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Gene Influencing in COVID-19 Infection, Disease Severity and its Pharmacotherapy

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ABSTRACT

Current pandemic COVID-19 has severely affected the world, having a mortality rate ranging from 1 to 10% which is different for many countries. The time interval from symptoms to clinical recovery is 6–8 weeks and to death is 2 to 8 weeks. The increase in severity and fatality in COVID 19 is primarily due to the presence of comorbidities like cardiovascular disease, pre-existing lungs disease, hypertension, diabetes, obesity and cancer. As we already know that humans show the difference in drug responses because of their varied genetic make-up. Therefore, Population genomics gives an insight into the genetic characteristic of a population and it is critical in determining susceptibility, severity and natural protection against infectious diseases. Hence, this study was done to evaluate the population genetic makeup which is necessary to identify those who are at risk or protection from disease and develop genomics information, that would be useful in providing insight about COVID-19 disease severity or outcomes. Some of the proposed genetic gateways in COVID 19 pathogenesis are mentioned in this review that includes roles of ACE2 gene, HLA gene, Chromosome 3P21.31, ABO locus, genes responsible for cytokine storm, TLR-pathway, Family Mediterranean fever and G6PD deficiency. This review also emphasises the current treatment available in COVID-19 like hydroxychloroquine, azithromycin, RNA polymerase inhibitors, interleukin inhibitors, antivirals, ivermectin, doxycycline and their pharmacogenomics viewpoint. Such Pharmacogenomic studies are very helpful for physicians to choose and give accurate first-line therapy for COVID 19 patients.

Key Words: COVID 19, Pharmacogenomics, Population genomics, Genetic gateways, cytokine storm, Therapeutics in COVID-19

INTRODUCTION

Currently, the world is badly hit by the COVID-19 pandemic. The case fatality rate of COVID-19 ranging from 1 to 10% that differs in various countries.¹ This variation may be due to unknown population size, frequency and accuracy of testing, proper maintaining of the registry, demographic parameters of population and capacity of healthcare systems. The pathogenesis of COVID-19 can be broadly classified into four stages - Stage 1 being pre or asymptomatic phase that lasts for a few days. Stage 2 is defined by symptoms of fever, cough, malaise, may progress to viral pneumonia with high viral load (within the span of 5 days) or improve gradually with the development of antibodies around 7 to 10 days. A very small fraction of patients may progress to stage 3, develop the symptoms of cytokine release syndrome

with high levels of pro-inflammatory cytokines and other host markers of inflammation (like CRP, ferritin, D-dimers, LDH etc.), lymphopenia and respiratory failure. This ultimately proceeds to Stage 4 which is acute respiratory distress syndrome (ARDS) and multi-organ involvement, seen in 60-70% of patients admitted to ICU.² The time interval from the appearance of symptoms to clinical recovery is 6–8 weeks and to death is 2 to 8 weeks.

COVID-19 associated morbidity and mortality increases due to the presence of co-morbidities like cardiovascular disease, pre-existing lungs disease, hypertension, diabetes, obesity and cancer. The elderly population are mostly affected, though younger patients are also suffering from acute conditions and dying due to this COVID-19. Even children were initially thought to be protected from severe disease conditions but Kawasaki disease and vasculitis type of acute

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inflammatory response³ has been noted in them. Therefore, the question rises here - can there be a genetic predilection for this pandemic COVID-19.³

As we already know that the humans show the variable difference in drug responses because of their diverse genetic make-up. This is because, drug metabolism, its efficacy and adverse effects are determined by the genetic makeup of the individual. The concept of pharmacogenetics and pharmacogenomics is well established already. Pharmacogenetics refers to the study of DNA sequence variation as it relates to differential drug response in individuals, i.e. the use of genomics to determine an individual's response. Pharmacogenomics refers to the use of DNA-based genotyping to target pharmaceutical agents to specific patient populations in the design of drugs.⁴

Since COVID 19 has no definite treatment till now, many drugs are being repurposed and used or are under investigation for use in this disease. Some studies already suggested that genetic makeup interplay the lack of efficacy and fatal side effects of hydroxychloroquine in the treatment of COVID 19.⁵ Pharmacogenomics is very helpful for physicians to choose and give accurate first-line therapy in critically ill patients, where ineffective therapy could be life-threatening for them. Other factors that influence the efficacy and toxicity of drugs used in COVID 19 could be irrational prescribing, polypharmacy, drug interactions, which needs to be evaluated further.

This review focuses on how the genetic make-up of the individual is influencing the pathogenesis and therapeutic outcome of COVID-19.

