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Pediatric Rheumatologists' Perspective on Corona Virus Disease 2019

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Abstract

Corona Virus Disease 2019 (COVID-19) has become a pandemic affecting the entire the world. Rheumatologists may play an important role in the management of COVID-19 cases owing to their experiences on inflammation and macrophage activating syndrome (MAS), one of the most important complications of COVID-19. Here, we present the applicability of pediatric rheumatology treatment methods on COVID-19 therapy, and management of children with rheumatic diseases using immune suppressive treatments, in this pandemic season. COVID-19 causes severe acute respiratory distress syndrome (SARS) in about 20% of infected patients. The virus specifically recognizes the angiotensin converting enzyme 2 (ACE2) receptor by its spike protein. In patients whose immunomodulatory capacities are not strong enough, the virus can trigger a severe cytokine storm. The rheumatologist may play an important role to avoid this complication with a timely treatment. In COVID-19 patients, by detecting elevated serum ferritin levels, cytokine storm syndrome can be recognized early, and the necessary treatments can be initiated on time. Anti-rheumatic drugs, such as hydroxychloroquine, colchicine, interleukin-1 and interleukin-6 blockers, JAK inhibitors, TNF inhibitors are used in the treatment of COVID-19 at different stages of the disease. Another very important issue is the management of patients with rheumatic diseases in this pandemic season. The increased risk of infection is an important concern in patients with rheumatic disease who are receiving immunosuppressive drugs. Various rheumatism associations have recommended the continuation of anti-rheumatism treatments to control of chronic inflammatory status, based on the experience so far.

Keywords: Corona virus disease 2019, cytokine storm syndrome, inflammation, pediatric, rheumatology

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Introduction

Corona Virus Disease 2019 (COVID-19) presented with severe acute respiratory distress syndrome (ARDS) has rapidly spread all over the world. Data from China have indicated that about 20% of patients developed severe ARDS. Particularly, older adults with serious underlying health conditions are at higher risk than younger ones. A minority of patients have presented with respiratory failure, septic shock, and multi-organ dysfunction, resulting in a fatality of 4%.[1] Although children with COVID-19 presents with mild symptoms, patients with chronic diseases who on immunosuppressive medications are at higher risk.

Highlight

- Pediatric rheumatologists' experience in cytokine storm and associated treatments may help to guide inflammatory complications of COVID-19.
- We recommend that a notably elevated ferritin value should alert clinicians for cytokine storm syndrome in hospitalized patients with COVID-19.
- During the pandemic season for rheumatic disease, the most important issues are the control of chronic inflammatory status and continuity of rheumatologic treatment.

Researches in COVID-19 pathogenesis and treatment options have led to a rapid rise of publications in the medical literature. In line this with, it has been realized that experiences in rheumatology are particularly applicable to COVID-19 complications such as cytokine storm, i.e macrophage activation syndrome, and inflammation associated treatments with hydroxychloroquine, anakinra, tocilizumab, and baricitinib. In this paper, we present a review of 31 manuscripts indexed in PubMed database until April 17 about COVID-19 in rheumatology patients.

Pathogenesis of COVID 19

The first step of the COVID-19 pathogenesis is that the virus specifically recognizes the angiotensin converting enzyme 2 (ACE2) receptor by its spike protein.[2,3] In addition, the cellular serine protease TMPRSS2 for HCoV-19 spike protein priming is also essential for the host cell entry and spread.[3] The ACE2 receptor is widely distributed on the human cells surface, especially the alveolar type II cells (AT2) which highly express TMPRSS2[4,5] and capillary endothelium. More recently, enterocytes have been shown to express ACE2 and target of virus.[6] However, in the bone marrow, lymph nodes, thymus, and the spleen, immune cells, such as T and B lymphocytes, and macrophages are consistently negative for ACE2.[4] The findings suggest that immunological therapy may be used to treat the infected patients. If host has not enough immunomodulatory capacity to control viral infection, the virus can trigger a severe cytokine storm especially with IL-2, IL-6, IL-7, GSCF, IP10, MCP1, MIP1A, and TNFα in the lung. The cytokine storm can stimulate the mechanisms resulting in pulmonary edema, dysfunction of the air exchange, acute respiratory distress syndrome, acute cardiac injury and a secondary infection.[7] Therefore, avoiding the cytokine storm may be the key for the treatment of COVID-19 patients.[1,8]

The Rheumatologist's Role in COVID-19

Rheumatologists are familiar with the treatment of cytokine storm syndrome (CSS)/ macrophage activation syndrome (MAS) in patients with Still's disease, systemic juvenile idiopathic arthritis, autoinflammatory diseases, systemic lupus erythematosus, juvenile dermatomyositis, and Kawasaki disease. Therefore, they can support the screening, diagnosis, and the treatment of CSS among COVID-19 patients. A set of diagnostic criteria is not available for the diagnosis of CSS in the COVID-19 currently. The CSS criteria used in hematologic and rheumatologic diseases can certainly be a guide to clinicians for the diagnosis of COVID-19.[9-12] These criteria were compared in **Table 1**. The serum ferritin measurement, which is a simple, cheap, readily available, and fast screening method, should be performed every hospitalized COVID-19 patient.[13] A notably elevated ferritin value (e.g. >700 ng/

