PHARMACOVIGILANCE IN THE ERA OF COVID-19: A CONCISE REVIEW OF THE CURRENT SCENARIO, IMPLICATIONS, AND CHALLENGES

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ABSTRACT

The pandemic of Coronavirus Disease 2019 (COVID-19) has now affected the entire globe which was first surfaced in China in December 2019. In absence of effective therapy to manage COVID-19, repurposed therapies were being used to manage the condition. In view of an urgent need for definitive therapy, multiple repurposed drugs, and investigational drug candidates are being tried in clinical trials which may lead to the emergence of unknown short term and long term adverse drug reactions (ADRs), and hence it is crucial to assess the safety of the tried therapeutic interventions. The lag in the pharmacovigilance activities in the midst of this pandemic fosters under-reporting of ADRs. Difficulty in causality assessment due to factors like wide variations in clinical presentation, concomitant use of multiple drugs, associated comorbidities, drug-drug and drug-disease interaction which forestalls the appropriate causality assessment. Hydroxychloroquine, a repurposed antimarial drug has been a part of hue and cry at present because of its in-question safety in patients with cardiac disorders. National and International Drug monitoring centers have stressed upon reporting of ADRs and to boost up the process and come up with various recommendations. We can overcome these issues by working cohesively, motivating HCPs and patients to report ADRs electronically, and by setting up dedicated pharmacovigilance rapid response team to tackle the issues at the earliest.

Keywords: Pharmacovigilance, ADR reporting, COVID-19, Drug repurposing, Hydroxychloroquine

INTRODUCTION

In current times of pandemic of Coronavirus Disease 2019 (COVID-19), the entire globe is fighting a war against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The COVID-19 started in the Wuhan district of China with few cases of pneumonia having unfamiliar etiology and later it got spread to other countries of the world following which on March 11, 2020, it was declared as a global pandemic by the World Health Organization (WHO) [1–3]. As of 15th July 2020, a total of 12,964,809 confirmed cases of COVID-19, including 5,70,288 deaths have been confirmed by the WHO. As per WHO, the United States of America, Europe, Eastern Mediterranean, South-East Asia are worst hit by this pandemic apart from the reach-in African and Western Pacific regions [4]. COVID-19 most commonly presents with symptoms like fever, dry cough, and fatigue [5, 6]. Having diverse clinical presentations, it can also present with less common symptoms like myalgia, rhinorrhea, headache, conjunctivitis, sore throat, diarrhoea, anosmia or ageusia, skin rash, or discoloration of fingers or toes [6–8]. The respiratory symptoms can range from mild flu to severe respiratory distress which can end up in progressive respiratory failure and sometimes death [7, 9]. The laboratory findings show lymphopenia, elevation in lactate dehydrogenase levels, and also associated with elevation of inflammatory markers such as C-reactive protein, D-dimer, ferritin, and interleukin-6 [9, 10]. The radiology findings with computed tomography (CT) scans show bilateral pulmonary parenchymal ground-glass opacity along with pulmonary consolidation, and the presence of multiple bilaterally diffuse nodules with peripheral lung distribution [11, 12]. With the fast spread, increased morbidity, and mortality of the COVID-19, tremendous efforts are being made by multiple pharmaceutical giants to discover the drugs, vaccines, or other interventions for prophylaxis or treatment of the disease and to minimize and halt the associated damage it has caused to the entire globe [13]. Currently, there is no definitive treatment available for COVID-19 but on a positive note, recently a few vaccines for COVID-19 have been approved in various parts of the world with emergency use authorization based on the limited data available. The entire world is trying out the medicines already in use for other diseases for its treatment but in the rush for treatments, we need to ensure not only the efficacy but also the safety of the drugs under trials. This paper discusses the scenario, impact, and challenges faced by pharmacovigilance monitoring during this pandemic.

