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Challenges posed by anti-inflammatory drugs in COVID-19 treatment

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Abstract---COVID-19 pandemic is the major outbreak that has exterminated many lives for past years and still not subsided completely. A number of vaccinations are in trials to eradicate the COVID-19 virus. This study deals with the challenges posed by anti-inflammatory drugs in the treatment of COVID-19. NSAID'S can mask early symptoms such as fever, myalgia in COVID-19 infected patients and can be used as adjunct therapy in severe COVID-19 treatment as they have anti-viral and anti-inflammatory properties. The risk of infection was found to be declined in the patients who had prior

aspirin exposure. Indomethacin must be used with caution as it exhibits coronary vasoconstriction effects in patients. Anakinra even at higher doses resulted quite safe in COVID-19, confirming its potential role in selected conditions like immune compromised patients with superinfection, contraindications to other anti-inflammatory drugs. Early management with tocilizumab prevents cytokine storm and mortality. Patients who received Hydroxychloroquine with azithromycin combination had frequent cardiac arrest. No reasons to pause NSAIDs and no evidence of mortality rate dissimilarity between ibuprofen and paracetamol in COVID-19. still paracetamol remains first line. WHO guidelines recommend to avoid corticosteroids in COVID-19 management. Thus, NSAIDs are beneficial in COVID-19 treatment. Physicians must rigorously monitor the patients for the effective therapeutic outcome.

Keywords---adjunct therapy, indomethacin, anakinra, tocilizumab, cardiac arrest.

Introduction

Wuhan, the capital city of Hubei province-chinafaced the major novel coronavirus (SARS-COV-2) outbreak on December 2019 which caused a severe acute respiratory syndrome and had affected among half of the countries in the world in less than 6 months of period reporting numerous coronavirus infected cases. The infected patients suffered from acute respiratory syndrome for about 7-10 days as the lower respiratory tract was the primary target for the corona virus. The incubation period is about 2-14 days and still standard treatments are not found, drugs like antibiotics,anti -inflammatory are used more in COVID-19 treatment [1]. The pathogenesis of the coronavirus in human is not clearly understood but a better knowledge would help in the improvement in the treatment and control of the pandemic[2].

The seasonal allergic rhinitis (SAR) has few alikephenotypes to COVID-19. According to World Health Organisation (WHO) COVID-19 infected patients experience runny nose, nasal congestion, aches, painanddiarrhoea. Mild infected patients who have signs similar to cold usually recover without any treatment [3]. Fever,non-productive cough, anosmia,ageusia,dysosmia, headache, fatigue, rihinorrhea, pharyngitis, pneumonia are the most common clinical manifestations experienced by the COVID -19 infected patients. According to National and International guidelines the primary way of controlling the spread was to find out fever [4]. people at any age may develop progressive and severe disease but it may be an independent risk in presence of comorbidities. The signs may vary among viral pneumonia, progressionillness,pneumonitis, Adult respiratory distress syndrome and may even be asymptomatic at initial stages if the COVID -19 infections [5]. In April 2020, the first report on COVID-19 patient was treated with corticosteroid after infection was released [6].About 20% severe disease and 4% fatality had been reported in china [7]

Acute pain is short time, heals and eradicate infection whereas chronic pain last for longer duration and are associated with pathological conditions. optimal effects of anti-inflammatory drugs may be experienced in week or months. Thus, treating COVID-19 infected patients appropriately may provide better therapeutic outcome [8]. Complication are linked to cytokine storm that causes acute respiratory distress syndrome, multi organ failure and death, rheumatoid arthritis is known to be susceptible to infections but studies shows that there are not more prone to COVID -19 but has higher complication [9]. Chronic pain is considered to be non-urgent during this pandemic, outpatients and interventional procedure are interrupted in order to reduce the spread of the COVID infection [10]. Chronic pain with COVID infection has no specific common treatments but anti-inflammatory and corticosteroids are used most [11]. Coronavirus and influenza in ICU patient are more prone to chance of superinfections especially pulmonary aspergillusco-infection [12]

