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REVIEW

Concomitant use of dexamethasone and tetracyclines: a potential therapeutic option for the management of severe COVID-19 infection?

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ABSTRACT

Introduction: The global coronavirus disease-2019 (COVID-19) pandemic has posed a critical challenge to the research community as well as to the healthcare systems. Severe COVID-19 patients are at a higher risk of developing serious complications and mortality. There is a dire need for safe and effective pharmacotherapy for addressing unmet needs of these patients. Concomitant use of dexamethasone and tetracyclines, by virtue of their immunomodulatory and other relevant pharmacological properties, offers a potential strategy for synergy aimed at improving clinical outcomes.

Areas covered: Here we review the potential benefits of combining dexamethasone and tetracyclines (minocycline or doxycycline) for the management of severe COVID-19 patients. We have critically examined the evidence obtained from in silico, experimental, and clinical research. We have also discussed the plausible mechanisms, advantages, and drawbacks of this proposed combination therapy for managing severe COVID-19.

Expert opinion: The concomitant use of dexamethasone and one of the tetracyclines among severe COVID-19 patients offers several advantages in terms of additive immunomodulatory effects, cost-effectiveness, wide-availability, and well-known pharmacological properties including adverse-effect profile and contraindications. There is an urgent need to facilitate pilot studies followed by well-designed and adequately-powered multicentric clinical trials to generate conclusive evidence related to utility of this approach.

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1. Introduction

The coronavirus disease-2019 (COVID-19) pandemic has emerged as a serious public health threat and has resulted in more than 93 million confirmed cases and over 2 million deaths, globally [1]. Although the majority of the patients present with mild or asymptomatic infection, about 20% of the patients with COVID-19 progress to a severe form of the disease [2]. Once the virus reaches alveoli, it affects the epithelial cells and alveolar type II cells or pneumocytes which are responsible for the secretion of surfactant [3,4]. Virus propagates within pneumocytes and this results in increase in viral load leading to apoptosis of pneumocytes [5]. Both severe acute respiratory syndrome (SARS) and COVID-19 infections present with diffuse alveolar damage with fibrin-rich hyaline membranes leading to acute respiratory distress syndrome (ARDS) [5–8]. Another serious complication which can be observed at this stage is the abnormal wound healing that causes scarring and fibrosis [5,6,9]. The pulmonary pathology in patients with severe disease demonstrates distinct vascular features including severe endothelial injury associated with intracellular coronavirus and cell membrane disruption. Histopathology of pulmonary vasculature shows widespread alveolar capillary microthrombi [10–12]. Disruption of renin angiotensin system (RAS) has been postulated to be involved in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-related cardiac and lung damage. Viral entry has been linked to downregulation of angiotensin converting enzyme-2 (ACE-2) expression leading to increased levels of angiotensin II and reduced angiotensin 1–7 levels further leading to imbalances in other RAS components affecting both circulating and tissue expression of mediators. Decrease in ACE-2 expression has been linked to reduced lung function and increased fibrosis and tissue inflammation [13,14].

SARS-CoV-2 is an RNA virus that triggers the release of interferons (IFN) and pro-inflammatory cytokines including interleukins and tumor necrosis factor-alpha (TNF- α) among others [8,9,15,16]. The above natural antiviral responses result in upregulation of nuclear factor-κB (NF-κB), which is known to modulate the transcription of several pro-inflammatory cytokines such as (IL-1α, IL-1β, IL-2, IL-3, IL-5, IL-6, -IL8, IL-12, TNF-α and IFN- γ) [15,16]. Release of large amount of pro-inflammatory cytokines, a phenomenon termed as 'cytokine storm', worsens the disease status and is linked to high mortality as well as morbidity including need for intensive care, and

