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Review Article

REVIEW: COVID19 AND ITS ROLE IN THE FLARE OF RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disorder in which the immune system attacks the body's tissues, including joints, whereas Covid-19 is an acute respiratory sickness caused by a virus that affects the immune system and can produce a variety of symptoms as well as death in some cases. A higher frequency of autoimmune inflammatory arthritis has been associated with respiratory diseases caused by various viral infections and these infections can cause flare-ups in inflammatory arthritic patients. The study focuses on the link between Covid19 and Rheumatoid arthritis as well as the various drugs used to treat the disease and their effects on the human body. The numerous comorbidities, as well as the impact of drugs and vaccination on individuals, were discussed. People affected with RA are already at risk of infection due to the disease itself or the conditions brought about by the treatment of drugs or due to several clinical opinions and therapies. The data from various researches explains the prevalence of COVID19 symptoms in rheumatoid arthritis patients is more than twice that of the effect.

Keywords: Glucocorticoids, DMARDs, NSAID, Vaccination.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a persistent inflammatory autoimmune disorder that affects junctures between the bones and cause cartilage degradation. It's aprogressive condition with high indisposition and premature death [1]. Having a global prevalence of 0.25 percent, RA is the most common rheumatic illness [2]. As a result of defective immune system functioning and long-term immunosuppressive drugs, patients having RA are distinctively prone to infections [3].

In December 2019, the SARS-CoV-2 (severe acute respiratory coronavirus 2 syndrome) virus was found in Wuhan, China. This isdistinct virus, according to phylo-genetic study, with 80 percent nucleic acid similarity to SARS-CoV-1. Dry cough, fever, dyspnea, and weariness, as well as lymphopenia, are all symptoms of this infection. The virus has spread rapidly over the world since outbreak promoting the World Health Organisation to designate it as a pandemic on March 11, 2020 [4].

In the time of expanding public health crisis, elucidating the relationship between COVID19 and the community of vulnerable individuals enduring the immune related rheumatological diseases is critical. As the study about the etiology of COVID19 is progressing, several anti-rheumatic medications are being considered as prospective therapeutic options [4].

People affected with RA are already at risk of infection due to the disease itself or the conditions brought about by the treatment of drugs or due to several clinical opinions and therapies [5].

Six significant comorbidities in rheumatic diseases which must be addressed, according to a European League Against Rheumatism (EULAR) initiative includes ischemic heart diseases, depression, infections, diseases concerning digestive system, and weakening and degradation of the bone, causing osteoporosis [6]. It's critical to evaluate the significant comorbidities associated with rheumatic diseases in the scenario of COVID-19 risk, as well as predict how the pandemic would affect comorbidity management and prevention.

2. ASSOCIATION BETWEEN COVID-19 AND RA:

A higher frequency of autoimmune inflammatory arthritis has been associated to respiratory diseases caused by various viral infections [7]. In addition, infections can cause flare-ups in inflammatory arthritic patients [4]. As aresult, COVID19 has a part in the progress of RA or disease flare-ups [8].The characteristics of COVID-19 arthralgia include bone and joint pain. Even after recovering from COVID-19 disease, around 27% of individuals have joint discomfort [9]. The patients often experience arthralgia and have lower bone density especially if they are using glucocorticoids. C-X-C motif chemokine ligand 10, IL-17, and TNF-α are all inflammatory mediators released in response to COVID-19 and the infection hasbeen previously associated to the onset of arthritis [10].

The COVID-19 evoked overexpression of the immune related inflammatory response via a citrullination-independent mechanism could be a possible causative factor in the emergence of RA [11] Despite this, more advanced data is required to be evaluated whether RA symptoms after the infection are connected or mere coincidence.

According to studies, patients with RA are more likely to contract COVID19. The prevalence of COVID-19 having symptoms in rheumatic patients is over twice the effect according to the data from several studies [12]. It's reasonable to conclude that RA patients have a greater chance of acquiring the infection based on the majority of clinical evidence.

3. DRUGS USED DURING RA WHICH HAS EFFECTS IN COVID19

3.1. Glucocorticoids

The importance of the use of GCs during COVID-19 pandemic condition is debatable. Preliminary research into their use in COVID-19 was unsuccessful, with detrimental effects sometimes outnumbering benefits [13]. Patients who were given corticosteroid had more clinical symptoms and a higher rate of infection, inflammation index, as well as greater abnormalities on chest CT, implying that its use was connected to the intensity of symptoms [14].

Persistent use of dosages greater than10 mg/day has been associated with a possibility of infections. GC at larger doses appears to provide a greater risk than csDMARDs, biologics, or JAK inhibitors [15].

