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IMPACT OF COVID-19 ON PHARMACOVIGILANCE IN INDIA: AN OVERVIEW

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ABSTRACT

Pharmacovigilance refers to medical pharmacology in which adverse effects, especially long-term and short-term adverse drug reactions are detected, interpreted and mitigated. Countries around the world concentrate on developing robust pharmacovigilance programmes. At present there are no approvedCOVID-19 treatments based on extensive evidence from clinical trials and thus infection prevention, control measures, and supporting treatment are involved. While most developed nations have well-organized pharmacovigilance programmes, in developing countries there is still a lack of basic infrastructure to enforce them. The Indian pharmaceutical surveillance system is an important clinical research centre for the medical and pharmaceutical industries. This study is an attempt to emphasis on different pharmacovigilance facets during the widespread pandemic in India.

Keywords: COVID-19, Pharmacovigilance

INTRODUCTION

In most of the countries after the thalidomide disaster of 1960s, pharmacovigilance systems were developed, when thousands of children were born with phocomelia as a thalidomide drug reaction, resulting in the shortening or lack of limbs **[1]**.

In the pharmacovigilance system, healthcare practitioners are of vital importance. They need comprehensive knowledge and experience in the field of drug safety that can contribute effectively to this field through early identification, management and reporting of medical safety issues. An

inseparable part of regular medical practice should be considered as a patient safety measure for health professionals **[2]**.

Using spontaneous monitoring methods, the protection of a drug could be checked after approval and in the entire life cycle **[3]**. Pharmacovigilance is the scientific research related to the identification, evaluation, understanding and prevention of adverse effects, especially long-term effects and short-term side effects of medicines **[4]**.

National Pharmacovigilance initiatives that play a leading role in raising public concern about the safety of drugs were implemented **[5-6]**. Pharmacovigilance has a major role playing in the evaluation of drug-related side effects, be it caused by oral medications or parenteral medicines. **[7]**.

Coronaviruses are a group of covered viruses with unsegmented, single stranded and positive RNA genomes. In addition to infecting a range of vertebrates (like pigs and chickens), six coronaviruses are known to infect and contribute to respiratory illness in humans. Severe acute respiratory syndrome coronavirus (SARS-COV) and Middle East respiratory syndrome (MERS-COV) are basically zoonotic and highly pathogenic coronaviruses, contributing to regional and global disease outbreaks. In late 2019 in Wuhan, China, a novel coronavirus was established as 2019 Novel Coronavirus (nCoV). The World Health Organization (WHO) was informed about the outbreak and the international community was notified along with sequence information rapidly by China after the causative agent was identified. Coronavirus are members of *Coronavirinae* (sub family) in the *Coronaviridae* family **[8]**.

Corona Virus Disease (COVID-19) has been triggered by SARS-COV-2, which rounds the planet and has made it deadlocked. Corona viruses are considered a family of viruses which cause cold, cough and respiratory problems.

This virus known as SARS-COV-2 threatens life and can significantly affect illness and mortality **[9]**. It was found in Wuhan, China which further spread to the World forming its hotspots in numerous countries such as Italy, France, Germany, England and of course, the United States of America and India **[10-11]**.

Corona Virus in India

The first case of COVID-19 in India was registered in Kerala on 30th January 2020 and cases increased thrice up to 3rdFebruary 2020 within three days. Most of these patients have already suffered from various diseases, like high blood pressure, diabetes, and cardiovascular diseases **[12-13]**.

The Indian Council of Medical Research (ICMR) and the Ministry of Family Welfare reported 649 cases, 42 recovery, 1 relocation and 13 national deaths as of 26thMarch. The rate of COVID-19 infection in India is registered at 1.7, significantly lower than in the worst-affected countries **[14-15]**.

