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Review Article

Rheumatology and COVID-19

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ABSTRACT

COVID-19 pandemic has affected every aspect of medicine, with the field of rheumatology being no exception. Although it is less common for a rheumatologist to manage critically ill COVID-19 patients directly, they face many questions from the frontline healthcare workers. At the beginning of the pandemic, numerous inquiries about managing rheumatic medications from primary care physicians and patients flooded the rheumatologist's office. As with every new disease, there was a paucity of data, lack of clear understanding, and guidance causing confusion and anxiety amongst the physician community and vulnerable population about managing rheumatic medications. The medical fraternity took the challenge head-on. Significant progress has been achieved within a relatively short period in understanding and tackling COVID-19, and rheumatologists were able to provide provisional recommendations about managing rheumatic medications. More recently, with the rolling out of COVID-19 vaccines, rheumatologists are again faced with questions from patients as to whether it is safe to take vaccines while on immunosuppressive medications. New challenges and questions continue to emerge in the form of COVID-19 sequalae, vaccine efficacy/availability and sustained immunity. This short review tries to touch upon facts about COVID-19, provide interim guidance about managing rheumatic medications, highlight areas of uncertainties, and discuss vaccination.

Keywords: COVID-19; SARS-CoV-2; Rheumatology; Immunosuppressive medications; Autoimmune

DESCRIPTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, in December 2019. Within the next few weeks, it rapidly spread across the globe and was declared a global pandemic by the World Health Organization (WHO) in March 2020. United States (US) documented its initial case in January 2020 and to date has recorded the highest number of deaths in the entire world. As per the Johns Hopkins data on December 12, 2020, there have been more than 71 million worldwide infections with close to 1.6 million deaths, with the US recording just short of 16 million cases and is very close to crossing the dubious landmark of 300 thousand deaths [1].

SARS-CoV-2 enters the human body by binding to angiotensin-converting enzyme (ACE)-2 receptors found on epithelial cells lining the respiratory, gastrointestinal, renal, hepatic, and cardiovascular system. The affected individuals could be mildly symptomatic (influenza-like symptoms), with some progressing to hypoxemic respiratory failure. The severe inflammatory response seen in this subset of patients with severe coronavirus disease 2019 (COVID-19) resembles cytokine release syndrome [2]. While respiratory problems like pneumonia and acute respiratory distress syndrome (ARDS) remains the most feared complications, it is not uncommon to see coagulopathy in the form of low grade disseminated intravascular coagulation, deep vein thrombosis, and pulmonary embolism.

Abnormal inflammatory markers like Interleukin (IL)-6, ferritin, and C - reactive protein (CRP) are significantly elevated in patients with severe manifestations of COVID-19. The biomarkers that predict poor outcomes in hospitalized patients include lymphopenia (especially CD4+ T cell) and elevated CRP levels, IL-6, d-dimer, and lactate dehydrogenase (LDH), among others [3]. The factors that have been associated with poor prognosis in COVID-19 patients include older age (>65 years) and preexisting comorbidities like obesity, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, and cardiovascular disease [4].

There was an initial dilemma about whether being on an ACE inhibitor or receptor blocker would increase or mitigate the risk of COVID-19; however, subsequent reports suggested it has no harmful effect, followed by recommendations that they can be safely continued or even initiated when needed [5].

While no definitive treatment exists for COVID-19, several medications, including convalescent plasma, have been granted emergency use authorization (EUA) by the Food and Drug Administration (FDA) since the onset of the pandemic. Remdesivir is a drug that prevents the creation of new coronavirus 2019 (COVID-19) viruses by inserting itself into new viral genes. It first

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received EUA for use in critically ill patients requiring oxygen, followed by full approval to use in all hospitalized patients with COVID-19, irrespective of their disease severity.

The WHO, however, recommends against using Remdesivir after its study failed to show mortality and other additional benefits [6]. The convalescent plasma with high antibody levels showed modest benefit when given early in the disease, and in a different study, when given in moderately ill patients, it did not show a reduction in progression to severe COVID-19 or all-cause mortality [7,8]. In November 2020, Bamlanivimab and Casirivimab combined with Imdevimab joined the line of EUA [9]. Bamlanivimab is a neutralizing IgG1 monoclonal antibody that acts against SARS-CoV-2 spike protein, preventing virus attachment and hence entry to human cells and is recommended in a non-admitted patient that has a high risk of disease progression. Monoclonal antibody cocktail of Casirivimab and Imdevimab (administered together) is approved for mild to moderate covid-19 that is deemed high risk for progression to severe COVID-19. The WHO solidarity trial consortium that included four repurposed antivirals drugs [Hydroxychloroquine, Remdesivir, Lopinavir (with ritonavir), and Interferon beta 1a] failed to show a significant effect on hospitalized COVID-19 patients, as depicted by overall mortality, initiation of ventilation or duration of hospitalization [10].

