

Osteoarthritis, Corticosteroids and Role of CYP Genes in COVID-19 Patients: A Mini Review

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Abstract

Objectives of this review is to evaluate the role of cytochrome P450 gene polymorphisms in COVID-19 infected patients with pre-existing OA on corticosteroids. The purpose of this review is to analyze whether polymorphisms of Cytochrome p450 isoforms (CYP2C9 and CYP3A4) affect the dosage of steroids in OA patients in COVID-19 infected patients. This review may provide more therapeutic options; suggest a few guidelines which may be useful in managing COVID-19 patients with pre-existing osteoarthritis. The important role of corticosteroids in treating patients infected with COVID-19 with preexisting osteoarthritis, its influence on incidence of mortality or morbidity may be highlighted. The influence of CYP enzymes and their polymorphisms suggest safety of treatments as well as the possible need for the dosage adjustment or their discontinuation.

Keywords: COVID-19, Osteoarthritis, Corticosteroids, Cytochrome P450, Polymorphism

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INTRODUCTION

Osteoarthritis (OA) is one of the most common joint disorders which affect around 80% of individuals above 55 years of age. Age is an independent risk factor for the severe COVID-19 infection. OA patients often exhibit a large spectrum of coexisting co-morbid conditions like diabetes mellitus, cardiovascular disorders and inflammation, which may increase complications of COVID-19 patients. Various drugs used in treating COVID-19 infection, corticosteroids, opioids, NSAIDs, paracetamol etc. have a wide range of iatrogenic influence, which potentially increase the incidence of COVID-19 secondary infection or complications. In this study, the role of corticosteroids and the influence of genes that metabolize these drugs, used to manage OA on the course of COVID-19 infection will be reviewed. As the pandemic with COVID-19 infection continues over a period of time, the conservative management of osteoarthritis may need an adjustment so as to avoid exposure of the patients to added risk factors. The main goal of this review is to analyze whether polymorphisms of Cytochrome p450 isoforms affect the dosage of steroids in OA patients with COVID-19. It may provide more treatment options, with added guidance to the treatment protocol of OA during the pandemic of COVID-19. The susceptibility to the complications of COVID-19 which are life threatening and the greater incidence of morbidity or mortality due to the infection with COVID-19 may act as a guide to orthopaedic surgeons regarding the safe treatment modalities and also regarding the possible need for the dosage adjustment or discontinuation.

Pharmacogenetics is the branch of science that explains the influence of genetic variations on the drug metabolism, drug targets or pathways of the disease resulting in varying drug response in terms of its efficacy or adverse drug reaction. The concept of “personalized medicine” is the present trend and a paradigm shift has been observed from the previous concept of “one drug fits all” to “right drug for the right patient at the right dose and time”. By combining modern medicine with molecular advances, the personalized medicine (PM) could target patients individually and improve the effectiveness and efficacy of the therapeutic approach.¹ Personalized

medicine is effective because of the difference in the genetic composition of individuals. In the act of medication, PM has worked with hereditary based evaluation of viability, antagonistic drug reactions, and appropriate dose regimen.² PM translated from System Biology clarifies the mechanism based illness improvement, infection hazard assessment, preventive medication, personalized sickness, and therapy observing.³ The development of methods to detect minute changes in molecular profiles in the early stages of disease development is where systems biology is most beneficial in preventive PM. In terms of Systems Pharmacology, integration into PM aims to identify the genes and proteins involved in drug treatment and resistance, so that they can be targeted to improve treatment outcomes through a synergistic impact.⁴ Currently various drugs are used in the treatment of COVID-19, without well established efficacy or safety. The use of pharmacogenomics is worth noting potential limitations in the treatment of COVID-19.⁵

It is very essential to investigate the possible roles of gene polymorphisms that affect the pharmacokinetics and pharmacodynamics of steroids so as to get to know inter-individual variations.

Corticosteroids (CS), OA and COVID-19

Corticosteroids are potent anti-inflammatory drugs used in treating osteoarthritis.⁶ These drugs are administered systemically as well as intra-articularly in OA patients. Prednisolone is the most commonly used steroid administered systemically among others.⁷ A few other molecules like methylprednisolone, betamethasone triamcinolone, dexamethasone, triamcinolone are administered as intra-articular injections.⁸ Corticosteroids bring about both anti- inflammation and immunosuppressive, with complex mechanism of action.