By 12thJune, 2020, India confirmed 8,20,916 cases of COVID-19 and 22,123 deaths **[16]**. India's mortality rate is 2.69%. America has 3,097,300 confirmed cases and 132,683 deaths with a mortality rate of 4.28%. Britain has a total of 288,137 cases and 44,650 deaths with a 15.49% mortality rate. With 18.54 percent, France has seen a total of 161,275 cases with 29,907 mortality **[17]**.

It faced a variety of unrivalled obstacles, making the situation physically, mentally and psychologically much more challenging for individuals around the world **[18]**.

Various techniques such as a classical epidemiological model were used to estimate the reproductive number of COVID-19 cases that assists in the determination of outbreak severity with the average number of people infected **[19]**. The countries with lower population cases per capita had a similar thing, i.e. vaccination with Bacille Calmette-Guerin (BCG). A higher number of COVID-19 cases have been reported in several countries like Iran, which stopped offering a booster BCG vaccine in 1999 **[20-21]**.

As of 3rdSeptember, 2020, India reported 3,853,406 corona virus cases out of which 2,970,492 recovered cases along with 67486 deaths **[22]**.

The vast bustle of Dharavi, in the heart of India's capital of finances and entertainment(Mumbai), spans just over 2.1 kilometres (520 acres) and is home to approximately a million people with over 277,136 / km^2 (717,780 / mi^2) population density. In April 2020, Dharavi had 491 cases with a 12 percent growth rate and an 18-day case doubling period. They also offered an enhanced duplication duration of 43 days for May 2020 and 78 days in June 2020 **[23]**. Dharavi has also recorded an impressive record of recoveries with 1735 recovered patients **[24]**.

The Dharavi Containment Strategy was focused mainly on the foundations of the WHO response to public health for COVID-19, recommended for country preparedness and response in its operational planning guidelines **[25]**. Pandemic surveillance is crucial for the core information on the basis of decisions recorded for pandemic response. It allows evidence-based approaches to be developed and incorporated during a pandemic **[26-27]**.

The COVID-19 will give you little information on India like our capacity for the health system; how many people listen to what the government says, our form of governance; and our social structure, if people will support each other and cooperate **[28]**. A substantial number of cases are moderate, but the mortality rate is substantially higher for older people. Children are less likely to be infected and less likely than adults to be hospitalized. The disease in children is less likely than adults and the incidence of infection in women is less likely than men **[29-30]**.

COVID-19 and Pharmacovigilance in India

The key components of the drug monitoring and reported records of adverse effects are to identify and determine the risk profile of the medication as soon as possible. The main step is to suspect an adverse drug reaction (a causal interaction) and to "validate or invalidate" it. The pharmacovigilance causality evaluation is a complex and time-consuming project **[31]**. It is even more difficult considering, the existing prohibitions on physical touch, travel, free movement, isolation and quarantine during a pandemic. Details of all accidents cannot be obtained, thereby impacting the completeness and accuracy of safety reports **[32]**.

The best example was the hue and cries for COVID-19 patients with hydroxychloroquine **[33-34]**. Concurrent medication (anti-microbial, antiviral, antifungal, diuretic, etc.) and electrical disruption are often normal for the effect of hydroxychloroquine on QTc. The data are currently not enough to determine the safety and risk profile of combining medicines in such a situation. The proposed COVID-19 medicines (antivirals) are further metabolized by cytochrome 3A4. Important drug-related interactions can occur with either substrate or inhibitor **[35]**.

Therefore, in the absence of evidence from randomized controlled experiments, physicians can use available real-life clinical results, in both treatment benefits and risks, to bring pharmacovigilance closer to health care systems. In particular the effectiveness of medicines, protection and vaccines for treating and preventing the novel-virus, the ISoP Risk communication Special Interest Groups (SIG) and the ISoP Communication team discussed the role of our professional societies to relay the COVID-19 information. ISoP has a great strength in providing professional and individual support in the work they do worldwide **[36]**.