INDIVIDUALS GENETIC MAKEUP VIS A VIS COVID-19 INFECTION AND SEVERITY

Studies related to population genomics provide insight into the genetic characteristic of the whole population which is important in determining susceptibility, severity and natural protection against infectious diseases. Hence knowledge and understanding about the genetic makeup makes it necessary to identify the people who are at risk or having protection from the disease which would be useful in providing acumen about COVID-19 disease severity or outcomes.⁶

Unfortunately, there are no genetic data available in terms of topographical variation of COVID-19 severity or outcome worldwide. The researchers have already identified few genes associated with the immune system's, as well as a protein that allows the coronavirus into our cells, those are related to COVID-19 susceptibility as well as severity. Some proposed genetic data are given below

Role of angiotensin-converting enzyme 2 (ACE 2) gene

ACE2 is important in maintaining homeostasis and balance of the renin-angiotensin system, vascular function, and car-

diovascular complications. The most frequent comorbidity found with COVID-19 are hypertension and diabetes, and both these conditions are modulated by ACE2. It has now become established that SARS-CoV-2 uses angiotensin-converting enzyme 2 (like SARS-CoV) to enter into the host cell and the expression of ACE2 influences SARS-CoV infection.^{7,8} The ACE2 gene located in the X chromosome (Xp22.2); encodes the angiotensin-converting enzyme-2.⁹ The transcriptional activity of the ACE2 gene become altered among functional variants of the ACE2 gene. The types of single nucleotide polymorphisms (SNPs) of the ACE2 gene varies among different populations.¹⁰ Multiple studies confirmed that at least 9 human ACE2 variants (i.e., S19P, I21V, E23K, K26R, T27A, N64K, T92I, Q102P and H378R) are more susceptible to viral binding, whereas another 17 variants of ACE2 (i.e., K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355 N, Q388L and D509Y) are protective against viral entry due to lower binding propensity to SARS-CoV-2 spike protein (receptor-binding domain).¹¹

The protective variants of K31R and Y83H of the ACE2 gene have been found at a relatively higher frequency among Asian populations than the global average. Whereas the frequency of T92I, a risk variant allele is relatively more in European as compared to a global average and another risk variant K26R mutation is often seen among Caucasians.¹²

Studies demonstrated that ACE-2 has a critical role in inflammatory processes. Genetic deficiency of ACE2 upregulates the production of cytokines (interleukins, interferons, chemokines) and induces vascular inflammation in ACE-2 knockout (KO), apolipoprotein E (ApoE) KO and ApoE/Ace2 double KO mice model.^{13,14} Study also demonstrate the ACE-2 expression is associated with various immune signatures like markers of natural killer cells (NK cells), T lymphocyte, B lymphocyte and host's interferon response.¹⁵ All the above conclusion goes in favour that ACE2 is also involved in post-infection downstream inflammatory responses apart from receptor for SARS-CoV-2.

Role of HLA gene (and antigen presentation) in inducing protective immunity against COVID-19

The human leukocyte antigen (HLA) molecules are the human version of the major histocompatibility complex (MHC), a group of genes that are present in many species. THE Human MHC complex consists of more than 200 closes together genes located on chromosome 6. HLA system is an important immune regulatory component that differentiates self and non-self-antigens and a primary agent in conferring adaptive immunity against infectious diseases. Several thousand polymorphisms has identified in HLA genes, so HLA exhibit extreme diversity. And this genetic diversity at HLA genes is responsible for inter-individual difference in the immune response against pathogens.¹⁶

MHC molecules act as a receptor for antigens from pathogens. The peptide-binding groove of the MHC class I molecules, bound to a viral antigenic peptide and then present the peptides to the virus-specific cytotoxic T lymphocytes (CD8+ T cells). Structural variation of the peptide-binding grooves (essential for binding to various peptides) is determined by variations within MHC class I genes.¹⁷ So, HLA genes are critical in MHC-peptide interactions, which determines the susceptibilities and immune responses to viral infection.