Corticosteroids' physiological and pharmacological actions are mediated by their binding to the glucocorticoid receptor (GR).⁹ Upon ligand binding, the glucocorticoid receptor translocates to the nucleus of cells, where it binds to GC response elements (GREs) and controls the transcription of thousands of genes. The GREs are subdivided into 3 broad categories – i) simple- GR binds as homodimer, ii) composite – GR binds along with another transcriptional regulators,

iii) Tethering- GREs recruited through protein: protein interactions [eg:- Activator Protein1 (AP1) or nuclear factor- κ B (NF- κ B)]. GR can function as a monomer at composite and tethering GREs. Although GR can stimulate or repress transcription from all three types of GREs, it is thought that GR works as a transcriptional activator at a normal palindromic GRE, whereas recruitment to tethering sites often results in repression. The tethering (also known as transrepression) of AP1 and NF- κ B activity, believed to account for suppression of inflammatory and immunological responses which are GC-mediated.¹⁰ In fact, corticosteroid exposure alters leukocyte trafficking (into, through, and out of the stromal compartments of the bone marrow, thymus, and peripheral tissues), immune cell activation, proliferation, and apoptosis, as well as the creation and suppression of inflammatory mediators.¹¹ The anti-inflammatory and immunosuppressive effects are desirable, but the metabolic and toxic effects are not, as they are the origin of the negative outcomes.¹¹ In a positive feedback loop of pathogenic inflammation, if coordinated recruitment of innate and adaptive immunity fails to successfully manage the pathogen, more immune cells will be activated. This results in the release of additional cytokines. This condition is known as cytokine storm syndrome (CSS), and it has been linked to ARDS and multiple organ failure in extreme cases.¹²

In COVID-19 patients the expression of IL-1B, IFN- γ , IP-10, and monocyte chemoattractant protein 1 (MCP-1) were found to be high. These inflammatory cytokines may activate the T-helper type 1 (Th1) cell response.¹³ The activation of Th1 cells is a crucial step in the activation of specialised immunity.¹⁴ Elevated levels of Th2 cell-secreted cytokines (such as IL-4 and IL-10), inhibit the inflammatory response were also seen in patients with COVID-19. A positive correlation was seen between the severity of the disease and inflammatory markers like serum IL-2R and IL-6 in patients with COVID-19.¹⁵ Other studies have found that, compared to COVID-19 patients from general wards, patients in the intensive care unit (ICU) display increased serum levels of granulocyte colony-stimulating factor, IP-10, MCP-1, macrophage inflammatory protein-1A, and TNF- α . A strong positive correlation was suggested between the cytokine storm and the severity of the

disease.¹³ In COVID-19, the inflammatory cytokine storm is closely related to the development and progression of ARDS and multiple organ failure.

Timely administration of glucocorticoids inhibits inflammation in case of cytokine storm in the initial phases.¹⁶ It also effectively prevents ARDS and safeguards patients' organ functions. For patients who are severely ill, with oxygenation indicators being in declining mode, with a fast imaging progress, and excessive inflammatory response, the short term (3–5 days) use of glucocorticoids may be appropriate. Administration of methylprednisolone at a dose of 1–2 mg/kg/day would be the most recommended.¹⁷ However a large dose of steroids may cause immunosuppression and thereby delay the SARS-CoV-2 clearance.

They act by inhibiting inflammatory cells, metalloproteases and metalloprotease activators. They also inhibit the pro-inflammatory factors by inhibiting their synthesis and secretion.¹⁸ These agents when used on long term basis, orally or parenterally, have been reported to be associated with adverse events like diabetes mellitus, osteoporosis, superinfection, CVD and immunosuppression.¹⁹ Adverse events are less likely with intra-articular administration, probably because of decreasing cortisol levels in blood within a few hours which returns to the baseline within 1-4 weeks. Intra-articular corticosteroids administration reduces inflammatory markers like CRP and ESR that lasts for a few months. It also results in a rise in plasma glucose in osteoarthritis cases with pre-existing diabetes.²⁰

A registered review in Cochrane analyzed published studies that evaluated systemic corticosteroid treatment for community acquired pneumonia, administered along with antibiotics, as compared to placebo or those without corticosteroids.²¹ The combined treatment declined the rates of mortality as well as morbidity in severe pneumonia cases. Decreased morbidity was noted in adults and children, but not mortality with pneumonia. Hyperglycaemia was the adverse effect reported in agreement with another review that included the clinical trials on pneumonia cases.²²

The situation regarding viral infections of the respiratory tract and effect of corticosteroids on complications and adverse events is inconclusive.