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Article highlights

- Severe COVID-19 infections pose a significant challenge to the worldwide healthcare systems owing to their high morbidity and mortality.
- Here we review the potential of concomitant use of dexamethasone and one of the tetracyclines (minocycline or doxycycline) for treating patients with severe COVID-19 infection based on the evidence available from experimental–in silico, in vitro, and clinical studies.
- Both dexamethasone and tetracyclines have potent immunomodulatory effects and other favorable pharmacological actions which can address the pathogenic pathways and mediators involved in severe COVID-19 infection.
- Both these agents complement each other on account of their pharmacological properties, cost-effectiveness, and well-known adverse effect profile.
- Based on the potential advantages of concomitant use of dexamethasone and tetracyclines for the management of severe COVID-19 infection, we urge academic institutions, public and private healthcare organizations and funders to facilitate well-designed clinical studies in order to generate conclusive evidence to support or refute the utility of this approach.

mechanical ventilation support among COVID-19 patients [17,18].

The matrix metalloproteinases proteins (MMPs), particularly MMP-2 and MMP-9, have been found to be associated with extensive lung damage caused by the degradation of the alveolar basement membrane [19]. Both activated macrophages and neutrophils are involved in the synthesis of MMP-2 and MMP-9, resulting in acute lung injury (ALI) [19]. Previously, it was observed that patients with SARS-CoV-1 presented with extensive macrophage infiltration [20,21]. Similarly, SARS-CoV-2 has also been associated with activation of MMPs, among patients with respiratory failure [22,23].

Therefore, we need effective therapeutic approaches which can address the above pathogenic mechanisms and reduce the mortality and need for intensive care and mechanical ventilation. Recently, glucocorticoids (GCs) (particularly dexamethasone) have attracted a lot of attention because of their potential benefits in the treatment of severe COVID-19 patients [24]. Low dose dexamethasone has shown mortality benefit among treated COVID-19 hospitalized patients [25,26].

Management of severe COVID-19 patients requires hospitalization as well as treatment with glucocorticoids that may lead to occurrence or flaring up of secondary infections, further posing health risk for these patients. Concomitant use of tetracyclines (TCs), particularly minocycline and doxycycline, due to their immunomodulatory and antimicrobial properties [27–29], can offer a potential therapeutic option for combining with dexamethasone therapy.

This review will focus on the need, plausible mechanisms involved, advantages and concerns of combining dexamethasone with TCs for the management of severe COVID-19 infection. To find the relevant published literature, we performed literature search using PubMed, Google Scholar and CENTRAL databases using keywords, 'COVID-19', 'coronavirus', 'SARS-CoV -2', 'dexamethasone', 'glucocorticoids', 'tetracyclines' 'minocycline', 'doxycycline'. AND/OR filters were applied wherever applicable and the literature search involved the articles published in English language and published from inception to 3 September 2020.

2. Potential of dexamethasone and other glucocorticoids in COVID-19 infection

GCs including dexamethasone are powerful anti-inflammatory agents and are indicated in a variety of inflammatory and autoimmune disorders [30,31]. GCs after binding to the cytoplasmic receptors form the glucocorticoid-receptor complex, which enters the nucleus and regulates the transcription of certain proteins such as NF-κβ. Further, NF-κβ is known to modulate the transcription of several other pro-inflammatory cytokines (IL-1α, IL-1β, IL-2, IL-3, IL-5, IL-6, -IL8, IL-12, TNF- α and IFN- γ) and by virtue of this action, GCs are capable of exhibiting a powerful anti-cytokine effect [30,32–35].

As most of the above-cited cytokines have also been implicated in the pathology of severe COVID-19, associated ARDS and cytokine storm [8,17], therefore, use of GCs can be an effective therapeutic approach for the treatment of critically ill patients [15]. GCs have also shown beneficial effects in acute lung injury because of their anti-fibrotic action [36]. Initially, researchers were uncertain about the role of GCs for the COVID-19 management, because of their immunosuppressive effects [37,38].