A study on severe COVID-19 patients with respiratory failure, exhibit extremely low HLA-DR expression along with the significant decrease in CD4 lymphocytes, CD19 lymphocytes, and natural killer (NK) cells count, which might indicate the immune-regulatory/response role of HLA in COVID-19.¹⁸ An in-silico analysis on genetic variability of binding affinity of MHC class I molecules with all the peptides of SARS-CoV-2, covering 145 HLA-A, -B, and -C genotypes showed that the HLA-B*46:01¹⁹ allele could increase susceptibility to COVID-19, as this allele displayed the fewest presenting/binding sites for SARS-CoV-2 peptides. Whereas HLA-B*15:03²⁰ could provide CD8+ T cell-based protective immunity, as this allele had the highest potency to present SARS-CoV-2 peptides to CD8+ T cell. And at haplotype level, HLA-A*02:02,²¹ HLA-B*15:03, and HLA-C*12:03²² showed highest and HLA-A*25:01, HLA-B*46:01, and HLA-C*01:02 exhibited the lowest number of predicted representation sites for epitopes from SARS-CoV-2 to CD8+ T cell. So, population contain later HLA sets are more susceptible to SARS-CoV-2 infection.²³

The topographical pattern/variation in the incidence of COVID-19 infection, severity and mortality indicating towards the population-specific HLA alleles may be a most critical determinant of the protective immune response against SARS-CoV-2 and ascertain the resistant or vulnerability to COVID-19 in individual or population.²⁴ For example, a recent study showed HLA-A*02 alleles (like A*02:01, *02:03, *02:05, *02:06, *02:07, and *02:11) have a higher frequency among North and central Indian populations, among these A*02:11 display highest occurrence at the repertoire level, and Indian populations are fortunate to have this allele commonly, whereas Caucasian and oriental populations have complete lack of this allele.²⁵ As mentioned above HLA-B*46:01 allele that could be related to increasing susceptibility to COVID-19, is seen among people of South-East Asian descent. But completely absent in Indian and African populations and rarely present in European populations, which make these population naturals resistant to COVID-19.²⁶

Studies already have concluded that olfactory dysfunction is one of the clinical presentations of mild to moderate COVID-19.²⁷⁻²⁸ It is a well-established fact HLA gene are inherent in olfaction,^{29,30} and olfactory receptor (OR) gene are seem-

ing to be MHC-linked with existing polymorphisms.^{31,32} Though the relationship between HLA polymorphism and olfactory dysfunction has not been studied in COVID-19 yet, but it may impart an insight into HLA related pathogenesis of disease further.

GENE RESPONSIBLE FOR THE CYTOKINE STORM

The most demanding clinical debate worldwide at present is why there is individual variability in developing cytokine storm, and this already has increased the interest in identifying underpinning genetic mechanisms.³³ Cytokine production is a natural immunological event and T lymphocytes are the most important producers of cytokines, which is regulated by genetic as well as epigenetic processes.³⁴ Genetic polymorphisms of the cytokine genes are related to the production of inappropriate amount cytokines, which imparts the natural susceptibility, severity or protection to infectious diseases.³⁵

Studies already established that the cytokine gene polymorphism pattern is influenced by ethnicity.³⁶ Till now no research has been done on cytokine gene polymorphisms and the risk of cytokine storm in COVID-19, but several studies have concluded the associations between cytokine gene polymorphisms like IFN- γ +874A allele³⁷ (low IFN- γ expression), IL12RB1³⁸ and susceptibility to SARS-CoV infection. A meta-analysis suggests the presence of the IL6 174C allele is associated with higher IL-6 production and pneumonia severity.³⁹

Future research for identification of the relation between various pro-inflammatory cytokine genes polymorphism and cytokine storm in SARS-CoV2 infection can certainly provide further insights on the COVID-19 pandemic.

Chromosome 3P21.31 and COVID-19

Studies concluded that among the cluster of six genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1), on chromosome 3p21.31 locus several are involved in Covid-19 susceptibility and severity. For example, SLC6A20, which encodes the sodium-imino acid (proline) transporter 1 (SIT1), which functionally connected with angiotensin-converting enzyme 2, the SARS-CoV-2 receptor.^{40,41} CC motif chemokine receptor 9 (CCR9) and the C-X-C motif chemokine receptor 6 (CXCR6) regulates the lung-resident memory CD8 T cells during immune response against respiratory pathogens, including viruses.⁴² The risk allele rs11385942-GA is associated with decreased CXCR6 expression and increased expression of SLC6A20, and LZTFL1 in human lung cells. It was found that risk allele 3p21.31 (rs11385942) was present in higher frequencies among patients who received mechanical ventilation. Even younger

patients who carry homozygous risk allele frequently suffered from severe disease and received mechanical ventilation than heterozygous or carrying the non-risk allele.⁴³

ABO locus and COVID-19

Diversity of the ABO gene located on chromosome 9q34.2 is the fundamental of the ABO (blood group) system, i.e. individual carrying a particular allele determines the blood group of that individual. The association between ABO locus and susceptibility for COVID-19 has been established (as susceptibility to SARS-CoV-1 infection⁴⁴) by genome-wide association study as well as nongenetic studies.^{45,46}