Severe acute respiratory syndrome (SARS)-CoV outbreaks of 2002 were widely treated with corticosteroids²³ and Middle East respiratory syndrome (MERS)-CoV of 2012 as well.²⁴ A randomized control trial reported that, the SARS-CoV RNA in plasma in cases on ribavirin who were treated with hydrocortisone therapy was higher compared to placebo.²⁵ Corticosteroid treatment leads to a delay in MERS coronavirus RNA clearance from the respiratory tract secretions as reported in MERS study.²⁴ A meta-analysis covering a large population of influenza pneumonia patients, corticosteroids were reported to be associated with higher mortality and a greater rate of secondary infection.²⁶ Patients with RSV infection, on steroid therapy were reported to have an impaired antibody response; however no significant differences were noted in viral load peak.²⁷ Contradictory reports are also available that support the utility of corticosteroids at a low to moderate dosage in SARS infected cases. Corticosteroids were reported to contribute to lower mortality and shorten hospital stay, in a retrospective study.²⁸ Pneumonia due to influenza a infection, corticosteroid administration in low to moderate dose were reported to reduce 30-day mortality in a prospective cohort study.²⁹ Guidelines from the American Thoracic Society and the Infectious Diseases Society of America advises added corticosteroid therapy only if there are other indications in patients with pneumonia or influenza pneumonia.³⁰

Until today, no anti-COVID-19 medicines have been approved by the WHO. Remdesivir, an RNA polymerase inhibitor and experimental C-adenosine nucleoside prodrug, is one of the few medications used to treat COVID-19 that has had some success.³¹ It has been established in multiple clinical trials to be a relatively safe medicine with linear pharmacokinetics.³¹ Another RNA polymerase inhibitor that has been tested on COVID-19 patients is favipiravir. Due to the non-CYP metabolic route of favipiravir, pathophysiological variables in COVID-19 patients are unlikely to have a major impact on favipiravir disposition.³²

The combination of lopinavir and ritonavir, which was licenced for the treatment of HIV, has been tested for protease inhibition against other coronaviruses, including SARS-CoV-2 in vitro and in COVID-19 patients. Some studies

have found efficacy (e.g., length of ICU stay, viral load clearance), whereas others have found no difference in COVID patients when compared to the comparator.³³

Chloroquine reduces the generation and release of TNF and IL-6, suggesting that it may reduce the cytokine storm in COVID-19 infected patients.³⁴ Another repurposed medicine for COVID-19, hydroxychloroquine, has been found to be less hazardous than chloroquine for inhibiting SARS-CoV-2 infection in vitro. By limiting T-cell stimulation and thus decreasing cytokine production, hydroxychloroquine can diminish the inflammatory response and cytokine storm (aggressive inflammatory response with the release of a significant amount of pro-inflammatory cytokines) in individuals severely infected with SARS-CoV-2. It can also prevent pro-inflammatory genes from being expressed by disrupting the interaction between DNA/RNA and toll-like receptors.^{35,36}

According to the initial report on COVID-19 infected patients receiving corticosteroids reported no association between the therapy and time taken for clearing viremia, hospital length of stay, or duration of symptoms.³⁷ However no clinical data is available that suggest the overall beneficial or detrimental role of corticosteroids in COVID-19 patients. Some light on future research prospects and indications for the use of corticosteroids for the treatment of COVID-19 has to be thrown. Indication of the drug might be due to its immunosuppressive and anti-inflammatory actions. There are no clear indications, however WHO guidelines suggests to avoid routine corticosteroid administration unless the usage is indicated in COVID-19 infection.^{38,39} Patients with osteoarthritis already treated with systemic corticosteroids, there is a lack of guidelines that suggest the discontinuation of steroids in COVID 19 patients.⁴⁰

Possible Role of involvement of CYP2C9 and CYP3A4 Genes in drug metabolism

The Cytochrome P450 system consists of a set of enzymes involved in drug metabolism having an active role in the phase I reactions. Enzymes of cytochrome p450 are mainly expressed in the hepatic tissue; however, they are also expressed in other tissues, like kidneys, skin, intestine, lung, and brain.⁴¹ The enzyme CYP3A4 is responsible for the metabolism of 50% of medications. The remaining

35-40% of the metabolism occurs through other variants of cytochrome P450.