Table 1.
Comparison of cytokine storm syndrome criteria in previously reported with COVID-19 patients

	HLH-04 criteria (9)	HScore (10)	MAS criteria in SJIA (11)	Covid-19 (13)
Fever	Yes	Yes	Yes	Yes
Splenomegaly	Yes	Yes		Unknown
Hepatomegaly		Yes		Unknown
Anemia	Yes	Yes		Yes
Thrombocytopenia	Yes	Yes	Yes	Yes
Neutropenia	Yes	Yes		Yes
Hypertriglyceridemia	Yes	Yes	Yes	Unknown
Hypofibrinogenemia	Yes	Yes	Yes	Yes
High AST		Yes	Yes	Yes
Hemophagocytosis	Yes	Yes		Unknown
Low NK cell activity	Yes			Unknown
Hyperferritinemia	Yes	Yes	Yes	Yes
Elevated soluble CD25	Yes	Yes		Yes
		Elevated serum GGT		High ALT
		Underlying immunosuppression		

HLH: Hemophagocytic lymphohistiocytosis, GGT: glutamic oxaloacetic transaminase, ALT: Alanin aminotransferase, AST: Aspartat aminotransferase

mL) should alert clinicians to additional diagnostic work-up so that therapeutic approaches can be considered without significant delay.[13]

Anti-rheumatic Agents in Treatment of COVID-19

Non-steroid anti-inflammatory drugs

Since the commonly used ibuprofen is believed to increase the expression of ACE2, using ibuprofen should be avoided during this pandemic if possible.[14-16]

Corticosteroids

In SARS and MERS cases, no association between use of corticosteroids and improved survival in patients was found. On the other hand, it was shown that the viral clearance from respiratory tract and blood was delayed by corticosteroids.[17] Therefore, corticosteroids are not recommended for patients with COVID-19.[18]

Hydroxychloroquine sulfate and chloroquine phosphate

Two antimalarial drugs act by blocking viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Additional immunomodulatory effects were found through inhibition of cytokine production, autophagy, and lysosomal activity in host cells.[18,19] Two trials one from China, another from France report some benefit to the COVID-19 patients, although both studies have been scrutinized with regard to methodology.[20,21] Other reports do not support efficacy of hydroxychloroquine.[22,23] More trials with larger cohorts under way and will be more informative. Nevertheless, the current protocols for COVID-19 treatment in Turkey or elsewhere include hydroxychloroquine.

Colchicine

Colchicine is used routinely in Familial Mediterranean Fever (FMF). It could inhibit both neutrophil recruitment to the sites of inflammation and the secretion of IL-1β. Trials using colchicine in COVID-19 cases were reported by Italian Medicines Agency (AIFA) (ClinicalTrials.gov identifiers: NCT04326790, NCT04328480, NCT04322565, NCT04322682).[24,25] As a result of these studies, treatment with colchicine of patients affected by COVID-19 may prove to be a viable path.

Anakinra

Anakinra, a blocker of IL-1β plays a central role in the pathogenesis of CSS and it has been recommended for the treatment of CSS.[24,25] In this treatment, the window of opportunity is the key point to the success of the treatments (**Figure 1**).

Tocilizumab

The high plasma IL-6 levels were reported in severe COVID-19 cases.[26,27] Tocilizumab was recommended as the first choice of treatment for CSS in the window of opportunity[25] (**Figure 1**).

JAK blockers

The SARS-CoV-2 enters targeted cells through receptor-mediated endocytosis. Some of the identified regulators of clathrin-mediated endocytosis are members of the numb-associated kinase (NAK) family, such as AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK).[28] Inhibition of AAK1 may stop the access of the virus into lung cells and also the intracellular assembly of virus particles.[29] Among the JAK blockers, only baricitinib effectively inhibits AAK1 and GAK. Baricitinib is also able to dampen CSS by reducing IL-6 and IFN-γ levels.[30]

TNF inhibitors

The viral spike protein is able to induce a TNF-α-converting enzyme (TACE)-dependent shedding of the ACE2 ectodomain which is crucial for the penetration of the virus into the cell.[31] Since this process seems to be strictly coupled to TNF-α production, it has been postulated that the use of TNF inhibitors may be effective in reducing both COVID-19 infection and the consequent organ damage.[32]

There is no consensus on how to treat COVID-19 patients. Turkish Ministry of Health and the Scientific Board's suggestions and guidelines which are constantly updated can help to manage the disease for clinicians.[33]