Questionable efficacy and risk of infection flare up remained a controversy [37–39], before the RECOVERY trial showed a clear-cut mortality benefit in hospitalized COVID-19 patients [24,40]. Before the results of RECOVERY trial were made public, remdesivir was the only option for severe COVID-19 patients, which modestly reduced the time to clinical recovery for these patients [41,42].

Interplay of various cytokines including IL-6 and TNF-α among others has been implicated in the pathophysiology of COVID-19 and is invariably associated with high morbidity and mortality [15–18]. Cytokine storm leading to systemic inflammatory response syndrome (SIRS) [17,18] poses a major challenge to worldwide healthcare systems and currently we lack effective therapeutic options to address the same. Dexamethasone and other GCs like methylprednisolone have potent anti-cytokine and anti-inflammatory effects, which are helpful for the management of SIRS [30–35]. GCs can play a significant role in COVID-19 associated cytokine storm and SIRS, as they affect both innate and adaptive immunity and latter has been shown to play a major role, as the onset of ARDS was found to be correlated with the appearance of a specific antibody against SARS-CoV-2 [43].

In a retrospective study involving sick patients with ARDS, it was observed that patients who received methylprednisolone showed a lower mortality as compared to those who did not receive it [44]. In the Guangzhou retrospective study, it was reported that use of GCs in critically ill SARS patients led to reduced mortality and shorter stay at hospital without increasing the risk of secondary infections and other complications [45].

Dexamethasone like other GCs has shown promising effects against variety of pro-inflammatory cytokines [46,47]. In

a study conducted by Schuld et al. [47], anti-cytokine effects of dexamethasone were studied on 17 depressed patients. Dexamethasone caused an increase in granulocyte count, and reduced IL-6 and TNF-α levels. In a study performed by Azab et al., dexamethasone was administered to patients undergoing cardiac surgery and it was found that patients receiving dexamethasone had shown significantly lower levels of IL-6, IL-8 and TNF-α. Also, these patients had lesser post-operative hemodynamic instability and hospital stay as compared to those who did not receive dexamethasone [48]. In a multicentre trial involving patients with moderate to severe ARDS, 139 received dexamethasone and 138 were included in the control group, and dexamethasone resulted in greater number of ventilator-free days versus the control group (day difference = 4 · 8 days, P < 0 · 0001). Also, the proportion of adverse effects did not differ between the two groups [49].

In the RECOVERY trial [40], administration of dexamethasone led to mortality benefits among COVID-19 patients who were on mechanical ventilation or oxygen alone. In this open label randomized controlled trial, 2104 subjects received dexamethasone and 4321 were in the usual care group. Overall, 23% (n = 482) patients receiving dexamethasone and 26% (n = 1110) receiving usual care died within 28 days (p < 0.001). Further, the mortality was significantly lower among patients in the dexamethasone arm, who received invasive mechanical ventilation (29% vs. 41%) or oxygen alone (23% vs. 26%). This trial served as the landmark in clearing the air over the beneficial effects of GCs among COVID-19 patients and led to a widespread recommendation of use of dexamethasone in the treatment protocols of COVID-19 infection [24–26,50,51].

Apart from dexamethasone, methylprednisolone has also shown promising results. In a case control study involving 117 subjects, the effect of methylprednisolone on clinical outcomes like ventilator-free days, extubation, and mortality were studied. Mean number of ventilator-free days were significantly greater in patients who received methylprednisolone (p = 0.04). Also, the probability of extubation was higher in subjects receiving methylprednisolone (p = 0.02), however no significant difference was seen in mortality (p = 0.087) [52]. In an updated meta-analysis (involving non-COVID subjects) including nine randomized trials, use of low-to-moderate dose prolonged methylprednisolone for ARDS resulted in decreased time to endotracheal extubation, reduced hospitalization stay and mortality and resulted in greater number of days free from mechanical ventilation and ICU stay [53]. Hence, this strategy can also be helpful in COVID-19 induced ARDS. Two more studies involving ARDS subjects reported mortality benefits, improvement in lung and extrapulmonary organ functions and reduced duration of ICU stay and mechanical ventilation [54,55]. In a multicentric observational study done by Salton et al., early institution of methylprednisolone therapy, in patients with severe COVID-19 pneumonia, resulted in a significantly lower hazard of death and decreased need for ventilatory support. Also, treatment with methylprednisolone was found to be safe without having any interference with viral clearance [56]