Patients who have been using GCs for a long time should proceed with taking the drug at a low dose possible [16]. Rapid GC cessation should be discouraged due to the potential of suppression of hypothalamic pituitary adrenal axis, which can be particularly problematic in challenging situations like a virus infection. Recent research suggests that effects of GCs including the suppression of the immune system can diminish inflammation during the infection, lowering fatality and hospitalization time [17].

An increased risk of infection is one of the dangers, and giving a dose in moderate to high range a canlead to barren prospects. As a result, rather than abrupt withdrawal, it is recommended to continue at a low dose practicable [13].

3.2. Conventional synthetic DMARDs (csDMARDs)

These include hydroxychloroquine and chloroquine which comes in the category of antimalarials. Other csDMARDs include methotrexate, leflunomide and sulfasalazine. The importance of DMARDs in the appearance, graveness, and controlling of COVID-19 has been widely recognised. At the onset of COVID-19, hydroxychloroquine was touted as a curative medication, but further clinical study found no advantages [18].

The antiviral ability of HCQ and CQ has been established *in vitro*, prompting multiple clinical investigations to confirm their efficacy in therapy, prevention, and post-exposure conditions [19]. A case study of rheumatoid arthritis patients found that individuals who use HCQ on a regular basis have the same probability of acquiring COVID19 as those who don't [20].

Nonetheless, hydroxychloroquine and chloroquine are reasonably secure drugs in the absence of verified COVID-19 exposure, and their use is not prohibited in the current epidemic. In the event of active infection, other csDMARDs such as sulfasalazine, methotrexate, and leflunomide should be stopped for a certain period of time, even if they are safe to take if there is no COVID19 occurrence [20].

As a result, the indications are unknown; nonetheless, it is thought to have an antiviral action by blocking viral entrance and the events occurring related to the invasion. HCQ is considered to be a less harmful drug which is more effective [21].

Overdosing can be harmful, and cardiovascular adverse effects are common (QT prolongation). Other contraindications include diseases affecting the retina and deficiency of G6PD [22].

3.3. Biologics and targeted synthetic DMARDs

The bDMARDs include Anti-TNF drugs, Anti-IL-1 drugs (Anakinra, canakinumab, rilonacept), Anti-IL-6 drugs

(Tocilizumab, sarilumab),Anti-IL-17 drugs (Brodalumab, ixekizumab (LY2439821), secukinumab (AIN457) and Anti-IL-23 drugs. tsDMARDs include JAK inhibitors.

Many immune-mediated inflammatory illnesses are treated using TNF inhibitors which target the proinflammatory cytokine TNF (IMIDs). According to acohort research, the therapy using TNF inhibitor was associated with a decreased occurence of COVID19-related hospitalisation or fatal effects when compared to other commonly used treatment regimens [23].

Blocking IL-6 has been useful in a variety of conditions, including RA [17]. IL-6 was recently shown to be a key cause of the inflammation related with COVID-19 infection [24]. Tocilizumab is taken for rheumatological diseases as fixed-dose subcutaneous formulation [25]. Anti-interleukin-6 medications are being repurposed for treating COVID-19 patients, who are primarily in latter stages of the disease. Even though anti-IL-6 drugs have potential benefits, the clinical evidence for tocilizumab is sparse and only partially available. While additional substantial clinical data on anti-interleukin-6 drugs efficacy in COVID-19 affected individuals is awaited, their toxic effects should be handled effectively [26].

IL-1 is a key mediator in CoV-19-induced lung inflammation and fibrosis, so inhibiting this pro-inflammatory cytokine could be beneficial [27]. Suppressing inflammation, avoiding innate immunity overwhelming, improving oxygen saturation, lowering neutrophil counts, and inhibiting Th17 cell production are some of the indications for anti-IL 1 drugs. The patients with RA acquiring COVID19 are recommended to suspend the treatment temporarily [28]. According to a recent study, the COVID19 E protein creates channels that are impermeable to Ca2+ ions. SARS-CoV-2 is thought to have a similar mechanism of action, which would explain the elevated levels of IL-1 reported in COVID-19 patients [29].

Patients should consider treatment termination with their rheumatologists, according to EULAR and PRES. If COVID-19 infection is reckoned, the ACR recommends temporarily stopping tDMARD medication. If COVID-19 is confirmed or suspected, NICE and the ACR recommend stopping tDMARDs, with the ACR making an exemption for IL-6 inhibitors, which can be continued in certain conditions. These guidelines are based on expert opinion, as there are few epidemiological verifications about the possible risk of tDMARDs in patients with rheumatic disorders developing significant COVID-19 disease sequelae [30].