A meta-analysis corrected for age and sex, confirmed that blood group O is associated with a significantly lower risk of acquiring Covid-19 than that of non-O blood groups, whereas blood group A was associated with a higher risk than non-A blood groups,⁴⁴ but interestingly no significant difference has been found in blood-group distribution among patients received supplemental oxygen or mechanical ventilation.⁴⁵⁻⁴⁷

The possible biologic mechanisms of these findings may be due to the presence of neutralizing antibodies against protein-linked N-glycans⁴⁷ (Coronavirus S protein trimers are covered by an extensive glycan shield, that is made of N-linked glycans and surrounds the receptor-binding domain. The presence of anti-A and anti-B antibodies in individuals with blood group O could prevent infection by blocking virus attachment and entry)⁴⁸ or other biologic effects of the detected variant, including von Willebrand factor stabilization.^{49,50}

TLR-gene in SARS-CoV-2 infection

Toll-like receptors (TLRs) are one of the several types of pattern recognition receptors (PRRs), which are capable to recognize molecules expressed on pathogens (the so-called pathogen-associated Molecular Patterns or PAMPs), or damaged cells (the Damage-Associated Molecular Patterns or DAMPs) and initiate the inflammation and/or innate immune response soon after a challenge by pathogens including SARS-CoV-2. TLR signalling is crucial in the regulation of cytokine expression during protective host immune response,^{51,52} and also, might have a critical role in inducing cytokine storm in SARS-CoV-2 infection.

It is now well established that the functional diversity of TLR molecules are also governed by genetic variation among TLR genes. The identified 10 TLR genes are expressed on five different chromosomes. TLR1, TLR6 and TLR10 are located on chromosome 4, TLR7 and TLR8 are located on the X chromosome, TLR5 on chromosome 1, TLR9 on chromosome 3, TLR2 and TLR3 on chromosome 4 and TLR4 on chromosome 9.⁵³

Currently, there are no studies on the role of TLR pathway in SARS-CoV-2 infection, but Previous animal studies had

demonstrated that TLR3, TLR3/TLR4 adaptor TRIF (Toll/IL-1R domain-containing adaptor inducing IFN) and Ticam2 (Toll-Like Receptor Adaptor Molecule 2) deficient mice are more susceptible to SARS-CoV infection as well as alterations in natural inflammation.^{54,55} The researchers (Radboud University Medical Center, Netherlands) found that rare loss-of-function mutation of X-chromosomal TLR7 was associated with impaired type I and II IFN responses and associated with primary immune deficiency among young COVID-19 patients. Though no association between TLR7 function and inborn error of immunity has been identified till now, the critical role of TLR7 for protection from coronavirus is well known now.

The interesting fact is that the TLR genes display a unique distribution pattern in various ethnic populations and also are the target of selection pressure. The critical role of TLR genes in determining different susceptibility and severity to SARS-CoV-2 infection needs to be tested further in detail.

The complement system and SARS-CoV-2 infection

The complement system is comprising of over 30 proteins; their activation and function are taking place in an organized manner by 3 activation pathways named the classical, the lectin, and the alternative pathway. All these pathways converge to a central component by activating C3 (by enzyme complexes—the classical/lectin (C4bC2a) and the alternative C3 convertases), which ultimately activate the downstream i.e. C3a, C4a, C3b, C4b and membrane-attack complex (MAC or C5b-9 complex). The function of the complement system is to eliminate pathogens (including viral infections)⁵⁶ through opsonization, attract and activate neutrophils and macrophages, intensify humoral immunity and cell-mediated response,⁵⁷ but uncontrolled activation may result in exaggerated acute or chronic inflammation, tissue injury, and the activation of coagulation. So, complement is a double-edged sword of our immune system. The complement system also interacts with TLRs and further activate the inflammatory immune cells, especially Th17 cells.⁵⁸

An animal study demonstrates SARS-CoV-infected C3^{-/-} mice had less respiratory dysfunction and low levels of cytokines and chemokines response in the serum as well as lungs.⁵⁹ Also, complement system hyper-activation (mediated by mannose-binding protein-associated serine protease 2 or MASP-2 and exaggerated by highly pathogenic coronavirus N protein) and lung injury were found among severe COVID-19 patients.⁶⁰ This suggests that complement components have important implications in the induction of the cytokine storm and inflammation in SARS-CoV-2 infection.