Therefore, there is an urgent need for appropriate therapies to reduce symptoms of COVID-19, avoid their degradation and

enhance their prognostic before an effective vaccine is available. Antiviral and immunomodulatory therapies have been introduced in clinical trials to assess their effectiveness and protection in treating and at least alleviating pulmonary complications of SARS-COV-2 infections **[37-39]**.

The risk of severe forms of coronavirus diseases is prevalent in cardiovascular patients **[40]**. Clinical symptoms are primarily pulmonary, although some cases can also be cardiovascular (**Figure 1**) **[41]**. Angiotensin Converting Enzyme-2 (ACE2) is an enzyme mainly located in the membrane, the form circulating *via* the splitting enzyme of the membrane anchor; is consistent with the angiotensin-converting enzyme, which was first defined in 2000 as ACE (but now more effectively referred to as ACE1) **[42-43]**. ACE2 down regulates Renin-Angiotensin-Aldosterone System (RAAS) and functions as an AngiotensinII (ATII) deactivator (also known as Angiotensin(1-8), a vasoconstrictive-active peptide, pro-fibrosis, a pro-inflammatory influence, stimulating aldosterone secretion with the binding of AngiotensinI (ATI) receptor modifying it to angiotensin (1-7), a peptide which is active with opposite properties to ATII **[44]**.

As an extracellular membrane enzyme, ACE2 appears to be the receptor for this coronavirus and thus it provides entry to SARS-COV-2/ COVID-19 in human cells **[45-46]**.

Precise identification and binding site for SA RS-COV-

2 glycoproteins with their ACE2 is the same as the research done **[47]**.

ACE2 is obviously a key function for COVID-19 infection and in particular for membrane expression and tissue activity. Exact functions in the contamination process can be complex and deleterious as the ACE2 receptor works with COVID-19 (and intensity is related to the expression of the membrane and tissue activity) **[48-49]**.

Angiotensin-converting enzyme inhibitors (ACEi) primarily inhibit ACE1, blocking the release of ATII. Action on ACE2 was never registered, and no such effect is thought to occur **[50-51]**.

COVID-19 free *in vitro* models reported an increased membrane expression of ACE2, particularly in the heart, due in ACEi and Angiotensin receptor blockers (ARB) treatment **[52-54]**. *Invitro* results were discordant for some human studies in healthy subjects (COVID-19free) **[55-59]**.

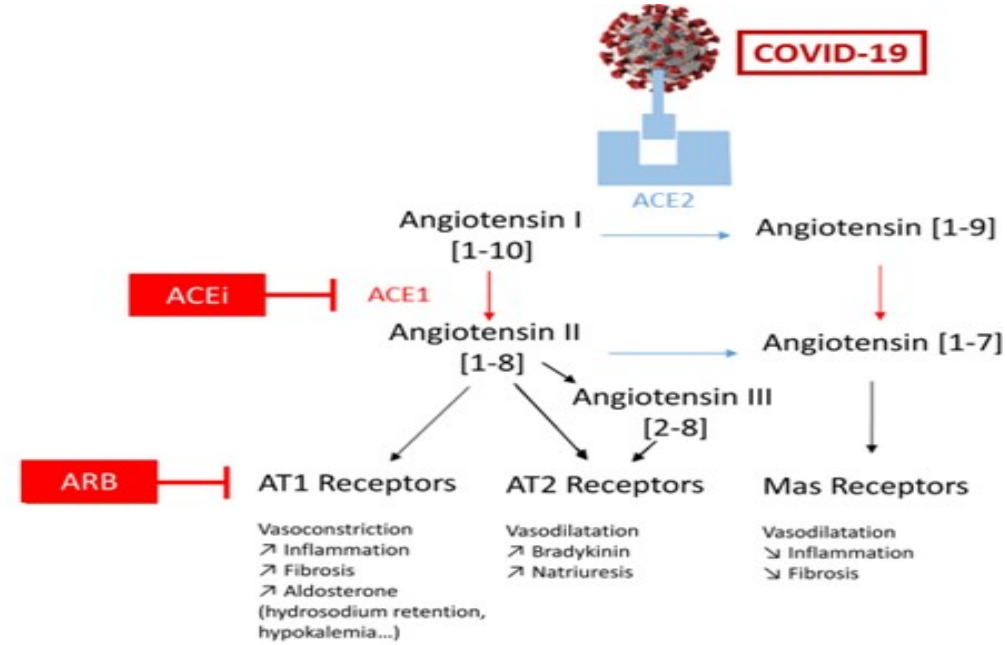

Figure 1: COVID-19 Infection and RAAS [59]