Although, direct studies involving use of dexamethasone in COVID-19 infection are limited, the results of RECOVERY trial highlighted its beneficial role in ARDS, through its anti-cytokine and other promising effects. As a result, dexamethasone has now become an essential component of the management protocols of hospitalized moderate to severe COVID-19 patients [24–26]. However, it is pertinent to note that beneficial effects of corticosteroids in these individuals are dependent on the selection of appropriate dose, in the right patient and at an opportune time. Higher doses may potentially interfere with viral clearance, as also administration in early stages of disease when viral suppression supersedes control of inflammation as a primary therapeutic strategy. A recent meta-analysis that evaluated corticosteroid treatment outcomes in COVID-19 patients found no beneficial or detrimental effects among high dose and low-dose treatment regimens. Their analysis was limited by considerable heterogeneity of studies reporting high dose and low-dose corticosteroids use. In this analysis, low-dose corticosteroids did not have a significant effect on the duration of viral shedding [57]. Although direct evidence from COVID-19 patients is lacking, corticosteroids when used in critically ill sepsis patients have been shown to increase the risk of hypernatremia (RR-1.64; 95%CI −1.32–2.03), hyperglycemia (RR-1.16; 95%CI-1.08–1.24), and neuromuscular weakness (RR-1.21; 95% CI-1.01–1.52) [58]. Similar findings have been reported by Annane et al. who conducted and reported a Cochrane systematic review to evaluate the effects of corticosteroids on treatment outcomes in pediatric and adult patients with sepsis [59].

3. Tetracyclines: potential in COVID-19 management

TCs are inexpensive broad-spectrum antimicrobials, having activity against a variety of microbes [60]. Minocycline and doxycycline have shown useful anti-inflammatory and immunomodulatory properties [61,62] and inhibit the release of several cytokines which are involved in the pathogenesis of COVID-19 [27,63]. Minocycline by virtue of its activities against the generation of proinflammatory cytokines, and proposed anti-viral effects, holds a promising potential for drug repurposing against COVID-19 [28,29].

Doxycycline via its pharmacological action, could be useful in targeting the pathogenic pathways involved in COVID-19 infection [27]. Both minocycline and doxycycline have a potential inhibitory activity against pro-inflammatory cytokines and MMPs, which have been implicated in the coronavirus infection, chemokine activation, and tissue destruction [64,65].

Minocycline has known activity against MMP-2 and MMP-9 and offers a promising role in the treatment of COVID-19 infection [66–75]. NF-κB signaling is important in regulating the release of various cytokines and it has been observed that NF-κB activation after SARS-CoV-2 infection results in the induction of various inflammatory cytokines, including IL-6, TNF-α and chemokines [75,76]. Both doxycycline and minocycline inhibit the NF-κB signaling [77–80], which implicates their potential role in cytokine storm associated with severe COVID-19 infection. As discussed earlier, doxycycline and minocycline exhibit antiviral activity against a variety of RNA viruses [28,29]. TCs (doxycycline and minocycline) may lead

to increased expression of zinc finger antiviral protein (ZAP) which is an inhibitor to the replication of RNA viruses (ZAP after binding to target viral mRNA, may repress the RNA translation) [81,82].