Rheumatologists routinely prescribe immunosuppressive medications to manage autoimmune rheumatic diseases. While it common to hold all immunosuppressive medications during an infectious episode to maintain the host's ability to fight the infection well, confusion arose when some of these rheumatic medications were noted to have in vitro anti-viral properties. As the American College of Rheumatology (ACR) provided early guidance, other articles also provided valuable insight when facing the dilemma about managing rheumatic medications during COVID-19 [11].

Early on during the pandemic, in vitro antiviral effects of hydroxychloroquine (HCQ) backed by small studies generated significant excitement. Subsequent rigorous studies, however, failed to show improved death incidence and clinical status of hospitalized patients with mild-to-moderate COVID-19 with or without azithromycin [12,13].

Corticosteroid (CST) use in critically ill patients with ARDS showed conflicting results in seven randomized controlled trials, but metanalysis of these trials concluded that CST use decreased the risk of all-cause mortality and duration of mechanical ventilation [14]. Current CST benefit recommendations are extensively based on an UK trial done on hospitalized patients requiring either supplemental oxygen or mechanical ventilation that showed mortality benefit at one month in those that received ten days of dexamethasone [15].

Janus kinase (JAK) inhibition is thought to decrease cytokine storm associated with severe COVID-19. Baricitinib, a JAK inhibitor approved for moderate to severely active rheumatoid arthritis, was granted EUA in COVID-19 patients to be used in combination with Remdesivir in hospitalized patients requiring ventilatory assistance [9]. A higher level of IL-6 is associated with higher levels of SARS-CoV-2 viremia, prolonged viral RNA shedding, progression to mechanical ventilation, and death. While tocilizumab (IL-6 inhibitor) continues to be used empirically in an intensive care unit (ICU) setting in those with severe COVID-19, a randomized trial failed to show its benefit in preventing progression to severe COVID-19 when given early in the course of the disease [16]. A case-control study of anakinra in COVID-19 patients that was limited by design (unmeasured confounding) plus high early event rate in retrospective controls reported fewer deaths and lower CRP levels, making its findings' clinical importance uncertain [17].

An extensive survey study conducted early in the pandemic did not identify rheumatic patients on immunosuppression to be at higher risk of severe complications from SARS-CoV-2 than the general population and conditionally advocated against the preventative withdrawal of DMARDs [18]. Another study reported a significant risk of infection in someone with active rheumatic disease, cautioning against stopping immunosuppressive medication for fear of getting COVID-19 [19]. A comparative cohort study that evaluated the impact of the inflammatory rheumatic disease on COVID-19 severity in the hospitalized patients concluded that neither having connective tissue disease but not inflammatory arthritis nor being on prior immunosuppressive therapies was associated with severe COVID-19 [20].

Another comparative cohort study reported that patients with rheumatic diseases were more likely to require mechanical ventilation without any difference in mortality [21]. The ACR guidance statement does not identify any risk factors for poor outcomes in COVID-19 that is specific to rheumatic diseases.

While there was some consensus on handling rheumatic medications before and during exposure, not much information was available about the timing of restarting immunosuppressive medications [11]. ACR came out with new COVID-19 recommendations in July 2020 about reinitiating treatment following COVID-19 infection [5]. The following Table 1 summarizes managing different rheumatic medications in the COVID-19 pandemic. The ACR guidance statement does not identify any risk factors for poor outcomes in COVID-19 that is specific to rheumatic diseases.

To decrease COVID-19 spread, we must optimize tele health use, decrease the frequency of routine laboratory surveillance when the risk associated with not testing is deemed low and delay initiating or re-dosing infusion treatments when disease flare risk is considered low (5).

While we continue to increase our understanding of COVID-19, there remain several unknowns. Though there is no consensus on the post-acute COVID-19 ("long COVID") definition, it is currently described as the presence of symptoms extending beyond three weeks from the initial onset of symptoms and chronic COVID-19 as extending beyond 12 weeks. It continues to baffle experts on why some patients who had experienced mild COVID-19 symptoms continue to experience prolonged post-covid-19 symptoms like fatigue and brain fog. In addition to general symptoms of fatigue, dyspnea, joint pain, and chest pain, specific organ dysfunction primarily involving the heart, lungs, and brain have been reported [22].

It is not entirely clear why some countries continue to experience higher mortality rates than others. The countries (like Brazil followed by Japan and Iran) that have the earliest vaccination policy for Bacillus Calmette-Guerin (BCG) have noted lesser mortality than those that introduced BCG vaccination later in life. The countries without universal vaccination policies (the US and Italy) had a higher mortality rate [23]. Even though WHO denies any role of BCG vaccine in COVID-19, randomized controlled trials using BCG is undoubtedly needed to determine if it influences the rapidity of response against COVID-19 [24].

Table 1: Restart 10-17 days after PCR result is positive for those who remain asymptomatic.