74% of physicians work in urban areas and represent 28% of the country's population. In countries like the US, the UK and Italy, the increase in new cases has plateaued or declined, while in India the curve remains increasing **[60-61]**. There were 174 answers based on a majority of 70 percent consensus with 95 percent trust level and an absolute error of 7 percent (143 in first e-mail and 31 in later recalls). Early studies have attributed cardiovascular factors to 40% mortality in COVID-19 patients. In addition, cardiovascular disease patients have an 11percent mortality rate.In 3 patients (69 per cent), every two deaths occur if they suffer an acute myocardial damage **[62-64]**.

Firstly, India is taking steps to avoid viral transmission. Secondly, ICMR and AYUSH Ministry laid down guidelines for the use of typical prevention strategies and treatment methods to improve immunity against COVID-19 **[65-66]**. Convalescent plasma therapy is highly recommended since SARS and MERS have been relatively effective **[67]**.

India is expert in medical/ pharmaceutical industry with manufacturing facilities, and the Government has carried out fast-tracking research to develop easy diagnostic test kits and low-cost vaccines **[68]**.

The Serum Institute of India has also begun to develop a SARS-COV-2 vaccine **[69]**. The walk-in sample kiosk (WISK) was introduced in Kerala, India by Medical College physicians to collect samples without direct exposure or touch **[70-72]**.

The purpose of the Pharmacovigilance is to obtain online information, work documentation and expertise while prioritizing new and relevant security issues.

GlaxoSmithKline has established a powerful Pharmacovigilance approach that integrates traditional, case-basic Pharmacovigilance methods with disproportionality and data viewing tools **[73]**.

The tools reside within a program context that promotes ongoing analysis, monitoring and management of security issues.

This highly innovative instrument and processes will help improve Pharmacovigilance efficiency and offer new analytical capabilities. The pharmaceutical companies will use a similar method to rapidly identify and analyze adverse drug reactions. Openness and communication will improve consumer reporting, which are positive steps towards growing customer engagement in the Pharmacovigilance system **[74]**.

CONCLUSION

Pharmacovigilance continues to play a crucial part in resolving the increased complexity and efficacy of drugs and their potential and often unspeakable damage capacities. If adverse effects and toxicity occur particularly if they have not been identified previously, they are registered, assessed and correctly reported to the public to understand the findings. The adverse effects reported by the Pharmacovigilance Program will likely benefit society with the vocabulary and knowledge of patient habits and activities because they are open to the public and to public health professionals and will also provide easy access for reporters. Newer and effective medications contribute to the safety and well-being of people. Given all aspects, it is highly positive that, considering all these challenges, Pharmacovigilance remains committed to tracking pharmaceutical products across the globe. Pharmaceutical safety has become a critical concern for public health in India, as regulators, product manufacturers, customers and medical professionals face a large number of challenges. In India, pharmaceutical surveillance continues to expand, evolve and improve. However, pharmacovigilance systems need to be established to follow up and take action more efficaciously on the issues of safety associated with medicines in order to improve the contribution to public health. In reality, the healthcare industry, pharmacovigilance agencies and practitioners and all healthcare professionals have collective responsibility for the protection and proper treatment of patients.

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CONFLICT OF INTEREST

The author declares that they have no conflict of interest.

COMPLIANCE WITH ETHICAL STANDARDS

Involvement of Human Participants and/or Animals: Formal consent is not required for this type of study.

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