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Study of the Worsening of Rheumatoid Arthritis After Sars-Cov2 Infection

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic is causing morbidity and mortality worldwide. Patients with rheumatoid arthritis (RA) have faced unique challenges during the pandemic, including concerns about the risk of infection, drug shortages, limited access to care, social isolation and mental health. The inflammation pathways generated by the two pathogens mentioned above, and the convergence that occurs between them, is what accentuates the inflammatory process, resulting in the worsening of RA. By studying the inflammatory process involved, it becomes correct to analyze the cells that trigger the entire pathological process, such as cytokines and interleukins, and understanding how the regulation of the NLRP3 inflammasome controls this immune response could be the solution to new therapeutic perspectives. In this project, we intend to review the pathogenesis and therapeutic similarities of patients with rheumatoid arthritis after COVID-19 infection, as well as evaluating new therapeutic challenges associated with autoimmune disease and improving the clinical condition of these patients.

Keywords: Rheumatoid Arthritis; COVID-19; Inflammasoma; Immune system.

Area of concentration: Immunology; Public health

INTRODUCTION

Autoimmune rheumatic diseases are a heterogeneous group of conditions characterized by the disruption of immune tolerance and the production of autoantibodies together with substances responsible for damage to various structures in the body (Yang et al., 2018). Although autoimmune diseases were initially considered uncommon, the effects associated with mortality and morbidity have contributed to highlighting the importance of studying and understanding these pathologies (Bogdanos et al., 2012), as well as constituting a complex and heterogeneous group that affects 3-5% of the world's population (Bogdanos et al., 2012; Yang et al., 2018; Júnior and Silveira, 2021).

Autoimmune rheumatic diseases are characterized by a drop in immune tolerance and damage to certain structures. The main diseases found in this category are: inflammatory myopathies (IM), systemic lupus erythematosus (SLE), systemic sclerosis (SS), Sjögren's syndrome (SS) and rheumatoid arthritis (RA) (Mosca M et al, 2011).

Rheumatoid arthritis is an inflammatory, systemic and autoimmune disease, characterized by chronic and progressive evolution, causing damage to the synovial membrane (McInnes; Schett, 2011). There is joint damage, functional loss and pain (Radu and Bungau, 2021). A study carried out in Brazil showed a prevalence of 0.2% to 1% of rheumatoid arthritis in adults, but some factors increase the chances of its development, including age (higher incidence between the third and fifth decade of life) and gender (more frequent in women than in men) (Radu and Bungau, 2021).

In May 2023, the World Health Organization (WHO) declared an end to the global health emergency caused by the Covid pandemic. It is worth noting that the disease still claims one life every three minutes and that thousands of people need intensive care units. And millions are living with the effects of Covid. In this sense, the COVID-19 pandemic has raised several interesting research questions, as well as clinical challenges in the context of rheumatic diseases (WHO, 2023).

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was considered an unprecedented global health crisis (World Health Organization, 2019). At the beginning of the pandemic, patients with rheumatoid arthritis (RA) expressed concern about the risks of COVID-19 due to treatments with immunosuppressants, an underlying inflammatory state and associated comorbidities. In addition, studies at the beginning of the pandemic suggested that patients with rheumatic diseases may have a higher risk of respiratory failure and death from COVID-19 (D'Silva KM, Wallace ZS, 2021).

Despite the multiple differences between COVID-19 and RA in terms of etiology, epidemiology, clinical characteristics, involvement and prognosis, they seem to have some similarities in pathogenesis and risk factors associated with the disease. For example, some external microorganisms can cause acute and chronic arthritis, either by their direct presence in the joints or the autoimmune reaction induced by the host (Mathew AJ, Ravindran V, 2014). In addition, patients with RA often have comorbidities such as diabetes mellitus, cardiovascular disease and lung disease, which further increases the risk of viral infections (Listing J, Gerhold K, Zink A, 2013). This increased risk of infection is associated with certain risk factors similar to those reported in COVID-19 (Zhou P et al, 2020).

Generally, the production of inflammatory cytokines in host cells requires inflammasomes (Broz, V.M. Dixit, 2016) and accumulating evidence suggests that the inflammasome plays a role in the pathogenesis of rheumatic diseases (Shin JI et al, 2019), in addition to also being activated by SARS-CoV-2 directly or through various cells or molecular signaling events (Zhao N, Di B, Xu LL, 2021).