Bhardwaj et al. [83], in their combinatorial computational study,attempted to identify potent inhibitors against SARS-CoV -2 main protease (M^{pro}). They evaluated various tetracyclines against native ligand N3 inhibitor in SARS- CoV-2 M^{pro} crystal structure. Analysis revealed that doxycycline and minocycline are potent inhibitors against SARS-CoV-2 M^{pro} and they proposed the role of doxycycline and minocycline in combinational therapy against COVID-19 infection. This computational analysis provided a signal toward the possible tetracycline activity against SARS-CoV-2, which adds to their immunomodulatory potential. In another *in silico* study by Xiao [84], 135 clinical drugs including minocycline, were screened for their activity against 3-chymotrypsin-like protease (3CLpro, or M pro) and minocycline was found to possess highest binding affinity against this target. The above two computational studies pointed toward potential antiviral (against SARS-CoV-2) effect of tetracyclines. Gendrot et al. demonstrated in vitro activity of doxycycline in SARS-CoV-2 infected Vero E6 cells with median effective concentrations of 4.5 μM that seems to be compatible with oral as well as intravenous routes of administration [85].

In a case series performed by Ahmad et al. [86], doxycycline in combination with hydroxychloroquine showed better clinical outcomes in moderate-severe COVID-19 patients. This combination reduced the mortality as well as reduced the need for hospitalization. Alam et al. reported clinical outcomes in 89 high-risk patients who received doxycycline (100 mg for 7 days) plus standard care within 12 hours of the onset of symptoms. Their observational study demonstrated early symptomatic recovery, reduced hospitalization as well as mortality in these individuals [87]. Cag et al. administered doxycycline in addition to hydroxychloroquine for 3 days in mild COVID-19 cases and doxycycline plus lopinavir in moderate-severe cases for 5 days and reported an overall mortality rate of nearly 4% [88]. Yates et al. treated four high-risk COVID-19 patients with known lung disease with doxycycline and reported rapid clinical improvement [89]. In a randomized controlled trial, Chowdhury et al. [90] compared the efficacy of a combination of ivermectin and doxycycline with hydroxychloroquine and azithromycin in patients with mild to moderate COVID-19 infection. Patients who received ivermectin-doxycycline achieved a negative polymerase chain reaction (PCR) test for SARS-CoV-2 with a mean duration of 8.93 days. In addition, these patients had symptomatic recovery with a mean duration of 5.93 days. Although, difference in time to become negative for PCR was not significant, the ivermectin-doxycycline combination resulted in a better effect than hydroxychloroquine-azithromycin combination. Doxycycline seems to have some potential advantages over azithromycin in terms of safety in elderly people and in those having cardiac risk factors [91], hence it is being considered as a potential drug against COVID-19 to be used in combination therapy affording greater benefits [81].

Byrne et al. [92] hypothesized the potential role of minocycline and doxycycline in a retrospective cohort study by assessing the ventilatory status of patients, who were prescribed tetracyclines within a year prior to ARDS diagnosis. Use of minocycline or doxycycline resulted in significantly reduced likelihood for mechanical ventilation, reduced duration of mechanical ventilation and ICU stay among ARDS patients. Although, this study was performed on non-COVID patients but ARDS is also a well-known complication of COVID-19 infection, hence both minocycline and tetracyclines hold the potential for addressing the same.

Gironi et al. reported a prospective observational study involving 38 adult patients having suspected/confirmed COVID-19 who were receiving tetracyclines for concurrent dermatoses during their home quarantine. It was found that TC treatment led to effective symptom resolution in all patients within 10 days. Interestingly, ageusia and anosmia responded promptly and disappeared within the first week of treatment [93].

Co-occurrence of secondary bacterial infections among COVID-19 patients is a matter of concern and it can result in significant morbidity and mortality [94]. Therefore, tetracyclines can be useful in treating such infections. Zhou et al. [95] reported the rate of occurrence of secondary bacterial infections in COVID-19 patients as 15%, however it was very high among non-survivors (about 50%). Tetracyclines, due to their broad-spectrum antimicrobial action [60], can be a useful therapeutic option in treating such infections.

