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Rheumatology: Current Research

Mini Review

Rheumatologists' Perspective on COVID-19

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ABSTRACT

The rheumatology community has been confronted with many challenges during the COVID-19 pandemic. Early in the pandemic, there were questions about managing rheumatic immunosuppressive medications, while of late, it has been about the COVID-19 vaccine. As the pandemic continues to evolve, and more high-quality studies are available to answer pressing questions, many unknowns remain. This summary attempts to provide a viewpoint from a Rheumatologists' angle about the current landscape of COVID-19.

Keywords: COVID-19; Rheumatology; Medication; Vaccine; Immunosuppressive

DESCRIPTION

Humankind is currently facing one of the gravest tests of their lifetime in the form of coronavirus disease 2019 (COVID-19). The causative agent for COVID-19 is a novel coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that originated in Wuhan, China, in December 2019 from an avian source. After its onset, it rapidly spread worldwide and was soon declared a global health emergency and subsequently a global pandemic in March 2020 by World Health Organization (WHO). With global infection rate and death crossing 72 million and 1.6 million, respectively, it is unlike anything that humans have faced since and 1918 influenza pandemic due to the H1N1 virus that infected 500 million people (one-third of the world's population) and left 50 million dead. So far, the United States (US) has recorded the highest number of infection and deaths worldwide–more than 16 million and more than 300 thousand, respectively [1].

As the COVID-19 pandemic unfolded in the US, hospitals, and their Intensive Care Unit (ICU)'s quickly got overwhelmed with patients experiencing respiratory symptoms. While most of the patients with COVID-19 had mild influenza-like symptoms that did not require hospital admission; some went on to develop respiratory distress requiring respiratory assistance. Overall a small percentage of patients developed severe COVID-19, had Acute Respiratory Distress Syndrome (ARDS) requiring mechanical ventilation, and Extracorporeal Membrane Oxygenation (ECMO) occasionally lead to death. Age >65 years, male sex and comorbidities like chronic kidney disease, chronic lung disease, cardiovascular disease, obesity, hypertension, and diabetes mellitus were identified as adverse prognostic markers [2]. Severe COVID-19 manifestation is thought to be secondary to cytokine storm. Hospitalized patients with COVID-19 with higher levels of c-reactive protein, d-dimer, interleukin (IL)-6, and lactate dehydrogenase and those with lymphopenia had worst outcomes [3].

To date, there is no effective treatment and therefore cure for COVID-19. Several medications (remdesivir, baricitinib combined with remdesivir), neutralizing antibodies (Bamlanivimab; Casirivimab combined with Imdevimab), and convalescent plasma has received Emergency Use Authorization (EUA) from Food and Drug Administration (FDA). FDA also recently gave EUA to two different messenger ribonucleic acid (mRNA) vaccines.

Amid early panic and lockdowns, rheumatologists started receiving calls from the frontline healthcare workers and also directly from patients, requesting guidance about managing rheumatic diseases and their medications during the COVID-19 [4]. Early in the pandemic, there was a paucity of data, and rheumatic patients on immunosuppressive were fearful of continuing it as they believed to be at higher risk of getting COVID-19. However, early studies conditionally cautioned against discontinuing rheumatic medications preventatively as an active rheumatic disease in itself was identified as a significant risk factor for increased rate of infection [5,6].

More studies showed that being on Disease-Modifying Antirheumatic Drugs (DMARDs) did not contribute to the

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unfavorable or severe manifestation of COVID-19 with the possible exception of rituximab [7]. Furthermore, the American College of Rheumatology (ACR) came out with a "living document" as guidance and reported no identifying risk factor specific to rheumatic disease that would confer adverse outcome with COVID-19 [8].

As a general rule, immunosuppressive medications are typically put on hold during an infection as it diminishes the hosts' ability to fight the infection well. Most DMARDs should be stopped when a person tests positive for COVID-19 except for hydroxychloroquine (HCQ) due to its *in vitro* antiviral properties. The other possible exceptions are IL-6 inhibitor (tocilizumab) and Janus kinase (JAK) inhibitor (baricitinib); in both these scenarios a case-by-case decision making should be undertaken (4). Of note, HCQ does not confer any protection, nor has it shown any favorable outcomes in those hospitalized with SARS-CoV-2 [9,10].

Historically, corticosteroids have had mixed outcomes in viral infections; they were deemed ineffective for SARS-CoV-1 and Middle Eastern Respiratory Syndrome (MERS) infection but have proven efficacy in treating Pneumocystis jirovecii (PJP) pneumonia. There were conflicting results about using corticosteroids in COVID-19, with some early studies showing an increased risk of secondary infection. However, beneficial effects on mortality were demonstrated in hospitalized patients requiring some form of respiratory assistance receiving ten days of dexamethasone therapy [11].

