A Comprehensive Review Of "Pharmacovigilance In COVID-19 Disease Management"

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➢ ABSTRACT:

A pandemic is an outbreak of an infectious illness that has spread across a broad area, such as multiple continents or the entire world, and has affected a huge number of people. According to the World Health Organization, pandemic is the worldwide spread of a new illness. When a novel influenza virus arises and spreads over the world, and most individuals are not immune, an influenza pandemic ensues. Viruses that have produced pandemics in the past have usually come from animal influenza viruses. At At present whole world is suffering from COVID-19 pandemic disease. Clinical research to find an effective medication against a new corona virus has moved at a breakneck pace. To meet an unmet medical need, the regulations have been made more flexible and convenient, but medication safety reporting has not been relaxed. Because patient safety is the first priority, pharmacovigilance efforts, particularly adverse event reporting, should continue as usual, regardless of clinical trials or clinical practise. The increased exposure to investigational medications with inadequate risk-benefit data necessitates more stringent safety monitoring, accurate adverse event reporting, and early assessment. Causation evaluation will be more difficult due to the current restrictions on physical contact, travel, and free movements, isolation, quarantine, and a large clinical workload during a pandemic. It's probable that not all adverse incidents will be documented in detail, compromising the completeness and quality of safety reports.

➢ Key words:

COVID-19, Pharmacovigilance, Treatment of covid-19, Remedesiver, Favipiravir, Hydroxychloroquine

➢ INTRODUCTION

A pandemic is an epidemic of an infectious disease that has spread across a large region, for instance multiple continents or worldwide, affecting a substantial number of people. A widespread endemic disease with a stable number of infected people is not a pandemic. Widespread endemic diseases with a stable number of infected people such as recurrences of seasonal influenza are generally excluded as they occur simultaneously in large regions of the globe rather than being spread worldwide. According to WHO a pandemic is the worldwide spread of a new disease. An influenza pandemic occurs when a new influenza virus emerges and spreads around the world, and most people do not have immunity. Viruses that have caused past pandemics typically originated from animal influenza viruses.

History of pandemic diseases in the world**:**

Plague of Athens (430 to 426 BC): During the Peloponnesian War, typhoid fever killed a quarter of the Athenian troops and a quarter of the population. This disease fatally weakened the dominance of Athens, but the sheer virulence of the disease prevented its wider spread; i.e., it killed off its hosts at a rate faster than they could spread it. The exact cause of the plague was unknown for many years. In January 2006, researchers from the University of Athens analysed teeth recovered from a mass grave underneath the city and confirmed the presence of bacteria responsible for typhoid.

World pandemics up to now -

- Antonin Plague (165 to 180 AD)
- Plague of Justinian (541 to 750 AD)
- Black Death (1331 to 1353)
- The 1918-1920 Spanish flu
- Cholera
- Dengue Fever
- Influenza
- Typhus
- Measles
- Yellow fever
- Smallpox [1]
- Covid-19

➢ COVID 19

COVID 19 isCorona virus disease which is defined as illness caused by a novel coronavirus now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV), which was first identified amid an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China.Coronaviruses are a family of viruses that can cause respiratory illness in humans. They get their name, "corona" from the

many crown-like spikes on the surface of the virus. Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the common cold are examples of coronaviruses that cause illness in humans.[2]

Origin of covid-19 -

The initial outbreak in Wuhan, China, the virus and disease were commonly referred to as "coronavirus" and "Wuhan coronavirus", with the disease sometimes called "Wuhan pneumonia". The first human cases of COVID-19, the disease caused by the novel coronavirus causing COVID-19, subsequently named SARS-CoV-2 were first reported by officials in Wuhan City, China, in December 2019. Environmental samples taken from this market in December 2019 tested positive for SARS-CoV-2, further suggesting that the market in Wuhan City was the source of this outbreak or played a role in the initial amplification of the outbreak. The market was closed on 1 January 2020. SARS-CoV-2 was identified in early January and its genetic sequence shared publicly on 11-12 January. The full genetic sequence of SARS-CoV-2 from the early human cases and the sequences of many other virus isolated from human cases from China and all over the world since then show that SARS-CoV-2 has an ecological origin in bat populations.