4. Benefits and drawbacks of concomitant use of dexamethasone and tetracycline in COVID-19 management

Both dexamethasone and tetracyclines (minocycline and doxycycline) are easily affordable, widely available and have been utilized in clinical practice for a long time. Their pharmacological properties, adverse effects and contraindications are well known. As far as the management of patients with severe COVID-19 is concerned, it poses a great challenge to our healthcare system because of the considerable mortality and risk of complications. We need promising pharmacological agents which are able to address the needs of COVID-19 patients. Dexamethasone and tetracyclines are known to have strong anti-inflammatory nd immunomodulatory properties [27,46,47,62] via inhibitory action on cytokines like IL-6, TNF-α among others, which are implicated in the pathogenesis of COVID-19 [8,9,15–17]. Co-administration f these agents can have an additive inhibitory effect on pro-inflammatory cytokines, and this can be beneficial in culminating the cytokine storm which is central to the damaging effects of COVID-19 infection. Apart from this, both GCs [30–35] and tetracyclines [76–80] can suppress the NF-κB signaling and it has been observed that in coronavirus infection, NF-κB activation leads to induction of a variety of proinflammatory cytokines, including IL-6, TNF-α and chemokines [75–77].

Hence, by virtue of the above properties, concomitant use of dexamethasone and tetracyclines, has the potential to address the pathogenic pathway and mediators of severe COVID-19 infection, and can serve as a lifesaving strategy. They are the cheaper alternatives to costly and controversial agents like tocilizumab (IL-6 inhibitor) and can target multiple

cytokines and other mediators. Moreover, both these agents are widely available in developing and developed nations and can be administered even at the primary health centers without any need for stringent monitoring. As GCs like dexamethasone can depress immunity and carry the risk of flaring up of infection or occurrence of new infections [37–39], hence, tetracyclines by virtue of their broad-spectrum antimicrobial action [60] and *in silico, in vitro,* and clinical activity against SARS-CoV-2 [83–93], can address this issue. Therefore, adding tetracyclines to GCs can be a rational approach for the management of COVID-19.

Apart from various advantages, there are a few concerns regarding the use of dexamethasone and tetracyclines in severe COVID-19 patients. Tetracyclines are pregnancy category D teratogenic drugs that should be avoided in pregnant and lactating women [96,97], hence in such cases, alternative treatment should be given. Due to their adverse effects on tooth development and growth, use of tetracyclines should be avoided in children up to the age of 8 years [96,97]. Dexamethasone is pregnancy category C drug, has shown harmful effects to fetus in animal studies. Therefore, it should only be used if the potential benefits outweigh the associated risks [31,98]. Similarly, the likelihood of other adverse effects and risk of drug interactions associated with the use of dexamethasone and tetracyclines must be considered before prescribing them to COVID-19 patients [26,96,97]. However, no drug interaction [99] has been observed between dexamethasone and tetracyclines, hence their concomitant use may be considered.

Another concern is the lack of clinical data regarding concomitant use of dexamethasone and tetracyclines in patients with COVID-19 infection. However, RECOVERY trial [40] and other clinical studies involving GCs have shown benefits or a potential role of GCs [52–55] among patients with COVID-19 and related complications like ARDS. As a result, use of dexamethasone has been encouraged for the management of COVID-19. Similarly, tetracyclines (doxycycline and minocycline) have also shown encouraging results in *in silico* [83,84], *in vitro* [85], and small sized clinical studies [86–93]. Long-term use of GCs can cause several adverse effects [31], but as severe COVID-19 is primary a life-threatening acute infection, dexamethasone is likely to be used for a shorter duration. The recommended duration of treatment with corticosteroids as per the World Health Organization (WHO) treatment guidelines is 7–10 days [100]. Therefore, short-term use of dexamethasone is unlikely to cause such adverse effects.