JAK inhibitors are biologics that block type I and type II cytokine receptors. They are being tested and used as a treatment for variety of disorders [31].

JAKinibs are recommended as a promising treatment for people affected with COVID-19 who are hospitalised. IFN-mediated antiviral response impairment, venous thromboembolism, and hypersensitivity are among the risk factors [32].

3.4. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

RA and ankylosing spondylitis are still treated with NSAIDs. NSAIDs are recommended as effective symptomatic therapies in early arthritis by the European League Against Rheumatism, providing that they are given at the lowest dose for the shortest time possible and that risks related to kidney, heart and digestive system have been considered [33].

However, it is unknown whether simultaneous NSAID medication is detrimental or safe in people with Covid-19. Anti-inflammatory drugs, on the other hand, may be able to prevent Covid-19's lethal cytokine storm. Interleukin-6 (IL-6) was reported to be reduced in human tissues and sputum after taking ibuprofen, a routinely recommended NSAID. Studies concluded that administration of NSAIDs is not related to an increased case of COVID19, hospitalization or fatality in covid19 affected individuals [34].

3.5. Vaccination

People having systemic rheumatoid arthritis are a subset for which general population data may not be applicable. Reduced vaccination immunogenicity due to the disease condition or the intake of antirheumatic medications and immunizations producing exacerbated side effects or flares of the underlying rheumatic disorders are all potential problems [35]. In a December 2020, international study of 1531 people with rheumatic disease of which 32 percent said they were unsure about vaccination [36], which could be due to these worries.

There are three primary forms of COVID-19 vaccines currently available for SARS-CoV-2 vaccination, each with a different mechanism of action: mRNA vaccines, vector vaccines, and protein subunit vaccinations. There is currently no substantial proof of the new vaccinations' safety and efficacy in people with rheumatic illnesses. RA patients are safe to take vaccines and generally immunogenic, according to data on the most common immunizations [37]. With the exception of studies in patients receiving rituximab, whose responses were severely hampered, most studies in patients receiving

c/b/tsDMARDs found same activity of immune reaction in patients receiving c/b/tsDMARDs. Antibody responses following influenza and pneumococcal vaccination have been linked to B cell depletion therapy [38]. According to the 2019 EULAR vaccination recommendations, the vaccine should be administered only after a period of 6 months after the previous course of B cell-depleting therapy, for the naïve B cell population to form new cells [39].

4. COMORBIDITIES IN RHEUMATIC DISEASES DURING COVID-19

Rheumatic disorders are long-term ailments which result in damage and comorbidities. As mentioned earlier there are six major comorbidities associated with RA which can affect the patients during COVID-19 [40]. Cardiovascular disease is most certainly the most prevalent comorbidity. Normal community has a 50% lesser risk of myocardial infarction than patients with RA and gout [41].

The incidence of various co-morbidities differs depending on rheumatic diseases. Comorbidities are frequently increased in patients with difficult-to-control disorders [42].

The onset of autoimmune illnesses has been related to COVID-19. Multisystem inflammatory syndrome in children (MIS-C) is an immune-mediated condition [43]. COVID-19's inflammatory pathways are very similar to those found in RA [44]. Even so, there is no demonstration that explains the cause of arthritis due to COVID-19 [45] that may be the exception to the rule. Likewise, there is no indication that COVID-19 can make the conditions of already existing arthritis even worse [46]. COVID-19 has been linked to diseases related to heart muscles and formation of fibrous tissues in the lungs which could have far more significant repercussions for patients with RMDs. Magnetic resonance imaging demonstrated active cardiac participation in 60% of COVID-19 patients, regardless of pre-existing conditions or severity [47]. A comparable study from China was also published [48]. The hardening of the fibrous tissues of the lungs after the acquirement of COVID19 is likely to be linked to old age, pneumonia severeness, and a previous history of any malfunction of lungs [49].

A risk factor calculating the comorbidities in RMDs should be constructed to anticipate severe COVID-19 and followed death.Such comorbidities should be aggressively addressed in order to mitigate these risks. The epidemic must focus our attention on comorbidities, not away from them [50].

5. CONCLUSION

RA patients have a higher chance of COVID19 outcomes. This topic of study is still up for debate. Because of the disease and the side effects of various treatments, persons with RA are already at risk of infection. The pandemic necessitates a focus on the medications employed as well as the disease's comorbidities.

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Conflict of interest

No conflict of interest.

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