Pathophysiology of COVID-19

The corona virus (SARS-COV-2) enters via respiratory tract and infect cells by using angiotensin converting enzyme and begins to multiply and replicate by ribosomes or endoplasmic reticulum where RNA proteolysis leads polypeptides, non-structural proteins, RNA DEPENDENT RNA polymerase, multiplied viral particles infect other cells through exocytosis. Innate and adaptive defence mechanism initiates host immune system where macrophages, dendritic cells, NK cells play a main role and T-cell preserves memory for future attacks and cytokines tries to eliminate viral infection. COVID-19 mainly targets lymphocytes. Type-2 cytokines (IL-4, IL-5, IL-6, IL-10, IL-13), T and B cells defect causes unruly viral replication, enhanced inflammatory response and leads to cytokine storm which further leads to multiple organ dysfunction [13]. A healthy immune response is essential to eliminate infected cells and prevent spread of the virus [14]

Pathogenesis of pain in COVID-19 infected patient

More than one third of COVID-19 patients experienced CNS symptoms like dizziness, epilepsy, ataxia, headache and PNS symptoms like dysgeusia, neuralgia, dysosmia and neurological symptoms agitation, ischaemic stroke which remains of unclear characteristics and may lead to severe infection. Decreased function of ACE-2 in the human dorsal spinal cord which results in Angiotensin-2 accumulation and decrease Angiotensin 1-7 may be the cause of pain induction in COVID-19 patients but needs further investigation. upregulation of IL-16 leads to muscle pain in COVID -19 patients even in viral infection which believed to reflect generalized cytokine response and inflammation. SARS -COV-2 induce elevated cytokine levels (IL-6, IL-10, TNF - α), strong inflammatory response in moderate to severe disease. Inflammatory ligands initiates inflammasomes which are involved in pro inflammatory cytokine production. Depending on many factors, microglial cells might promote either toxic neuroinflammation or regression. Analgesic and inflammasomes role are unclear [15].

Various categories of drugs and its potential role in the treatment of COVID-19 infection

NSAIDs include nonselective cyclooxygenase (COX) inhibitors (such as aspirin (acetylsalicylate), ibuprofen, diclofenac, and naproxen), as well as selective COX2 inhibitors (such as celecoxib, rofecoxib, etoricoxib, lumiracoxib, rofecoxib, etoricoxib, valecoxib) [16]. NSAIDs such as Aspirin, Ibuprofen, Celecoxib, Indomethacin is used to manage Acute/Chronic [cancer] pain. Acetaminophen is most preferred for fever and algia during illness [17]. NICE's recommendation on 3 April recommended that paracetamol should be used over NSAIDs for managing fever in patients with suspected COVID-19 until more evidence is available [18]. People on low dose aspirin for secondary prevention of cardiovascular disease should pursue their treatment. Aspirin exerts its anti-inflammatory effects only at much higher doses (eg, 1-4 g per day) [19]. The study of Aspirin resulted that, prior exposure to Aspirin decreases the risk of developing infection. The main adverse effects of NSAID'S are CV, GI, Renal, complications. They are commonly used by COVID-19 patients for symptomatic relief and its usage in this disease is controversial. there is no proper evidence to comment that NSAID's can progress a disease severity. NSAID's can cause prolonged illness in respiratory tract infected patients which can increase the risk of bacterial superinfection and hypercoagulation which results in thrombosis. NSAID's may inhibit immune reactions against the virus enhances the pro-inflammatory cytokine storm in lungs of COVID-19 patients through activation of inflammatory macrophages. If NSAID's synergise with SARS-COV-2, it enhances the chance of severe intestinal damage [20]. No evidence of a harmful effect of routinely prescribed NSAIDs on COVID-19 related deaths [21] the recommendation for people already on regular NSAIDs for other indications, is to continue them, unless there is an alternative indication to cease [22].