All available evidence to date suggests that the virus has a natural animal origin and is not a manipulated or constructed virus. Many researchers have been able to look at the genomic features of SARS-CoV-2 and have found that evidence does not support that SARS-CoV-2 is a laboratory construct. If it were a constructed virus, its genomic sequence would show a mix of known elements. All available evidence for COVID-19 suggests that SARS-CoV-2 has a zoonotic source.[3]

➢ TREATMENT**:**

Currently, only one medication has been approved to treat COVID-19. No cure is available for COVID-19. Antibiotics aren't effective against viral infections such as COVID-19. Researchers are testing a variety of possible treatments.

The FDA has approved the antiviral drug Remdesivir (Veklury) to treat COVID-19 in hospitalized adults and children who are age 12 and older in the hospital. The FDA has granted an emergency use authorization for the rheumatoid arthritis drug Baricitinib (Olumiant) to treat COVID-19 in some cases. Baricitinib is a pill that seems to work against COVID-19 by reducing inflammation and having antiviral activity. The FDA states Baricitinib may be used in combination with Remdesivir in people who are hospitalized with COVID-19 and are on mechanical ventilators or need supplemental oxygen.

Several monoclonal antibody medications are available. These include a combination of Bamlanivimab and Etesevimab, a combination of two antibodies called Casirivimab and Imdevimab, and Sotrovimab. These drugs are used to treat mild to moderate COVID-19 in people who have a higher risk of developing serious illness due to COVID-19. Treatment consists of a single intravenous infusion given in an outpatient setting. To be most effective, these medications need to be given soon after COVID-19 symptoms start and prior to hospitalization.

The U.S. National Institutes of Health has recommended the corticosteroid Dexamethasone for people hospitalized with severe COVID-19 who are on supplemental oxygen or need mechanical ventilation. Other corticosteroids, such as Prednisone, Methylprednisolone or Hydrocortisone, may be used if Dexamethasone isn't available.

Many people with COVID-19 may have mild illness and can be treated with supportive care. Supportive care is aimed at relieving symptoms and may include:

- Pain relievers (ibuprofen or acetaminophen)

- Cough syrup or medication

- Rest

- Fluid intake

There is no evidence that Ibuprofen or other nonsteroidal anti-inflammatory drugs (NSAIDs) need to be avoided.

If you have mild symptoms, your doctor may recommend that you recover at home. He or she may give you special instructions to monitor your symptoms and to avoid spreading the illness to others. You'll likely be asked to isolate yourself as much as possible from family and pets while you're sick, wear a mask when you're around people and pets, and use a separate bedroom and bathroom.[4]

➢ <u>PHARMACOVIGILANCE STUDY OF COVID-19 MANAGEMENT:</u>

WHO defines pharmacovigilance as the "science and activities related to the detection, assessment, Understanding and prevention of adverse effects or any other possible drug-related problem".[5]

It focuses on investigating and monitoring adverse drug reactions after medicinal productsare licensed. Adverse drug reactions are a response that is noxious and unintended and that occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for modifying physiological function. [6]

They may vary in presentation and occurrence and are commonly divided into type A (augmented pharmaceutical response) and type B (bizarre or hypersensitivity) adverse drug reactions.[7]

An example of a type A reaction in relation to antiretroviral (ARV) drugs for treating HIV is the negative effect of Tenofovir on bone mineral density, which may increase fracture risk. An example of a type B reaction is Efavirenz-related hypersensitivity in the form of a skin rash with systemic symptoms.[8]

The global system of pharmacovigilance was first developed following the thalidomide tragedy in the 1960s, where thalidomide was used to treat nausea in pregnancy, resulting in serious teratogenic events among infants exposed in utero. [9]