All immunosuppressive medications can be safely restarted within one to two weeks of symptoms resolution or between two to three weeks after negative Polymerase Chain Reaction (PCR) result in an asymptomatic patient, in those who has had mild COVID-19 (without pneumonia). The decision to restart immunosuppressive medications after severe COVID-19 should be undertaken based on individual scenarios.

Interest in rheumatologic medications like IL-1, IL-6, and JAK inhibitors was ignited not because of their antiviral properties but due to their ability to decrease cytokine storm syndrome seen in COVID-19. Cytokine storm is a cluster of related syndrome seen secondary to various entities like infection (influenza and COVID-19), malignancy, genetic syndromes (hemophagocytic lymphohistiocytosis), and drug therapies (Chimeric Antigen Receptor T cell [CAR-T]). Though the common denominator is excessive release of multiple cytokines leading to hyperinflammation and multiorgan failure, there remain some critical pathophysiological differences [12]. Cytokine storm features of COVID-19 include a lesser degree of elevation of cytokines (except IL-33), mostly just one cell lineage suppression (lymphopenia), and uncommonly seen organomegaly (usually shrunken spleen and lymph nodes) [13,14].

Several other aspects of COVID-19 continue to baffle the scientific community. It remains unclear why some patients with a definite history of COVID-19 fail to mount an immune response. The antibody titers to SARS-CoV-2 can sometimes rapidly decline. This leaves two burning questions – how long does the immunity last after natural infection, and can someone who has had COVID-19 be reinfected multiple times? The other puzzling piece is protracted sequelae of COVID-19 seen in few who have only had mild to moderate COVID-19 infection not requiring hospitalization. Standard features in these subsets of patients include fatigue and brain fog, along with dyspnea, chest pain, joint pain, and specific organ dysfunction (heart, lungs, and brain) [15].

Many viruses have been linked to Autoimmune Rheumatic Disease (ARD) initiation by mechanisms like molecular mimicry, epitope spreading, presentation of cryptic antigens, and bystander activation. It remains to be seen if the close similarity between COVID-19 associated ARDS and exacerbation of Connective Tissue Disease (CTD)-Interstitial Lung Disease (ILD) can incite organ-specific autoimmunity in a specific group of individuals [16,17]. A new entity-Multisystem Inflammatory Syndrome in Children (MIS-C) has been reported three to four weeks after SARS-CoV-2 infection in the pediatric population. More than 50% of these children had no underlying medical condition and was also noted in those children who had asymptomatic or mild COVID-19 course [18].

As the two new vaccines get a nod from FDA, a glimmer of hope has appeared on the horizon. The preliminary data of these mRNA vaccines appears promising (close to 95% effectiveness), and there is little doubt about their safety. However, challenges persist in the form of adequate and timely distribution of vaccines, people's willingness to take them, and lack of data about its use in immunosuppressed patients. A low albeit theoretical concern remains about the reactivation of underlying autoimmune disease due to the vaccine's immune response. Prior studies have reported decreased humoral response to influenza and pneumococcal vaccine while being on agents like methotrexate, abatacept, and rituximab [19,20]. Hence, while we await more data about vaccine efficacy in patients on immunosuppressive agents, it is not unreasonable to suggest holding methotrexate and abatacept for two weeks after getting the vaccine and trying to vaccinate least three weeks before dosing rituximab.

As social distancing became a strict norm during the pandemic, many smaller medical practices, infusion centers, and outpatient surgical centers temporarily closed, disrupting routine medical care of patients with chronic conditions, including patients with chronic ARD. Most of these disruptions proved short-lived as the medical fraternity quickly adjusted and came out with safety guidelines. As a silver lining to this chaos, telemedicine access was quickly ramped up across the board and was effectively and seamlessly executed. Telemedicine is here to stay for the foreseeable future. It will likely have far-reaching consequences with a mostly positive impact on patients with ARD. Many of these patients previously had to travel several hours to see their Rheumatologist due to their relative scarcity.

The scientific community should be applauded for the robust and unparalleled response that they have shown in fighting this unprecedented pandemic due to SARS-CoV-2.

DISCUSSION AND CONCLUSION

As we continue to enrich our understanding of COVID-19 from the robust clinical trials, it is pertinent that we adhere to time tested modalities like frequent hand washing, wearing the face mask, and social distancing to limit its spread.

CONFLICT OF INTEREST

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