Another important concern with dexamethasone is the infection flare up and secondary infections, hence a close monitoring, adequate antibiotic cover and use of antiviral agents , along with other supportive measures can be helpful.

5. Conclusion

There is a dire need for promising agents for the management of severe COVID-19 infection, and the potential benefits of this combination therapy seem to outweigh the associated risks. This further demands well-designed clinical studies to explore the potential use of dexamethasone and tetracyclines in the setting of severe COVID-19 infection.

6. Expert opinion

Patients with severe COVID-19 infection are at higher risk of developing cytokine storm, ARDS, and multi-organ damage [2,101,102]. Generally, they need ICU admission and prompt treatment to prevent the likely complications and mortality. This group of patients requires special attention and there is an urgent need for potentially effective and safe therapies.

As of now, the treatment options are scarce and effective targeted therapies for the treatment of COVID-19 infection are lacking. However, till now, the mainstay of treatment is the isolation of infected patients with supportive medical care and glucocorticoids.

Repositioning of inexpensive and affordable drugs, based on their pharmacological properties for the management of COVID-19, holds a great potential in such a global pandemic scenario [103,104]. Dexamethasone has shown clear-cut mortality benefits among hospitalized patients with COVID-19 infection (RECOVERY trial) and it has been widely acknowledged as a part of treatment regimens to be used in such patients. Pharmacological properties of dexamethasone (immunomodulatory and anti-inflammatory) make it a potential agent for addressing the pathogenic pathways and mediators, responsible for developing serious complications among severe COVID-19 patients. Due to the complex pathogenesis of COVID-19, multiple drugs are needed to prevent the associated complications and mortality. Tetracyclines possess a multifaceted pharmacological profile and offer significant potential for the management of severe COVID-19 infection. Their broad-spectrum antimicrobial action, potent immunomodulatory action, proposed antiviral effect against SARS-CoV-2, places them among the agents with most favorable potential for drug repositioning. The proposed therapeutic roles of dexamethasone and tetracylines seem to complement each other as their additive effects on cytokines and other mediators of COVID-19 infection can play an instrumental role. Risk of flaring up of existing infection or appearance of secondary infections with the use of dexamethasone can also be addressed by the concomitant use of tetracyclines since they possess broad-spectrum antimicrobial properties.

Moreover, this potential combination offers a cost-effective option and can be used in both developing and developed nations, in place of expensive experimental therapies with questionable efficacy and safety. Dexamethasone and other GCs have already been studied for their effects in COVID-19 patients and are widely accepted as a part of treatment regimen in hospitalized COVID-19 patients. Tetracyclines, particularly minocycline (based on the pharmacological profile and *in silico* studies) and doxycycline (based on the pharmacological profile and small sized clinical studies) have a profound action on proinflammatory cytokines, MMPs and other mediators involved in the pathophysiology of COVID-19. Based on the above facts, they are among the leading emerging candidates for addressing the unmet needs of patients diagnosed with severe COVID-19 infection.

Based on their pharmacological properties including adverse event profile and contraindications and long-term familiarity of prescribers with their clinical use, both dexamethasone and tetracyclines are the ideal agents to be considered for drug repositioning in management of severe COVID-19 disease.

Presently, we lack clinical studies involving the concomitant use of these agents, however, it is very much feasible to investigate their concomitant effects, among severe COVID-19 patients, as most of these patients will already be prescribed dexamethasone. Small pilot studies, involving one arm of usual care with dexamethasone (as a part of routine care of severe COVID-19 patients) and other arm involving one of the tetracyclines (minocycline or doxycycline) over and above the usual care, can be carried out even in academic settings without the need for substantial funding. Subsequently, well-designed and adequately powered multicentric trials will need to be carried out in a similar fashion in order to generate a more robust evidence. Institutional bodies, government health authorities, and private or corporate funders should collectively encourage and support these research activities, so that the unmet healthcare needs of severe COVID-19 patients can be addressed as a priority.

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