and free movements, isolation, quarantine, and huge clinical workload during pandemic, causality assessment will be more challenging. It may not be possible to capture details of all adverse events, thereby affecting completeness and quality of safety reports. A substantial number of COVID 19 patients will receive investigational drugs along with multiple other medications for clinical manifestations and drug therapy for lifestyle diseases. Causality assessment will be a challenge due to overlapping toxicities, multiple confounding, contributory factors, and insufficient data on safety and risk profile of combining drugs. Assessment will be unable to precisely determine the causality as certain or unlikely, although, it will be valuable in categorizing the causal association as “possible” adverse drug reactions and their scientific basis. Several of these detailed reports, when collated, can identify risk factors for possibilities of prevention or avoid harm. In the current situation of pandemic and uncertainty of experimental new and old repurposed drugs, causation needs to be viewed for the study drug with a public health perspective. After all, this is the best time tested approach to generate evidence and drug evaluation to prevent damage to prospective patients.

Keywords: Causality assessment, COVID-19, pharmacovigilance

INTRODUCTION
Not a single event over the last century has had such an impact on human life, such as the COVID-19 pandemic. It is a devastating serious public health risk, hard and at times scary. Unfortunately, there is not a single drug treatment with proven efficacy, and almost all drugs being tested are repurposed and used on compassionate ground.

The world is desperate to find ways to slow the spread of the novel coronavirus and discover game changer. Interestingly, a web search term COVID 19 clinical trials revealed the ever-increasing number of clinical trials...
registered across the globe. To address this unmet medical need, the central regulatory authorities in India immediately announced fast track review and approval process for all clinical trial applications for COVID 19 drugs and vaccine. Moreover, the new norms of social distancing and lockdown during pandemic may not facilitate the conventional methods of data collection. Recognizing the impact on various clinical trials related activities, the central regulatory authorities allowed sponsors, investigators, and ethics committee to modify the conduct of trial, taking into account the participants’ safety, decide mutually on case to case basis and emphasized the use of the electronic system. These notifications made the clinical trial process flexible and convenient in this extraordinary vulnerable situation. Although the regulators acknowledge the challenges involved, there is no relaxation in drug safety reporting. The pharmacovigilance activities, especially clinical safety reports, should continue as usual because patient safety is the priority. This indicates that the show must go on without any compromise on patient safety, compliance with good clinical practice, and trial integrity.

**DRUG SAFETY REPORTING**

In view of the enthusiasm, urgency and rush to find out effective drug treatment and vaccine for COVID 19, the question is, how do we ensure the safety? Several new and old drugs ranging from anti-malaria to anti-viral and immune-modulators with the potential effect on novel coronavirus are being deployed, tested for clinical care and research. The use of drugs on compassionate grounds, exposing the participants to the investigational product with limited evidence of risk-benefit makes it more vital to adapt robust safety monitoring, adverse event reporting, and assessment. However, majority of the trials during pandemic are primarily designed to define clinical benefits and outcomes with less attention to adverse events and safety aspects. On the other hand, there is no acceptable gold standard study design to determine a true drug safety issue. Hence, various heterogeneous sources such as randomized controlled clinical trials, real-time observational studies or spontaneous adverse event reports are used for safety assessment. This will help the policymakers to make a decision to continue or discontinue the use of the proposed drug(s) in clinical care and research. Therefore, it becomes the collective responsibility to ensure and support the collection of drug safety data for timely review, causality assessment and real-time signal detection. Although this will be an opportunity for pharmacovigilance experts, clinicians and regulators to collaborate, assessment of suspected adverse event reports, especially causality appraisal, will be a difficult task.

**CAUSALITY ASSESSMENT OF DRUG SAFETY REPORTS**

The basic essence of the pharmacovigilance and suspected adverse event reports is to detect the risk profile of the drug at the earliest and identify the population at risk. The assessment of safety reports comprises evaluation of probability (causal association or link) of the relationship between exposure to medicine and the occurrence of adverse events. The essential primary step is to suspect an adverse drug event (a causal link) and then “prove or disprove it.” Conventionally, the enthusiasm for the assessment depends on the seriousness of the adverse event, the need of subsequent actions to either patient(s), modify prescribing information (regulatory) and undertake further confirmatory studies. Formal algorithms and statistical methods are available for causality assessment, although, WHO-UMC and Naranjo Probability scale are widely used and internationally accepted for an objective assessment. The assessment criteria are based upon some specific features of the event of interest including time relationship between drug administration and appearance of the event, pharmacological characteristics of the suspected drug (pharmacokinetic and pharmacodynamic actions), medical plausibility (clinical presentation and supporting investigations), likelihood or exclusion of other causes, de-challenge information and re-challenge, if done. Besides these, clinical judgment by experts is also essential. Conventionally, causation is done with respect to the patient treated; however, in the current situation of pandemic and uncertainty of experimental new and old repurposed drugs, it needs to be viewed for the study drug with a public health perspective. In fact, causality assessment during pandemic is more crucial as the causation results will help in early identification of drug-related harm and prevent at-risk patients from exposure.