Complement genes polymorphisms have identified to be associated with multiple diseases, including various infectious diseases. For example, loss of functional single nucleotide

polymorphisms (SNPs) in complement factors, such as C5 (rs17611) and C3 (rs2230199), can increase the risk of bacterial infection, autoimmune disease (like systemic lupus erythematosus) and malignancies.^{61,66} But till now there are no data available on complement gene polymorphism and risk and severity of SARS-CoV-2 infection. Apart from the functional variance of genes encoding TLR and cytokine, genes determining the function of the complement system also could furnish an insight into the immensity of inflammatory responses (cytokine storm) in COVID-19.

FAMILIAL MEDITERRANEAN FEVER (FMF)

FMF is an autosomal recessive, monogenic, autoinflammatory hereditary fever syndrome that was first described in Mediterranean populations (also affecting Jewish⁶², Turkish, Armenian, North Africans and those of Arabic descent).⁶³ It is characterized by short, recurrent bouts of fever that last 12–72 h, with raised inflammatory markers (TNF alpha, IL1 and IL 6), polyserositis and dermal manifestations.⁶⁴

MEFV gene on chromosome 16p13.3 encodes a protein named pyrin (also called marenostin or TRIM20) an important modulator of innate immunity like clustering of the inflammasome. In response to intracellular threats, inflammasome activates inflammatory mediators and regulators of innate immunity.⁶⁵ Gain-of-function mutations of the MEFV gene are, producing clinically heterogeneous phenotypes with the variation of pyrin functions, for example, it may intensify the inflammasome sensitivity and delay resolving of innate immune responses. So, mutations in MEFV may be associated with cytokine storm in COVID-19. For instance, MEFV mutations have been reported among Jewish, Japanese,⁶⁶ Spanish⁶⁷ and Iranian⁶⁸ populations.

Colchicine or tocilizumab is used to treat FMF to reduce the severity, duration and complication of the disease, and these two medicines are being investigated/used in adult patients diagnosed with COVID 19 infection⁶⁹⁻⁷⁰ Further genetic research may provide more insight about the relation between MEFV gene and COVID-19.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

G6PD deficiency (X linked dominant polymorphisms) increase the oxidative stresses of the cells. G6PD is the rate-limiting enzyme in the pentose phosphate pathway and produce NADPH, which maintains the balance of reduced glutathione (GSH) and oxidized glutathione (GSSG) in cells. Glutathione is the physiological anti-oxidant that protect cells against oxidative stress.⁷¹

The insight of G6PD deficiency may interplay with severe COVID-19 infections, come from several observations like – (1) males predominantly suffered from severe disease (2) previous documentation of susceptibility to a common al-

pha coronavirus (229E) infection in G6PD deficient cells (3) G6PD deficiency reduces the production of IL10 and other anti-inflammatory cytokines but increases IL6 and other pro-inflammatory cytokines among patient experienced severe trauma.⁷² (4) animal experiments demonstrate that G6PD deficiency intensifies the cytokine responses and cause hyper inflammation (mostly increased IL1 β , IL6, and IL10 levels) following acute endotoxemia.⁷³ More detail research may establish an association between G6PD deficiency and COVID-19 further.

G6PD deficiency affects around 400 million people, distributed globally, especially in (current or previous malaria-endemic areas likely due to evolutionary advantage against malaria) blacks from Africa and America (lowest prevalence, 12%) sub-Saharan Africa or Brazil, Sardinia, Greece, Kurdish Jews (highest prevalence, up to 70%), South China, Thailand and India.⁷⁴ Topographical distribution data of COVID-19 infection and G6PD deficiency may also strengthen the above observations.

PHARMACOGENOMIC CONSIDERATIONS OF COVID-19 THERAPIES

Significant interindividual variability in response to drug therapy exists in patients. Genetic diversity can affect the disposition (pharmacokinetics), efficacy, tolerability and safety (pharmacodynamics) of a drug. Such interindividual variability can be managed successfully by pharmacogenomics knowledge to obtain the best desired therapeutic outcome and least adverse drug reaction. It is noteworthy that pharmacogenomics data are now being included in drug labels, intended to facilitate the selection of an appropriate drug or adjusting the dose to an individual patient to optimize therapeutic outcome. In this subsequent part, we will discuss the current therapeutics in COVID-19 and their pharmacogenomics viewpoint.