The data revealed that, osteoarthritis patients on current NSAIDs prescription were collated to patient with current prescription of co-comadol /co-dydramol there is no susceptibility increase in COVID-19 [23]. Evaluating NSAIDs in management of COVID-19, A clinical trial was found prescribing antiviral therapy which was not mentioned in NSAID prescription [24]. NSAIDs may mask early symptoms such as fever and myalgia in COVID-19 infected patients and can be used as adjunct therapy in severe COVID-19 treatment as they have antiviral and anti-inflammatory properties but further clinical trials are needed to do to work them as adjunct therapy [25]. They are discontinued in ICU admitted COVID infected patient with rheumatoid arthritis [26]. physicians should rigorously screen for COVID-19 symptoms and inform patients before prescribing any medication [27] chronic use of NSAIDs was not associated with COVID-19. Chronic use of NSAIDs might even be protective against both the occurrence and the severity of COVID-19 [28]. NSAID use might confer a modest benefit with regard to survival [29]

Prescription of Ibuprofen and Naproxen in individuals who tested positive for COVID-19 can reduce the Hospitalization. Individuals pre-medicated with Naproxen do not required mechanical Ventilation during Hospitalization. Ibuprofen in pericarditis may upregulate ACE-2 and SARS-COV-2 bind to the target cells by binding to ACE-2, which may facilitate the infection. The use of

NSAID's may worsen the existing infection [30]. Ibuprofen is currently proven beneficial based on the pathogenesis of COVID-19 especially in early COVID-19 management, disease progression or even may reverse lymphocytopenia [2]. ibuprofen exacerbated four COVID-19 patient condition. NSAIDs must be used with caution in treating COVID-19 infected patient as present study reveals ibuprofen exacerbated four COVID-19 patient condition. Naproxen works by inhibiting nucleoprotein binding to RNA and virus replication, needs further evaluation regarding naproxen safety and efficacy as it may be a good option [24]. The Randomised clinical trials performed for naproxen showed decreased mortality and hospitalization for patients [31]. Study reveals no clear evidence of difference in mortality rates and therapeutic outcome between ibuprofen and paracetamol [32].

Indomethacin has potent Anti-viral activity against SARS-COV-2 infected patients. In sustained release formulation of Indomethacin (75mg BID), achieve a complex response in 3 days for treatment in patients infected by SARS-COV-2. NSAID's and Indomethacin leads to Nephrotoxicity. Therefore, it's usage is not recommended in severe complicated SARS-COV-2 infection with deficiencies in renal function/ GI risk factors. Indomethacin exhibits Coronary- vasoconstrictor effects, this suggests that caution is required for using this drug in Coronary artery disease [20]. An inexpensive anti-inflammatory drug more potent than aspirin. COX inhibition of indomethacin could lower IL6 levels in nasopharyngeal respiratory tract secretion. Adverse effects include renal dysfunction, gastritis, platelet dysfunction which may be detrimental in severe COVID-19 infected patients especially with multi-organ dysfunction co-morbidity resulting in cytokine storm but low doses of Indomethacin (25mg thrice a day) for adequate organ function inpatients has no evidence of cytokine storm but when along with H2 blockers like gastro protective agents may be prudent and lower TNF and IL-6 like inflammatory mediators [33]. Celecoxib, present the progression of disease. High dose of celecoxib (0.2g BID) was not associated with a risk of Myocardial Infraction, whereas in low doses can increase the risk the Myocardial Infraction (0.2g OD). Thus, NSAID's are beneficial in controlling the development of COVID-19[20].