Ideally, Pharmacovigilance systems take a life-cycle Approach, focusing not only on the properties of the prescribed medicine but also on how it is Formulated, dispensed and administered. This Approach is a

continuum throughout the process of drug development, from initial research and Development activities to final consumer use and is Commonly divided into two stages:

Pre-marketing surveillance: Adverse drug reactions from preclinical screening and Phase I, II and III clinical trials;

Post-marketing surveillance: Adverse drug reactions from the post-approval stage and throughout a drug's market life.[10]

Pharmacovigilance in clinical trials:

Clinical trials were utilized all through the planet to see the security and adequacy of a chemical or natural compound with significance its activities on indications or a known illness prepare. Trials are closely observed by agent conjointly the medicate company included inside the inquiry about and advancement of a restorative item.

There are four particular stages of a drug's clinical test cycle after creature considers are completed.[11]

This stage I trials include a very little bunch (<100) of volunteers with the focused-on illness. The ponders are unblinded, uncontrolled and habitually final but one month. Stage II trials watch the adequacy, dosage reaction and resilience, and unfavourable impacts of the sedate. These trials incorporate a greater bunch of subjects (ordinarily 200-300) with the focused-on illness handle and have fine characterized and controlled inclusion/exclusion criteria. Clinical test trials are more often than not placebo-controlled or active-controlled comparison thinks about and final a few months. Stage III trials are the extreme step,sometime recently the sedate designer can apply for promoting authorization. Stage III clinical trials centre totally on the drug's security and adequacy in assorted sub-groups with broader inclusion/exclusion criteria counting concomitant drugs and concurrent maladies than clinical test trials. The risk-benefit proportion is created, checked and overhauled in like manner. After fruitful completion of clinical trial clinical trials and authorization for showcasing, the sedate company may conduct clinical trial stage IV so as to still screen the medicate on a distant bigger scale and in an awfully less controlled globe environment. [12]

Need of pharmacovigilance:

It is widely accepted that clinical development of medicines is a complex process which require huge amount of time for its completion. Once a drug is marketed, it leaves the secure and protected scientific environment of clinical trials and is free for consumption by the general public.At this point, most medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals. Hence, need of pharmacovigilance arises which include, securing the early detection of new adverse reactions or patients' subgroups of exceptional sensitivity; and introducing certain measures in order to manage such risks.Moreover, it is essential that new and medically still evolving treatments are monitored for their effectiveness and safety under real-life conditions after being marketed. Furthermore, more information is generally needed about use in specific population groups like children, pregnant women and the elderly, about the efficacy and safety of chronic use in combination with other drugs. [13, 14]

Objectives of Pharmacovigilance:

The main objectives of pharmacovigilance involve exhibiting the efficacy of drugs by monitoring their adverse effect profile for many years from the lab to the pharmacy; tracking any drastic effects of drugs improving public health and safety in relation to the use of medicines; encouraging the safe, rational and cost-effective use of drugs; promoting understanding, education and clinical training in pharmacovigilance; and effective communication to the generic public. [15]

How contagious is the corona virus –

The transmission rate is relatively high. Early research has estimated that one person who has it can spread it to between 2 and 3.5 others. One study found that the rate was higher, with one case spreading to between 4.7 and 6.6 other people. By comparison, one person who has the seasonal flu will pass it to between 1.1 and 2.3 others.

The CDC reports, there is evidencethat, it can be transmitted if you get within 6 feet of someone who is infectious for a total of 15 minutes throughout a day. It had previously been believed the exposure had to be 15 minutes at a time. For prevention, wash your hands for at least 20 seconds before and after bringing things into your home. The coronavirus can linger on hard surfaces, so clean and disinfect countertops and anything else.