CYP3A4 is a constitutively expressed variant of CYP system expressed in hepatic tissue.⁴² Substrates for the cytochrome P450 enzymes can be either endogenous like lipid derivatives and retinoids or exogenous like chemicals, drugs or plant products. The members of cytochrome p450 metabolize more than 80% of the commonly prescribed medications.

Enzymes of cytochrome p450 that are expressed in hepatic tissues are found to be polymorphic. Commonly observed polymorphisms were that of CYP2C9, CYP2C19, and CYP2D6.⁴³ CYP gene mutations lead to under expressed, abolished or over expressed CYP protein products which leads to altered drug metabolism by a specific enzyme. This may lead to a potential adverse drug reaction in the host. Adverse reactions of drugs are a great burden, estimated cost being more than \$100 billion annually and it may be responsible for around 100,000 deaths per year in USA.⁴³

Health data available from COVID-19 patients have suggested an elevation of liver transaminases (AST, ALT). The data also suggests a severe hepatic stress during COVID-19 infection.⁴⁴⁻⁴⁶ Elevated cytokine levels suppress the expression of CYP, thereby interfering with the drug metabolisms, resulting in decreased drug elimination. Drug toxicity effects can be observed locally as well as systemically within 48-72 hours of active viral infection. CYP enzymes like CYP3A4, CYP2B6, and CYP2C9 are downregulated during cytokine storm of COVID-19. Cytokines are responsible for the altered hepatic CYP expression.⁴⁷ Regulation of CYP enzymes may vary, either a single cytokine may influence the expression of multiple enzymes or multiple cytokines may alter the single enzyme expression.

Corticosteroids are another group of medications that have emerged as a treatment option for COVID-19. The association of glucocorticoids (GC) and the enzymes of Cytochrome P450 family is complex. GCs are metabolized partially by CYP3A enzymes. Hence co-administration of CYP inhibitors with steroids causes over suppression of hypothalamus pituitary adrenal axis and enhances the effects of exogenous GCs.⁴⁸ Contrary to these, GCs also induce the enzymes of cytochrome P450. In vitro

experiments on mammalian cell lines are available that evaluated the association between GCs and CYP and in vivo studies performed in rodents, focused on CYP2C11.⁴⁹ A significant risk reduction was observed in patients requiring oxygen supplementation or those on ventilators with the administration of steroids compared to usual care group in the RECOVERY trial.⁵⁰ Dexamethasone acts both as an inducer as well as a substrate for the CYP3A4 enzyme.^{51,52} Hyperglycemia and fluid retention may be the major adverse effects of reduced dexamethasone metabolism.⁵³

Future Research Perspectives

A study may be designed that evaluates the pattern of CYP3A4 and CYP2C9 polymorphism in patients with COVID-19 infection with pre-existing OA on corticosteroids.

Drug effectiveness and toxicity are mainly determined by the genetic background of the individuals.⁵⁴ Studying the genetic composition as well as polymorphisms/mutations plays a crucial role as these can influence the expression patterns of CYP enzymes which in turn influence the drug responsiveness. This emphasizes the role of personalized medicine and opens up a new era in its practice. If there is an association between clinical effectiveness of corticosteroids in reducing inflammation and hence the pain management of OA patients diagnosed as COVID-19, with respect to CYP3A4 and CYP2C9 polymorphism patterns, it may be of great value in personalizing the treatment.

Significance of such study and Impact on society

The study may be able to find the association between mutations of CYP gene polymorphisms on steroid metabolism and its influence on the perception of pain in COVID-19 patients already on steroids with pre-existing OA. This may emphasise the role of CYP gene polymorphism in predisposing OA patients to an added risk of COVID-19. The study may acknowledge the important public health message of careful monitoring of OA patients on steroids with COVID-19. The study emphasises on the pain management by focusing on the polymorphisms of cytochrome p 450 at the genetic level and their association with the steroid metabolism. Anti-inflammatory role of corticosteroids and effectiveness in pain management is determined by the polymorphisms of CYP450. The question

whether these polymorphisms and their association with steroid metabolism, predispose OA patients to COVID-19 infection will be explored. Additionally, because of the paucity of data and lack of well-designed studies that answer the questions on the efficacy, safety and role of corticosteroids in OA and its association with COVID-19, our study may provide a permanent solution by providing treatment option to COVID-19 patients with OA at genetic level.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

UA drafted the manuscript, compiled information from the literature. VBS carried out literature search. SA supervised and reviewed the manuscript.

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None.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

Not applicable.

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