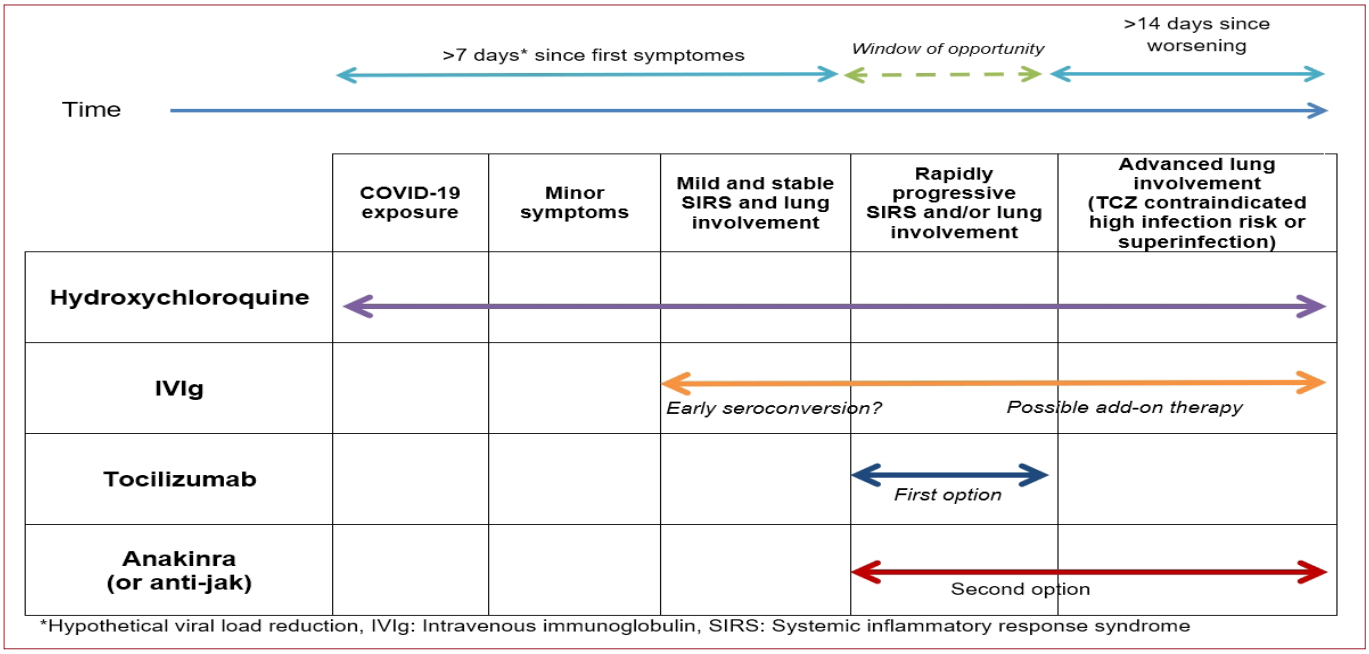

Figure 1. Hypothetical timing of some anti-rheumatic drugs in COVID-19 infection. This figure is adapted from the reference 25.

Management of Patients with Rheumatic Diseases in COVID-19 Season

The rapid and uncontrolled spread of the epidemic creates concerns for rheumatic patients, which are inherently characterized by being under increased risk of infection due to the rheumatic disease itself and to the iatrogenic effect of immunosuppressive agents such as corticosteroids and synthetic or biological disease-modifying drugs they are on.[30]

Risk factors for severe COVID-19 infections are older age, smoking, and underlying chronic diseases such as hypertension, diabetes mellitus, cardiovascular diseases and rheumatic diseases.[16] The American College of Rheumatology (ACR)[34], the European League Against Rheumatism (EULAR)[35] and the Italian Society of Rheumatology (SIR)[36] advise not to discontinue or reduce immunosuppressive therapy in patients with rheumatic diseases. The recommendations from several rheumatology societies were summarized in **Table 2**. According to the experience of COVID-19 so far, the most important point about prevention of the disease is the control of chronic inflammatory status and continuity of anti-rheumatic treatment.[16,25,30,37,38]

Table 2.
Summary of recommendations from rheumatology societies for patients with rheumatic diseases during COVID-19 outbreak[34-37]

1. Practicing sneeze/cough hygiene, regular hand washing, avoiding touching the face, keeping away from crowded places, social distancing, avoiding busy public transport and cancelling unnecessary travel is recommended.
2. Use of a mask is recommended for those with suspected and confirmed infection. In such instances, N95 respirators with appropriate fit to the face are advisable.
3. Abrupt discontinuation of glucocorticoid therapy should be avoided, even during active infection. Do not discontinue immunosuppressive treatment.
4. If patients are on disease-modifying anti-rheumatic drugs, including biologics, small molecules, and other immunosuppressive agents, standard practices may be followed to discontinue them should one develop infection.
5. Routine face-to-face appointments should be delayed until the outbreak settles. Both patients and healthcare personnel should consider substituting face-to-face appointments with video appointments if feasible.
6. Patients should be updated about appropriate flu and pneumococcal vaccination practices.

Conclusion

Anti-rheumatic drugs may be useful during the coronavirus COVID-19 pandemic to control viral infection or inflammation associated with rheumatic disease.

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