Symptoms of corona virus-

People with COVID-19 have had a wide range of symptoms reported – ranging from mild symptoms to severe illness. Symptoms may appear 2-14 days after exposure to the virus. Anyone can have mild to severe symptoms. People with these symptoms may have COVID-19:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhoea[16]

Co-morbidities and COVID 19 - The medical definition of Co-morbidities is when a person has more than one underlying health-related conditions present in them at once. Each condition is considered as comorbidity, and sometimes comorbidities could be present in the form of physical or mental conditions. Older adults are more likely to get severely ill from COVID-19. More than 80% of COVID-19 deaths occur in people over age 65, and more than 95% of COVID-19 deaths occur in people older than 45. [17]

How do comorbidities impact Coronavirus infection - People who have a weak immune system are more susceptible to contract coronavirus? Studies have shown that people with pre-existing conditions face a higher mortality rate when compared to people affected with no comorbidities.

Comorbidities that could put you at risk of contracting coronavirus – Doctors around the world treating the affected individuals during the pandemic, in their findings have said that over 48% of the patients who passed away after the treatment had underlying comorbidities. Out of the 48%, more than thirty percent were diagnosed with Hypertension, nineteen percent with diabetes, and close to eight percent with cardiovascular conditions. [19, 20]

Some of the major comorbidities are

- Cancer
- Chronic kidney disease
- Chronic lung diseases, Asthma, cystic fibrosis
- Hypertension
- Diabetes (type 1 or type 2)
- Cardiovascular diseases
- HIV infection
- Liver disease
- Immunocompromised state (weakened immune system)
- Heart conditions (Heart failure) [17]

- **Some of the pandemics and related data** [18,19,20]

Disease	Occurrence year	Countries affected	Treatment available	People affected /Deaths
1.Typhus	1489-1922	Europe, Germany and worldwide	Antibiotic Doxycycline and follow up for fever	Nearly 15 million deaths
2.Small pox	1789	Australian continent	Tecovirimat (TPOXX), Supportive care and vaccination	40 thousand to 1.5 lack deaths
3.Spanish Flu	1918-1920	Pacific Island,Arctic	Open-air treatment was used, Aspirin, And suppository medicines	20-100 million Deaths
4.Cholera	1817- 1975	Indian subcontinent ,China,Russia,North America	Rehydration therapy,Doxycycline azithromycin and ciprofloxacin	Billions of deaths
5.Tuberculosis	19 Century	Europe, Asia	Isoniazid, rifampicin, pyrazinamide, and ethambutol for two months	
6.HIV / AIDS	1966-1972	Africa, USA,can be seen worldwide	Antiretroviral therapy (ART). ART can't cure HIV, but HIV medicines help people with HIV live longer, healthier lives.	32.7 million Deaths
7.Swine Flu	2009-10	China,Mexico, India	Tamiflu, zanamivir and cold and flu follow up	1.5 to 5 lack deaths
8.Covid 19	2019	China, USA, INDIA and major part of the world	Monoclonal Antibody Tamiflu, Respiratory support, Increasing Immune Response, Treatment followed by symptoms. Since there is not any particular treatment **Vaccination** is the most important key and taking care is much necessary.	39 Lacks till date

The latest treatments for COVID-19

Aspirin: Patients with COVID-19 are at higher risk of blood clots, which can be fatal. As aspirin is known for its anti-clotting properties researchers have decided to add it to the treatment trials. About 2,000 patients will be randomly selected to receive a daily dose of aspirin, with results compared to a similar number of patients who receive standard care without the drug.[21]

An antiviral: The antiviral drug Remdesivir was hailed at an early stage of the pandemic as a potential treatment for COVID-19. By early June, NICE had published guidance on who it should be considered for, stating that 'Remdesivir when compared with placebo was associated with clinical improvements in some of the outcomes and fewer serious adverse events'. But despite a placebo-controlled trial showing that Remdesivir shortened recovery time by a third in some patients, a major trial by the World Health Organization, the Solidarity trial, found that it had little or no impact on survival. Work continues to find out whether these conflicting results could be the result of using the drug in different populations or at different stages in the infection. [22]