Hydroxychloroquine

Hydroxychloroquine (HCQ), a derivative of the antimalarial drug chloroquine, is mainly indicated as an immunomodulatory agent in the management of systemic lupus erythematosus and rheumatoid arthritis. It was repurposed for the treatment of Covid-19 based on previously conducted in-vitro and animal studies which showed antiviral activity of chloroquine against influenza, chikungunya, SARS-CoV-1 and seasonal infections caused by other coronaviruses.⁷⁵⁻⁷⁸ Since the SARS-CoV-2 follows a similar process of pH-dependent internalization (by endocytosis and lysosomal fusion) for entry into the host cell and further replication, as the above viruses, it was thought that HCQ would also prove beneficial in treating Covid-19 and was quickly adopted for clinical use. Subsequently, preliminary results from the Solidarity trial (including the French Discovery trial data) and the UK's Recovery trial failed to show any significant reduction

in mortality with HCQ when compared to standard of care. It rapidly fell into disrepute and was withdrawn from most national treatment guidelines and also discontinued as a treatment arm in the WHO Solidarity trial.^{75,76} The Government of India guidelines, in contrast, continues to recommend the use of HCQ in selected patients with mild symptoms having high-risk features, and in moderate cases of hospitalized COVID-19 patients. The ICMR also recommends the use of HCQ for prophylaxis in frontline workers based on encouraging results from a case-controlled study.⁷⁷

The metabolism of both chloroquine and hydroxychloroquine occurs with the help of the microsomal cytochrome P450 enzymes CYP2D6, CYP2C8 and CYP3A4, all of which are known to exhibit genetic polymorphisms. Several allelic variations in CYP2D6 have been reported in man leading to differing phenotypes such as poor metabolisers (CYP2D6*4), intermediate metabolisers (CYP2D6*10), extensive metabolisers (CYP2D6*2) and ultrarapid metabolisers.⁷⁸ Studies have also reported distinct ethnic variations in the frequency of occurrence of such polymorphisms.^{79,80} Although studies in the Indian population are limited, research has found the CYP2D6*2 alleles to be the most frequent variant in the Gujarati (47%) and South Indian populations (34.8%). The Gujarati population (13%) were also found to exhibit high levels of CYP2D6*4 along with the Punjabi population (24%), while the Bengali population (21%) were found to have high levels of CYP2D6*10.⁸¹ Thus, the pharmacokinetics of chloroquine and hydroxychloroquine may vary greatly among different ethnic groups, which may imply their safety and efficacy. Interestingly, both these drugs are also known to inhibit CYP2D6, which should be kept in mind when drugs like ondansetron, haloperidol, etc, which are CYP2D6 substrates with a propensity to prolong QT interval, are prescribed concomitantly. On the other hand, the effectiveness of drugs like codeine and tramadol, which are prodrugs requiring activation by CYP2D6, may be compromised when co-prescribed with chloroquine or hydroxychloroquine.

Apart from the risk of QT prolongation, both these drugs are also known to cause retinopathy with high doses or on prolonged usage. Retinopathy is less frequent in individuals who possess the minor allele of ABCA4.⁸²

Azithromycin

Based on the results of an observational study, it was suggested that combined therapy of azithromycin and hydroxychloroquine was more effective in COVID-19 than hydroxychloroquine alone.⁸³ Although azithromycin causes lesser drug-drug interactions than other macrolide agents, co-therapy with hydroxychloroquine may increase the risk of prolonged QT interval leading to fatal arrhythmias.⁸⁴ Individuals with 2677GG (rs2032582) and 3435CC (rs1045642) diplotypes in ABCB1 (P-glycoprotein) gene have been seen

to attain a higher maximum plasma concentration of azithromycin than those with 2677TT/3435TT diplotypes.⁸⁵ So, efficacy and drug interaction varies with genetic polymorphism.

RNA Polymerase inhibitors

The nucleotide analogues, Remdesivir, favipiravir and ribavirin have been used to treat COVID-19. All these agents are converted to their active forms by various intracellular enzymes and later inhibit viral RNA polymerase to exert their anti-viral effect.