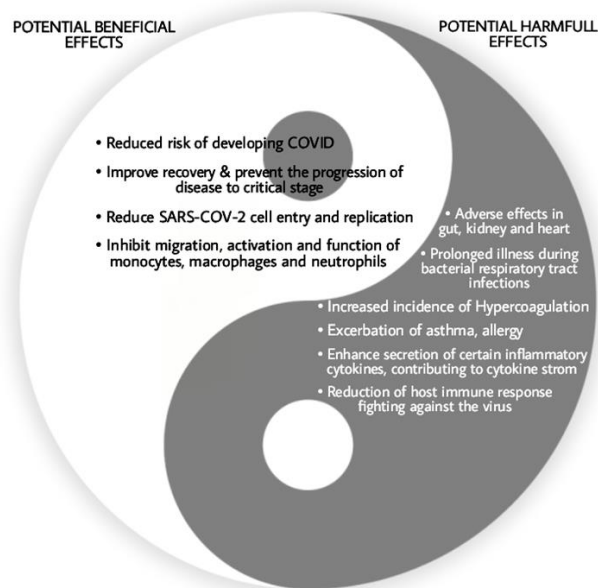


Figure 1. Yin and Yang of NSAIDs in COVID-19: potential effects [20]

NSAID's have shorter duration of action; therefore, it is used only in minimal lowest dose when compared to corticosteroids. Several studies say that Anti-inflammatory [IL-6, IL-1] can benefit patients stricken with COVID-19. Corticosteroids (glucocorticoids) can cause Immune suppression in host and their usage is advocated in the treatment of SARS-COV-2. When steroidal injection is given locoregionally (affected tissue), there is still systemic reuptake of medication, when particular steroids is given as a short epidural injection, it significantly decreases the morning levels of Corticosteroids this states that steroidal injection cause short term Adrenal suppression. These drugs significantly delay COVID-19 presentation and reduce immune response to the virus. The potential harm of steroidal injection in individuals who might be incubating later develop COVID-19. Use of Non-particulate steroids (Dexamethasone) in COVID-19 patients, shown reduced mortality among those receiving invasive mechanical ventilation or oxygen [30]. Use of corticosteroids is effective in reducing Immunopathological damage in early Acute phase of infection.

Currently these drugs are used in advanced cases of complicated COVID-19 pneumonia, according to its response Corticosteroids are prescribed in right dose at right time for appropriate patients. Corticosteroids are used in patients with pericardial disease and advanced COVID-19 infection when the host inflammatory response is predominant and harmful. Must monitor Hyperglycaemia, Hyponatraemia, Hypokalaemia whenever Corticosteroids are prescribed. In case on contraindication to NSAID's, corticosteroids are prescribed. Example: Prednisolone: 0.2-0.5mg/day are indicated in low/moderate doses as a second line option with colchicine. Whenever, corticosteroids, Anakinra is prescribed a careful monitoring of possible superinfection is warranted. Although there is a warning on the use of NSAID's in the setting of COVID-19 infection, which require

additional investigation. When corticosteroids, Anakinra is prescribed, possibilities of superinfection are monitored closely [34]. N-protein of SARS COVID-19 is responsible for triggering pulmonary inflammatory response and acute lung injury which resulted in pro-inflammatory cytokine imbalance which was successfully alleviated by dexamethasone [35]. Steroids, selective cytokine blockade (Anakinra, tocilizumab) and JAK inhibitors are currently recommended. Methyl Prednisolone in COVID-19 patients along with pulmonary critical care patients shows lower mortality rates [36]. The use of corticosteroids in COVID-19 infection is highly controversial. The study's results in two ways;

- The use of corticosteroids results in higher mortality, longer length of stay, hypokalaemia and superinfections.
- Its usage results in delay in virus clearing, not improving the survival, hospital duration
- Indeed, corticosteroids can prevent the cytokine storm by decreasing inflammatory response and limits the lung damage progression [37].