Mechanism of Action of Remdesivir

Remdesivir is a monophosphoramidate nucleoside prodrug that undergoes intracellular metabolic conversion to its active metabolite nucleoside triphosphate (NTP). As described for several other direct-acting antivirals, the active metabolite of Remdesivir (Remdesivir triphosphate [Remdesivir-TP] or GS-443902) subsequently targets the machinery responsible for the replication of the viral RNA genome, a highly conserved element of the viral life cycle. Nucleoside analogues are synthetic compounds that work by competition with endogenous natural nucleoside pools for incorporation into replicating viral RNA. While these compounds mimic their physiological counterparts, the incorporation of the analogue molecule disrupts subsequent molecular processes. The drug target and the exact processes that lead to the inhibition of viral replication. Remdesivir, a monophosphoramidateprodrug of C-adenosine nucleoside analogue, can be incorporated into viral RNA chains and thereby initiate the premature termination of RNA replication. It displays a significant anti-CoV activity in vitro. Previous studies showed that Remdesivir could inhibit the replication of SARS-CoV, MERS-CoV, and bat CoV strains in primary human airway epithelial cells and regulate cell entry through hACE2 receptor. Remdesivir acts during early-stage infection and dose dependently reduces RNA levels, which parallels a decrease in virus titters. Remdesivir displays an EC90 (90% effective concentration) value of 1.76 mm towards SARS-CoV-2 in Vero E6 cells, indicating that it is effective in non-human primates. Besides, it is noted that SARS-CoV-2 requires RdRp gene to replicate, which can be covalently bound to Remdesivir, hence terminating chain elongation. Moreover, Remdesivir also suppresses virus infection in human liver cancer Huh-7 cells, a cell line that is susceptible to SARS-CoV-2. Furthermore, Remdesivir has been given on a compassionate use basis to COVID-19 patients, and the results indicated that a 10-day course of the antiviral drug (200 mg on day 1, followed by 100 mg daily for 9 days), might exhibit potential clinical benefits for these patients.[23]

Drug-Drug Interactions of Remdesivir:

Clinical drug-drug interaction studies of Remdesivir have not been conducted. In vitro, Remdesivir is a substrate of cytochrome P450 (CYP) 3A4 and of the drug transporters organic anion-transporting polypeptide (OATP) 1B1 and P-glycoprotein. It is also an inhibitor of CYP3A4, OATP1B1, OATP1B3, and multidrug and toxin extrusion protein 1 (MATE1). Minimal to no reduction in Remdesivir exposure is expected when Remdesivir is co-administered with Dexamethasone, according to information provided by Gilead Sciences. Chloroquine or Hydroxychloroquine may decrease the antiviral activity of Remdesivir; co-administration of these drugs is not recommended. Remdesivir is not expected to have any significant interactions with Oseltamivir or Baloxavir, according to information provided by Gilead Sciences. [24]

Favipiravir

Favipiravir has proven efficacy against a broad range of influenza viruses, including A (H1N1) pdm09, A (H5N1), and A (H7N9) avian virus. Additionally, it may halt the replication of several other RNA viruses, including arena viruses, phleboviruses, Hantaviruses, flaviviruses, Western equine encephalitis virus, noroviruses, and Ebola virus.

Mechanism of action of Favipiravir:

Favipiravir (prodrug) is a purine base analogue that is converted to active Favipiravir ribofuranosyl-5B-triphosphate (Favipiravir-RTP) by intracellular phosphoribosylation. It is a selective and potent inhibitor of RNA-dependent RNA polymerase (RdRp) of RNA viruses. Favipiravir is incorporated into the nascent viral RNA by error prone viral RdRp, which leads to chain termination and viral mutagenesis. The RdRp existing in various types of RNA viruses enables a broader spectrum of antiviral activities of Favipiravir. After RNA viral incorporation, Favipiravir-RTP works as a mutagen, which is capable of fleeing coronavirus repair machinery. The Favipiravir-RTP adds to the pressure on CoV nucleotide content, which already has a low cytosine (~17.6%) in the SARS-CoV-2 genome. In total, along with the increased frequency of mutation, Favipiravir-RTP has a positive effect on SARS-CoV-2 by a cytopathic effect, which is induced by the virus, reduction in the number of viral RNA, and infectious particles. Favipiravir has a strong binding affinity to RdRp with a docking score of −6.925. Hence, Favipiravir targets the Achilles heel (RdRp complex) of SARS-CoV-2.[25]