Remdesivir has been approved for restricted emergency use as a treatment option for COVID-19 by the DCGI based on a favourable risk-benefit ratio in randomized, double-blinded, placebo-controlled trials.⁸⁶ The uptake and metabolism of Remdesivir depend on P-glycoprotein and OATP1B1 transporters, and CYP2C8, CYP2D6, and CYP3A4 enzymes respectively.⁸⁷ Although there is a dearth of data on the pharmacogenomics of Remdesivir, polymorphisms of the genes coding for the above transporters and metabolizing enzymes may affect its pharmacokinetics and hence drug response in terms of the desired outcome, adverse drug reaction and drug interactions.⁸⁸

The DCGI has also approved favipiravir for “restricted emergency use” in mild to moderate cases of COVID-19.⁸⁹ Although no pharmacogenomic data on favipiravir is available, there is a theoretical possibility that since it is metabolized by aldehyde oxidase and also xanthine oxidase, to some extent, variations of these enzymes in different individuals may affect the pharmacokinetics of this drug.⁹⁰ Though not studied separately, there are certain theoretical possibilities that the effectiveness of Favipiravir is depended on the polymorphism (SNPs) of metabolizing enzyme - aldehyde oxidase. Fast metabolizers (FMs) (hAOX1-N1135S and hAOX1-H1297R, 2- to 4-fold increased catalytic efficiency) usually may have poor response to Favipiravir whereas, poor metabolizers (PMs) (hAOX1-R802C and hAOX1-R921H, 2.4- to 1.5-fold reduced activity) may exhibit drug toxicity.⁹¹

Ribavirin, a drug used for hepatitis C, has also been considered in the treatment of COVID-19 and is being taken up in various research studies as a treatment modality. The trough concentrations of ribavirin are known to differ greatly in the presence of polymorphic variants of the influx transporters SLC29A1, SLC28A2 and SLC28A3, with significantly higher trough concentrations achieved in those with the SLC29A1 variant.⁹² Also, individuals with ITPA (inosine triphosphatase) variants with decreased activity in red blood cells are less prone to the hemolytic side effect of ribavirin.^{93,94}

Interferon (INF) β -1b

IFN- β 1b, which was found to be effective in the treatment of SARS and MERS is also being explored as a potential

therapy for COVID-19 as monotherapy and also in combination with other drugs like lopinavir/ritonavir.⁹⁵ In a study of patients of multiple sclerosis treated with IFN- β 1b, patients with variants of IRF6 were found to be at a higher risk of drug-induced liver damage.⁹⁶ In another cohort study of IFN- β 1b-treated multiple sclerosis patients, those with HLA-DRB1*15 were found to be at a lower risk of developing biologically significant levels neutralizing antibody than those having the HLA-DRB1*04 allele.⁹⁷

Antiretrovirals

Lopinavir and ritonavir combination was among the first drugs which were considered for the management of COVID-19.⁹⁸ Both these drugs are metabolized by CYP3A4 and CYP3A5 enzymes, and therefore polymorphic variations in their encoding genes may lead to differences in their pharmacokinetics.⁹⁹ In all clinical situation, lopinavir and ritonavir are always used in combination, and the study shows CYP3A5 genetic polymorphism did not affect the trough plasma concentrations of these drugs.¹⁰⁰

The plasma concentration of darunavir depends on the influx of transporters SLCO1A2, SLCO1B1, and efflux transporters like MRP1.¹⁰¹ Study demonstrate that those having SLCO3A1 rs8027174 GT/TT genotypes had a lower clearance of darunavir, while a 2.5 times higher central volume of distribution was seen in those who were homozygous for rs4294800 A allele.¹¹⁰

Interleukin inhibitors (Tocilizumab, Sarilumab, Anakinra, Siltuximab)

Since interleukins, mainly IL-6, play a major role in the development of the cytokine storm, interleukin inhibitors are being used to manage severe cases.¹⁰²

Tocilizumab (TCZ) is a monoclonal antibody that binds to both membrane-bound and soluble IL-6 receptors. In a study conducted on patients of rheumatoid arthritis receiving tocilizumab, single-nucleotide polymorphisms rs12083537, rs2228145, and rs4329505 were seen to be associated with clinical response, of which presence of the major allele (A) of rs12083537 and the minor allele (C) of rs4329505 was found to show poor response with regards to swollen joint count.^{103,104} Polymorphisms in the UGT1A1 gene are strongly associated with increased levels of unconjugated bilirubin levels in patients during tocilizumab therapy. The rs6742078 TT genotype is at risk of attaining higher levels of unconjugated bilirubin.¹⁰⁵

Sarilumab also binds to both membrane-bound and soluble IL-6R α to exert its anti-IL6 action. Genetic variations in the UGT1A1 gene may also be responsible for the rise in bilirubin levels during therapy with sarilumab.¹⁰⁶

Anakinra competitively inhibits IL-1 from binding to its cell membrane receptor, thus blocking cell signalling. Literature

search on the pharmacogenomics of anakinra revealed only one study which showed that the presence of the rarer T allele at IL-1 α (+4845) was associated with clinical response to treatment.¹⁰⁷

Janus kinase inhibitors (ruxolitinib, baricitinib)