The operational structure of pharmacovigilance

Pharmacovigilance (PV) is a science of monitoring Adverse Drug Reactions (ADRs). WHO defines it as the "Science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problem" [14]. Pv not only monitors drugs but also the biological products, blood products, herbal, vaccines, medical devices, traditional and complementary medicines in view of identifying new ADRs associated with products and safeguard the patients [15–17]. The process of PV includes primarily ADR data collection from the clinics or self-reporting of ADR which is communicated to ADR monitoring centers (AMCs) by filling up the ADR monitoring form/Individual Case Safety Report (ICSR) form which is reviewed, analyzed and causality assessment is done. If found authentic, the ADR is reported to the National Coordination Centre (NCC), Indian Pharmacopoeia Commission (IPC) through an online software called VigiFlow. At NCG, these ICSRs are reviewed to assess the quality of data and if found appropriate, it is forwarded to the "Uppsala Monitoring Centre (UMC), Sweden" which is a global ADR monitoring center, Sweden. UMC analyses the data and adds it up to the global database called "VigiBase", which is maintained by UMC [19]. The NCC also sends these data to the Central Drugs Standard Control Organisation (CDSCO) from time to time or whenever enquired to monitor the safety of various drugs used in India [20, 21]. The data accumulated and generated from Pv is basically utilized in various ways like signal generation, post-approval regulation of the drug or vaccine, conducting continued medical education to update the healthcare professionals (HCPs) [18, 20]. WHO Programme for International Drug Monitoring with UMC has set up an online resource database named "VigiLyze" which delivers useful search and analysis functions along with providing a quick and clear overview of global VigiBase data in an instant graphical format [22].

Need of pharmacovigilance in era of Covid-19

Pharmacovigilance monitoring is a crucial component in monitoring the safety of the therapies being given to COVID-19 patients. Though...
numerous therapies are being used and tested, yet we lack robust data to answers the questions of effectiveness and safety by various drug candidates in view of the rapid drug discovery process at the time of this pandemic. In view of the dire need for an effective drug or vaccine against COVID-19, if we primarily focus the weight on the efficacy of the trial drugs in the investigational candidates, it would be difficult to ensure the short and long-term safety of these agents. Many of the existing drugs including antimalarials like hydroxychloroquine and chloroquine, antivirals like lopinavir/ritonavir or remdesivir or favipiravir, antiprotozoals like ivermectin, immunomodulators like corticosteroids, and monoclonal antibodies like tocilizumab or sarilumab are being repurposed for the treatment of COVID-19 [13]. For gathering and pooling sufficient information regarding efficacy and ADRs of therapies used against COVID-19, it is essential to record and report all adverse events swiftly and correctly to the pharmacovigilance database which will initiate a timely review of reported data and signal generation or crucial safety data which the HCPs and prescribers are in urgent need of [19]. Currently, the reports of various suspected ADRs for these tried therapies that have reached VigiBase, have been published as a “Report from the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre” which can help HCPs to be cautious and use these therapies rationally [23]. Presently, VigiLyze is also being used to visualize and analyze the safety data swiftly for drugs used in COVID-19 [24]. Therefore, ensuring and supporting the collection of high-quality data from adverse event reports is crucial for the safe use of pharmacotherapy in these patients.

**Reporting of ads to NCC-IPC**

In India, the ADR can be reported by both HCPs and patients by any of the following means [25]:

1. **By filling up the Suspected ADR reporting form available at the PvPI, NCC(IPC) website which is available in English, Hindi, and other Vernacular Languages.**

2. **Mobile application from Google play store named "ADRpvPI"**

3. **Helpline Number Managed by NCC PvPI for ADR reporting for the HCPs and general public: 1800 180 3024.**

NCC-IPC has formulated a new “suspected ADR reporting form (for drugs used in prophylaxis/treatment of COVID-19) for voluntary reporting by HCPs”. Apart from the usual information to be shared in the ADR form this new version has few newly added features to be reported like status on pregnancy, lactation, relevant tests/laboratory data with dates like chest X-Ray, ECG, biochemical examination, ophthalmological examination, test for COVID-19 (RT-PCR test or rapid antibody test), recent travel information, relevant medical/medication history, drug interaction, concomitant medication including a drug used for co-morbidities, and complementary medicines with therapy dates [26]. This additional information and knowledge regarding COVID-19 patients can help assist in the causality assessment in a better way. The above suspected ADR form for drugs used in COVID-19 can be downloaded from the URL: https://www.ipc.gov.in/images/Suspected_ADR_Reporting_Form_converted_2020.pdf

**Importance of pharmacovigilance: a learning from hydroxychloroquine episode**

There was an increased demand for hydroxychloroquine (HCQ) and chloroquine (CQ) after the news of it being a magical drug [27]. In the initial *in vitro* studies, HCQ was found to be effective in the treatment of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) [28, 29]. Even the initial studies have shown a benefit with HCQ and CQ in patients with SARS-CoV-2 [30, 31]. Few studies have shown that HCQ when given with azithromycin led to a reduction of the viral load in COVID-19 patients [32, 33]. Followed by various positive results, the Ministry of Health and Family Welfare, Government of India (GoI) with The Indian Council of Medical Research (ICMR) formulated guidelines dated 23rd Mar 2020 to use HCQ in the following people [34]:

1. All asymptomatic healthcare workers working towards containment and treatment of COVID-19 and working in non-COVID hospitals/non-COVID areas of COVID hospitals/blocks.