Chloroquine

Chloroquine is an antimalarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946. Hydroxychloroquine is used to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, in addition to malaria. In general, Hydroxychloroquine has fewer and less severe toxicities (including less propensity to prolong the QTc interval) and fewer drug-drug interactions than chloroquine. [26]

Mechanism of Action of Chloroquine:

Its mechanism of action (MOA) includes the interference in the endocytic pathway, blockade of sialic acid receptors, restriction of pH mediated spike (S) protein cleavage at the angiotensin-converting enzyme 2 (ACE2) binding site and prevention of cytokine storm. Chloroquine, a potent broad-spectrum antiviral agent, is commonly utilized as an auto-immune disease or anti-malarial agent. Chloroquine may stop a virus infection by elevating the endosomal pH necessary for virus-cell fusion and disrupting the terminal glycosylation of hACE2 receptor. Recent work has shown that chloroquine inhibits SARS-CoV-2 infection at entry and post-entry stages in a Vero E6 cell line. After oral administration, chloroquine is distributed throughout the body, especially in the lungs. Apart from its antiviral activity, chloroquine also exhibits immunomodulatory activities, which in turn leads to a synergistic enhancement of its antiviral effect in vivo. Chloroquine has been considered as a potential drug for the treatment and prevention of COVID-19 pneumonia. However, a recent study has found that chloroquine is ineffective for the treatment of COVID-19. Given the controversy about the effectiveness of this antiviral agent, it is important to determine whether chloroquine has potential applicability for SARS-CoV-2 treatment and prevention. [27]

Arbidol

Mechanism of Action of Arbidol:

Arbidol is a broad-spectrum antiviral agent that blocks influenza A and B viruses by inhibiting virus-cell membrane fusion. Low level evidence shows that Arbidol taken alone or concomitantly with other antiviral drugs produces therapeutic benefits for COVID-19 pneumonia. In China, many randomized control trials are currently under way to assess the efficacy of Arbidol on COVID-19 pneumonia performed a retrospective cohort trial on healthcare workers and family members who have been exposed to a confirmed case of COVID-19. The authors found that Arbidol could decrease the risk of SARS-CoV-2 infection in both hospital-care and family care settings. Compared the efficacy of Arbidol and Lopinavir/ Ritonavir in 50 patients with laboratory-confirmed COVID-19, and the results demonstrated that COVID-19 patients treated with Arbidol recovered more rapidly than those treated with Lopinavir / Ritonavir.[27]

Pharmacovigilance and assessment of drug safety reports during COVID 19:

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.

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.[28,29]

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.[30]

Causality assessment of drug safety reporting:

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."

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.

Challenges of causality assessment:

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.[31]

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.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, pre-existing medical conditions/co-morbidities, elderly patients, alcoholics, are possibly either contributory or confounding factors.

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.[32,33]

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.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.[34]

➢ CONCLUSION:

The pandemics are transmissible and life-threateningdiseases. Covid-19 is pandemic cause by SARS – COV2 which out breaked from food market of Hubei, Wuhan, CHINA. Seems to have transmitted from bat.The transmission rate is quite high and constantly changing its DNA strain causing challenge to health workers and scientist. The proper treatment takes time, since there is not any proper treatment yet for Covid the vaccination seems to be important key in prevention and selfcare is an important factor.

Currently, there is still no effective drug to treat SARS-CoV-2. Clinical treatment of COVID-19 is mainly symptomatic treatment. From the current clinical cases, the SARS-CoV-2 is more dangerous to the elderly and patients with other diseases. In COVID-19 prevention, wearing masks and reducing crowd aggregation is the most cost and effective approach. Fortunately, many scientists and enterprises are stepping up the development of antiviral agents and vaccines, some of which have begun clinical trials. We believe that in a short period of time, effective scientific measures will prevent the infectious spread of COVID-19.

To treat such pandemic disease the drugs are given which are useful harmful too. So, 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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