Coronavirus replication may be suppressed with some corticosteroids (ciclesonide and mometasone), inhaled corticosteroids may protect against pain during virally induced asthma exacerbation [3] but are mostly discontinued in COVID infected patients with inflammatory bowel disease [38]. Methyl prednisolone + Dexamethasone: shows lower mortality rates, shortens ICU stays in patients receiving respiratory support. Young patients who is receiving Glucocorticoids, along with chemotherapy, have not developed severe COVID-19 complications. Glucocorticoids had no beneficial effects in the treatment of COVID-19 infection, because it increases the length of ICU stay, has higher mortality but may reduce pain, seriousness impact during late phase of COVID infection [39].

Chronic opioid therapy may cause Immune suppression and heterogenous effects with unlike opioids this can affect the patients negatively by increasing the risk of infection/ decreasing the ability of immune response in patients. For these reasons, opioid therapy is used only after an adequate trial with opioid with minimal immunosuppressive effects and minimal side effects are prescribed at starting dose and titrated according to its efficacy and side effects, if possible [30]. Opioids are known to cause serious adverse effects like immune suppression and so morphine and fentanyl, but when opioids act on hypothalamic pituitary adrenal axis and ANS system provides beneficial effects [40].

NSAIDs is the main drug of choice for Acute and Recurrent pericarditis along with colchicine. If NSAID's are necessary to control Acute pericarditis and to treat systemic symptoms of COVID-19 infection, their use is limited. So far there is No clear evidence for use of NSAID's in COVID-19 patients. Colchicine is a Microtubule-disrupting agent, they interfere with the Inflammasome and mitigate the inflammatory process. It's works by mediating its Anti-inflammatory effects by inhibiting tubulin polymerization, so that it is used in the treatment of tissue inflammation and fibrosis. It also has an Anti-viral property against various Respiratory virus and disrupts genome replication and reduces need of ventilation. use of colchicine in COVID-19 patients along with pericarditis is not contraindicated [33]. Colchicine controls Innate immunity dysregulation and Cytokine release syndrome in COVID-19 patients. It is used as an adjunctive

therapy because of its potential inhibitor effect on cytokine release, particularly on IL-1, IL-6 by interfering with NLRP3 inflammasome. It has broad Anti-inflammatory and anti-viral properties. The beneficial effects of this drug, rapid decreases of plasmatic IL-6 levels, thus it confirms its potential role in patients with signs of systemic inflammation before entering into the critical stage of the disease. The study finally evaluated that colchicine can reduce the rate of progression of disease to critical stage [36].

Anakinra is an IL-1 antagonist, in advanced COVID-19 condition, there is a cytokine storm syndrome, this is due to overproduction of IL-1. Anakinra is considered in these conditions which reduces Hyperinflammation Respiratory distress in COVID-19 patients. Anakinra use in COVID-19 condition is not contraindicated and might become soon a new standard of treatment for advanced cases [33]. Anakinra is an IL-1 antagonist, in advanced COVID-19 condition, there is a cytokine storm syndrome, this is due to overproduction of IL-1. Anakinra even at high dosages resulted quite safe in COVID-19, confirming its potential role in selected conditions (compromised patients with superinfection / contraindications to other Anti-rheumatic drugs).

In COVID-19 patients, Tocilizumab is found to be effective, because it improves the respiratory parameters, rapid suppression of subsequent fever, and also normalizes the inflammatory biomarkers (CRP, D-dimer, LDH) in some cases, pulmonary improvement was also documented. Early administration of tocilizumab helps in preventing cytokine storm and also reduces mortality. Ongoing clinical trials, give you the data regarding Safety, Efficacy, correct timing of administration of the Tocilizumab, in future [36]. Tocilizumab is a Humanised Anti-IL-6 receptor monoclonal antibody, is administered in IV in treatment of COVID-19 disease, because it suppresses IL-6 signal, restore T-cell count in patients. Sarilumab is an Anti-IL-6 receptor monoclonal antibody, which is given in COVID-19 patients to reduce pulmonary inflammation and prevent respiratory distress [41]. Tocilizumab works by blocking IL 6 signalling and inflammatory response [26]. it may accumulate in lysosome and raise PH level of endosome which may interfere with virus entry, exit from host cells which in turn in interfere in ACE-2 receptors where SARS-COV-2 binds [42].