2. Asymptomatic frontline workers, like surveillance workers posted in containment zones and paramilitary/police personnel involved in COVID-19 related activities.

3. Asymptomatic household contacts of laboratory-confirmed cases.

The recommendation also says that it should not be administered in known cases of retinopathy, hypersensitivity to HCQ or CQ, any aminoquinoline compounds, G6PD deficiency, pre-existing cardiomyopathy, and cardiac rhythm disorders, and prophylaxis in children under 15 y of age and pregnancy and lactation [34].

Later on, the COVD-19 Treatment Guidelines Panel, National Institute of Health (NIH) recommended against the use of CQ or HCQ for the treatment of COVID-19, except as a ‘trial drug’ in clinical trials [35]. A retrospective study in the USA did not identify any significant reduction in mortality or the need for mechanical ventilation with HCQ treatment with or without azithromycin [36]. Similar results were reported by WHO where it stopped the use of HCQ in SOLIDARITY trial concluding that HCQ did not reduce the mortality of hospitalized COVID-19 patients when compared with standard of care [37]. It was found that in patients with COVID-19, a combination of HCQ and azithromycin was associated with QTc prolongation are associated with cardiotoxicity (prolonged QT syndrome) with prolonged use particularly in patients with hepatic and renal dysfunction [38, 39]. Both the drugs have long half-lives hence even sequential use of them should be cautiously done [35]. At the time when all the evidence was against the use of HCQ, an observational study in India gave a ray of hope showing benefit with HCQ prophylaxis among HCPs [40]. Following this, ICMR constituted the National Task Force for COVID-19 which revised the guideline for HCQ use and recommended to be used only in the high-risk cases like [41]:

1. Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19.

2. Asymptomatic household contact of laboratory-confirmed cases.

The guideline also mentions that the use of HCQ should only be done under the prescription of a registered medical practitioner and patients are advised to contact the HCP in case of any adverse events. Along with chemoprophylaxis with HCQ, people should follow the recommendations to prevent the spread and worsening of the condition of the patients with COVID-19 [41]. Along with the prophylactic administration of HCQ, the self-reporting of ADRs to the pharmacovigilance centers or Pharmacovigilance Programme of India (PvPI) helpline/Application should be done [42].

The above scenario of HCQ proves the importance of pharmacovigilance in any drug therapy or drug discovery. In the trials, HCQ had mixed results or even showed no benefits however it posed an enhanced possible risk increase in the number of ADRs or drug interactions which could worsen the condition of the patients. ICMR’s recommendation to report all the ADRs is a crucial step as this will aid the policymakers to come down to a decision regarding a particular drug candidate whether new or old, to continue or discontinue the use of the particular drug or vaccine candidate in clinical care and research [23].

**Covid and pharmacovigilance: challenges**

In current times, pharmacovigilance activities have taken a toll due to the pandemic of COVID-19. Due to the high infectivity of the virus, the usual contact with the patients and the healthcare professionals (HCPs)/residents has diminished to a great extent. The lockdown imposed along with working with a decreased workforce has made it difficult for the AMC to report the ADRs at the same pace and quantity. Hence, it becomes a collaborative responsibility of the HCPs to come together and ensure proper acquisition and collection of ADRs with timely reporting and causality assessment in the AMC. Proper reporting and expedited review of ADR reports will help in signal detection and generation of any substantial safety profile of the tried therapies. The causality assessment in COVID-19 patients seems to be a tedious task because of multiple reasons like a large array and variations in clinical signs and symptoms, evolving and newer manifestations, concomitant use of multiple drugs, presence
of other comorbidities and associated pharmacotherapies, drug-drug and unknown drug-disease interaction in COVID-19 makes it difficult to deal with and may hamper the appropriate causality assessment. The difficulty in causality assessment and ensuring its quality has been an issue as mentioned in the "Report from the WHO Collaborating Centre for International Drug Monitoring Uppsala Monitoring Centre" [23]. The above report also mentions the issue with restricted data available at present regarding this pandemic and the inconstancy or lack of certainty over other confounders (like the underlying disease). Confounders like extremes of age, pregnancy, and hepato-renal dysfunction can further make the causality assessment onerous. Apart from this, a large number of cases in the hospitals end up in enormous clinical workload which would again lead to a lack of strict ADR monitoring during the pandemic. In the midst of this pandemic, it is not always possible to do all the baseline blood tests before starting any investigational/off-label drug along with following up blood tests to monitor the toxicities which would again make it difficult to review and analyze the ADRs even if they are reported.

CONFLICT OF INTERESTS
Declared none

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