**CHALLENGES OF CAUSALITY ASSESSMENT**

However, causality assessment in pharmacovigilance is a challenging and time-consuming task. The complex nature of adverse events, wide variations in clinical manifestations, background frequency of the adverse event, characteristic of the disease process, and use of multiple drugs with the same temporal sequence, etc., are some of the factors that may not facilitate the analysis. With the current restriction on physical contact, travel and free movements, isolation, and quarantine during pandemic, it will be even more challenging. It may not be possible to capture details of all events, thereby affecting completeness and quality of safety reports. Possibly, these reports may lack the essential data with missing mandatory items like full description such as...
onset, characteristics, and time course of the adverse event. Second, the suspicion is usually retrospective and desired baseline laboratory investigations are often not available. In case the patient is treated on outdoor basis, the de-challenge and outcome details are missing. Application of algorithms and assessment of these incomplete drug safety reports will be practically impossible.

The adverse reactions due to the drug may vary from mild symptoms to serious life-threatening or significant medical event and can be rare or common. The time relationship between intervention and appearance of adverse event is vital criterion. An adverse event immediately after the drug therapy establishes a strong causal association while an AE after a long latent period can be missed, requires long-term follow-up, adequate resources, and expertise for safety evaluation. Adverse events with high background frequency, especially fever, cough, pneumonia at times of crisis also poses a challenge. In addition, there can be multiple contributing factors for drug-induced adverse events. The use of concomitant drugs with overlapping toxicities, preexisting medical conditions/co-morbidities, elderly patients, alcoholics, are possibly either contributory or confounding factors. This requires a careful evaluation to what extent each of these factors contributes to the occurrence of adverse events. Baseline laboratory tests and investigations along with monitoring at regular intervals will certainly facilitate assessment by excluding the potential alternative causes. In light of the huge clinical workload and lack of systematic monitoring during the pandemic, only a team of proactive professionals strictly following the treatment protocols will capture the details. The hue and cry for the use of hydroxychloroquine for COVID 19 patients have been the best example. The effect of hydroxychloroquine on QTc interval is also shared by concomitant drugs (antimicrobials, antiviral, antifungal, diuretics, etc.) and electrolyte disturbances. Nonavailability of specific diagnostic tests and critical details will make the causal assessment inconspicuous. Conversely, simultaneous withdrawals of all the suspected drugs with overlapping toxicities in case of an adverse event, de-challenge criteria become irrelevant. While re-challenge is unethical and never attempted to prove causality. Unique drug-induced effect also known as phenomenological reaction (S. J. Syndrome or acute dystonia) are rare; therefore, it becomes imperative to look for alternative causes for considering causal relationships. Further, a substantial number of COVID 19 patients treated for lifestyle diseases will be taking long-term medications along with an experimental drug. Possibly these patients may also receive multiple other medications for associated clinical manifestations. Currently, the data is not sufficient for evaluating the safety and risk profile of combining drugs in such a situation. Furthermore, the proposed COVID 19 drugs (antivirals) are metabolized through cytochrome 3A4 pathway; either substrate or inhibitor may result in significant drug–drug interactions. To better understand these complexities, the specific patient population should be monitored with prespecified clear questions and objectives using appropriate data collection tools and analytical plan.

Unfortunately, causality assessment by algorithms methods is limited to ascertain causality precisely as “certain” or “unlikely” in the presence of multiple confounding variables. However, they are valuable in the evaluation of causal association as “possible” adverse drug reactions and their scientific basis. Often “possible” is viewed as a downgraded category. However, it means that there is evidence for “reasonable possibility” to suggest a causal relationship between the drug and the adverse event. Several of these detailed reports when collated can identify risk factors for possibilities of prevention or avoid harm. After all, this is the best way to prevent damage to the prospective end users.

CONCLUSION

Eventually, the compassionate use of drugs may become a standard-of-care threatening collateral damage. What is required is more robust high-quality data for timely review and generate high-quality evidence. Systematic monitoring of all adverse outcomes, adverse events must be recorded and reported for a meaningful causality and risk-benefit assessment balancing individual safety and scientific necessities. It is likely that the number of safety reports may increase during the pandemic. To cope up, an efficient pharmacovigilance rapid response expert team to assess the drug safety reports on a weekly basis and respond to the concerns immediately will help in this regard.

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Conflicts of interest
There are no conflicts of interest.

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