These drugs are also being explored as potential agents in COVID-19 therapy due to their immunomodulatory action. Although the pharmacogenomics of these two drugs has not been studied yet, the fact that both ruxolitinib and baricitinib are substrates of CYP3A4 suggests a theoretical possibility of differences in their activity in individuals with different variants of CYP3A4.¹⁰⁸ Additionally, the uptake of baricitinib depends on the OAT3 transporter which is encoded by SLC22A8, the pharmacogenomics of which have been studied in a different substrate drug.^{109,110}

Corticosteroids

Corticosteroids being potent immunosuppressants are the mainstay of management of ARDS and lung damage associated with severe Covid-19.¹¹¹ The results of several research studies on the pharmacogenomics of corticosteroids have found that there is increased response to these drugs in individuals with CRHR1 (rs1876828), T gene (rs3127412 and rs6456042), TBX21 gene (rs2240017) and ORM-DL3 (rs2872507). On the other hand, those with FCER2 (rs28364072), ST13 (rs138335 and sr138337) and GLCCI1 (rs37972) were found to show decreased response to corticosteroids¹¹². No specific pharmacogenetic information on the effectiveness of corticosteroids for ARDS was found.

Ivermectin

Although data on the effectiveness of this combination in Covid-19 patients is limited, it is now being recommended by some authorities in treatment as well as prophylaxis of COVID-19. Ivermectin is a known substrate for both the MDR1 and the CYP3A4 which probably act synergistically and determining its pharmacokinetics.¹¹³ The MDR1 gene polymorphism is often associated with a decrease in P-gp expression or its activity, thereby affect the absorption and tissue concentrations of ivermectin and other substrates of MDR-1.¹¹⁴ The CYP3A4*1B variant allele, associated with the decrease of CYP3A4 activity, was detected in 69-82% African and 4-9% Caucasian population but has not been detected in the Asian population.¹¹⁵ The CYP3A4*3 variant was reported in only 2% of Caucasian populations.¹² Individual carrying the above variants have better ivermectin absorption. Genetic polymorphism also determining the ivermectin toxicity. Studies conducted in dogs have found that ABCB-1 polymorphisms which lead to loss of p-glycoprotein function results in neurotoxicity and fatal toxicosis.¹¹⁶ Since ABCB-1 is also responsible for the efflux transport of ivermectin in man, further studies on the pharmacogenomics of ivermectin are warranted in humans.

Siltuximab

Siltuximab is a monoclonal antibody that directly neutralizes interleukin (IL)-6, an inflammatory cytokine detected at elevated levels in multiple inflammatory conditions, including COVID-19. It specifically binds to IL-6, thereby inactivating IL-6 induced signalling. Siltuximab exerts its actions through activation of Stat3 downstream antiapoptotic regulatory genes *BcL-XL*, *MCL-1* and survivin. Genetic polymorphisms may result in inhibition of Stat3 phosphorylation and those gene expressions result in reduce the therapeutic potential of liver cancers.¹¹⁷

Doxycycline

Doxycycline is an antimicrobial agent but also possess antiviral as well as anti-inflammatory activities. It reduces the cytokine storm and prevents lung damage.¹¹⁸ Cost-effectiveness, acceptable tolerance¹¹⁹ and ease availability have made doxycycline, a potential and rational option in patients with COVID-19. The pharmacokinetics of doxycycline in the elderly, renal impairment, undernourished and hyperlipidaemic patients, patients with infection had already been studied. But data on the impact of sex, pregnancy, lactation or liver impairment on doxycycline pharmacokinetics is lacking.¹²⁰ The study demonstrated the varied response of doxycyclin with age. It was seen that above the age of 65 years, serum concentrations of doxycycline are more and the volume of distribution is reduced, though the definite reason behind this variation is unknown.¹²¹

CONCLUSION

From the above discussion, it is now quite clear that certain genes play a major role in the pathogenesis and severity of COVID-19 and also, how an individual's genetic makeup metabolizes and processes present COVID-19 therapies vis a vis therapeutic outcome. Further genetic studies need to be conducted for future application and recommendation of pharmacogenomics in this pandemic. This type of individualisation of therapeutic strategies in COVID-19 shall further optimize the therapeutic outcome i.e. improves the safety and efficacy and decreases the adverse effects. As the feasibility and availability of rapid genetic testing (pre-emptive pharmacogenetic testing, point-of-care genetic testing) for proper and wider implementation of pharmacogenomics are a great challenge presently, in any situation the treatment of COVID-19 should be delayed or waited for genetic testing.

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