JAK inhibitors (Baricitnib, tofacitinib) inhibits the virus entry into lungs, but shows adverse effect like leukopenia so must be used with caution[4p]. they mainly target JAK STAT signalling [43]. JAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis [44]. Hesperidin, an herbal medication which poses anti-inflammatory and anti-oxidant properties. This blocks the coronavirus from entering host cell through ACE2 receptors which can prevent infection and may improve host cellular immunity against infection [45]. The viral load in patients is reduced by Hydroxychloroquine which is reinforced by combination with Azithromycin [35]. Study reveals that Hydroxychloroquine may reduce mortality rates [46]. Cardiac arrest was more frequent in patients who received combined therapy of Hydroxychloroquine and Azithromycin, which concerns about the drug safety in these patients. Therefore, there is still a lack of clinical evidence to support its therapeutic use because of its significant side effects [36]. Chloroquine phosphate is widely used in treating a patient with SARS-COV-2 infection, because it shortens a disease course [40]. Chloroquine and

Hydroxychloroquine induced Cardiomyopathy, QTC interval prolongation which is synergic with Azithromycin and possibility of cardiac arrhythmias is widely reported. Hydroxychloroquine is considered to be safe and effective than chloroquine which produce more toxic effects ^[47]. Antiviral agents such as Ribavirin, Lopinavir, Ritonavir, Remdesivir which also exert some Anti-inflammatory properties acts by suppressing the virus absorption in cell ^[48]. Study reveals it has shortened the time of recovery of adult patients ^[49]. Favipiravir is an anti-viral agent that selectively and potently inhibits the ribonucleic acid (RNA) dependent RNA polymerase of RNA viruses and is thought to be an effective drug for severe acute respiratory syndrome coronavirus 2^[50].

Some combination of drugs categories and their outcome in treatment of COVID-19

- Anti-Malarial (CQ+HCQ) + Anti-inflammatory drugs (Glucocorticoids, IL-6 Antagonist, JAK inhibitors) = Has improved the clinical outcome.
- Azithromycin + hydroxychloroquine (× 6days) = Has efficacy to eradicate the virus.
- Hydroxychloroquine+ Chloroquine = Hydroxychloroquine is safe against COVID-19 infection.
- Janus kinase-2 inhibitors (fedratinib): This drug is beneficial in reducing cytokine storm associated with COVID-19^[45]

These drugs have either direct or indirect anti-inflammatory actions and may either have activation or inhibition of ACE2 receptors ^[8].

Conclusion

The presence of pandemic does not alter baseline risks of NSAID's use, which should be avoided. Although there is a warning on the use of NSAID's in the setting of COVID-19 infection, which require additional investigation. so, it is used with caution when treating a patient with renal or cardiovascular disease or advanced age. Thus, there is no reason to remove NSAID's as an option for treating appropriate patients in pain, if they are without possible or confirmed COVID-19 symptoms. Ibuprofen was found to be safe, there is no evidence of high mortality rates between paracetamol and Ibuprofen but paracetamol still remains first line therapy. Any therapy that influence COVID-19 course must be discussed with physicians in treating diseases. Currently, WHO guidelines do not recommend corticosteroids use in COVID-19 infected patients but justified for concurrent conditions such as sepsis, COPD, asthma. when corticosteroid and anakinra is prescribed, possibilities of superinfection is monitored closely. In this pandemic, on daily basis clinicians decide the first line pharmacological therapy, whether or not to discontinue existing therapy, efficacious alternative when previous approach fails. Although SARS-COV-2 infection may be asymptomatic or cause, immunologic complication may occur in some cases. Once immunologic complications like MAS/HCH occur, anti-viral treatment alone is not enough and should be continued with anti-inflammatory treatment. This review clearly demonstrates that the available data is not clear to comment on any drug and its controversies in the treatment of COVID-19 infections

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