Rheumatic Drugs/ COVID-19 exposure	Not exposed to COVID-19 (any underlying AIRD) *	Exposed to COVID-19	COVID-19 positive (mild to moderate symptoms)	Severe COVID-19	Post mild (no pneumonia) COVID-19	Post severe COVID-19
NSAIDs	↑	↑	↑	↓	↔↑	↔
CST	↑	↑*	↑*	↑	↑*	↑
DMARD (cs)						
HCQ/CQ	↑	↑	↑	↑	¬↑	↑
SSZ	↑	↑	↓	↓	↔↑	↔
MTX,LEF	↑	?	↓	↓	↔↑	↔
DMARD (b)						
IL-6 mediated	↑	↑↔	↑↔	↑↔	↑	↔
Non IL-6 mediated (TNF inhibitors)	↑	↓	↓	↓	↔↑	↔
DMARD (ts) (JAK inhibitors)	↑	↓	↓	↓	↔↑	↔
CSA, MMF, AZA, tacrolimus	↑	↓	↓	↓	↔↑	↔
IL-1 inhibitor (anakinra)	↑	?	?	?	↔↑	↔

Note: NSAID: Nonsteroidalanti-inflammatory drugs; CST: Corticosteroids; DMARD: Disease-modifying antirheumatic drugs; cs: Conventional synthetic; b:Biologic; ts: Targetedsynthetic; HCQ:Hydroxychloroquine; CQ:Chloroquine; SSZ: Sulfasalazine; MTX: Methotrexate; LEF: Leflunomide; IL: Interleukin; CSA: Cyclosporin A; MMF: Mycophenolate mofetil; AZA: Azathioprine; JAK: Janus Kinase; TNF: Tumor Necrosis Factor; AIRD: Autoimmune Rheumatic Disease; *: Stable, Active or Newly Diagnosed; ↑: Continue or initiate; ↓: Stop; ↔: To be decided on case-by-case scenario; ?: Inadequate date; ↑↔: Can be continued in select situation; ↑*: Continue at the lowest possible dose ; do not discontinue abruptly; ↔↑: Restart within 7-14 days of symptoms resolution.

It is currently unclear as to how long the protection lasts against re-infection after natural infection with COVID-19. Antibodies typically appear around 5-14 days after onset of symptoms, and though they correlate with clinical severity, they do not seem to correlate with the rapid decline in viral load. Sometimes the antibody levels decline rapidly. There continues to be wide variation in commercially available kits to measure SARS-CoV-2 antibodies. While the immune response to a vaccine is considered a surrogate marker and may not transform into protection against an intended agent, theoretically, stronger seroconversion might be associated with a better safeguard against the viral agent.

For a pandemic to end, it has to either run its course (by infecting and consuming all the susceptible individuals) or the susceptible population gain herd immunity (~65-70% in case of SARS-CoV-2) mostly by mass vaccination. The United Kingdom became the first nation to approve the EUA of a COVID-19 vaccine on December 2, 2020 [25] and was soon followed by USFDA on December 11, 2020. These novel messenger ribonucleic acid (mRNA) vaccines incorporate lipid nanoparticles (wrapped on mRNA) into human cells. These mRNA encodes a protein and, after incorporation, instructs the host cell to produce this protein, which then stimulates an immune response against this protein, generating antibodies against SARS-CoV-2. While this is welcome and promising news to have been able to develop a vaccine in an unprecedented amount of time (9 to 10 months), several questions remain. It is unclear whether these mRNA vaccines prevent infection altogether or decreases disease spread in a population. Most vaccines do not provide absolute protection against infection, which will likely be the case with the SARS-CoV-2 vaccine. The 95% efficacy rates offered by these mRNA vaccines are likely preliminary, and as more data gets analyzed, efficacy rates may change. There is currently no data about its safety and efficacy in the immunosuppressed population. Moreover, there is a lack of information about these novel nucleic acids or viral vector vaccines on patients' autoimmune disease activity.

Prior studies have shown that humoral response to seasonal influenza, pneumococcal vaccine, and hepatitis B vaccine can be reduced while on certain immunosuppressive medications. As we await more vaccine data in the rheumatology population, it is reasonable to advocate proven strategies like holding methotrexate for two weeks after vaccination and vaccinating before starting rituximab [26]. FDA approval requires comprehensive safety data analysis and benefits far outweighing any risk from the vaccine. While we strive to achieve the lofty goal of global vaccination and hope to end the pandemic, we must continue to follow proven and effective mitigative strategies (face mask, goggles, social distancing, and frequent hand washing) to limit its spread.

CONCLUSION

It has almost been a year since SARS-CoV-2 was first identified, and it continues to ravage human lives, more so than ever before. While immunosuppressive medications increase the risk of infection, the evidence so far supports continuing their use in individuals with AIRD who are not exposed to the SARS-CoV-2 virus. When patients with AIRD is exposed to COVID-19 and tests positive, it is preferable to stop most DMARDs and potent immunosuppressants. The current provisional recommendation is to safely restart most immunosuppressive medications approximately two weeks after recovery from mild COVID-19. In contrast, the decision to restart

them in those who had severe COVID-19 should be considered on a case-by-case basis.

CONFLICT OF INTEREST

The author(s) report no conflict of interest in preparing this manuscript and has not received any financial support from any commercial entity.

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