The treatment of RA and other rheumatic diseases aims to reduce morbidity and mortality, and features biological therapies or disease-modifying drugs (DMARDs) (Mota et al. 2015). Inflammation driven by the NLRP3 inflammasome accompanies the pathogenesis of autoimmune diseases, which includes rheumatoid arthritis and makes the NLRP3 inflammasome an attractive drug target. Meanwhile, NLRP3-mediated immunity is a critical response for host defense against bacteria, viruses, and fungi (Hise et al, 2009; Witzenrath M, et al, 2011; Niu J et al, 2019).

Therefore, a balance between activators and inactivators of NLRP3 inflammasomes is necessary to maintain immune homeostasis (Liu D et al 2020), but there are no therapeutic agents currently available with this function. Therefore, it is necessary to understand the mechanism of the NLPR3 inflammasome in order to explore promising therapeutic strategies for autoimmune diseases such as RA in the future.

OBJECTIVES

The purpose of this study is to review the pathogenesis and therapeutic similarities of patients with RA after COVID-19 infection, as well as to evaluate the therapeutic challenges associated with autoimmune diseases and improving the clinical condition of these patients, in addition to facilitating the understanding of the basis of the disease by academics and health professionals.

METHODOLOGY

The work was carried out in the form of a bibliographic review with data analysis in the literature, with the aim of gathering studies on the worsening of rheumatoid arthritis post-COVID-19 and the prospects for new treatments. This review article is the product of bibliographic research carried out in the international databases PubMed (US National Library of Medicine) and Scientific Electronic Library Online (scieLO), by consulting articles published in the last 5 years (2019 - 2024). The bibliographic survey was carried out from April 2023 to December 2024. From the researched material found, references were selected that presented content that contributed to the fulfillment of the objective of this work, reinforcing the theoretical-conceptual basis of the subject in question, as shown in the table below.

N°	Título	Autores/ano	Conclusão
1	Epidemiology, pathogenesis, clinical presentations, diagnosis and treatment of COVID-19: a review of current evidence	Rahman et al./ 2021	The COVID-19 pandemic has proved to be the biggest global public health crisis, with direct respiratory transmission rapidly amplifying its spread.
2	SARS-CoV-2 and the pandemic of COVID-19	Adil et al./ 2021	SARS-CoV-2 is a life-threatening virus, and in addition to its symptoms, the sequelae can lead to hospitalization. As a result, strategies for both intensive hospital care and reducing transmission are important until vaccines are developed to control the disease.
3	COVID-19 Transmission, Current Treatment, and Future Therapeutic Strategies	Salian et al./2021	The studied molecular means of SARS-CoV-2 with greater transmission capacity compared to other variants, and within this focus the approach of new clinical strategies, such as the redirection of drugs for treatment.
4	Virology, Epidemiology, Pathogenesis, and Control of COVID-19	Jin et al./ 2020	The transmission potential of SARS-CoV-2 is a major public threat worldwide. Transmission is via droplets and indirect or direct contact. There is a need to seek interventions with the aim of reducing the serious condition of patients.

5	Immunity, endothelial injury and complement-induced coagulopathy in COVID-19	Perico et al./2021	The clinical presentation of each individual is unique, however, depending on the viral load, the following can be found: immune dysfunction, generalized endothelial damage, complement-associated coagulopathy and microangiopathy. Considering the socio-economic situation and the treatment available, a better understanding of the mechanisms must be sought in order to provide the correct therapy.
6	Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19)	Umakanthan et al./2020	The COVID-19 disease has proved to be impactful with the rapid increase in the number of infected people, causing a major global mobilization. In addition to the need for a better understanding of its mechanism, there is a need for a strategy for treatment and prevention.
7	Cutaneous Manifestations of COVID-19: A Systematic Review	Singh et al./2021	SARS-CoV-2 has an asymptomatic clinical presentation, the study of a new manifestation and its pathogenesis is significant for further evidence.
8	A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment	Parasher/ 2020	The COVID-19 disease has proven to be a global health emergency. The treatment that has proved effective at the moment is support with oxygen therapy, antivirals, steroids and antibiotics.
9	The Pathogenesis of Rheumatoid Arthritis	McInnes e Schett/ 2011	Increased understanding of the immunological mechanisms of rheumatoid arthritis has led to the development of a considerable number of new therapeutic agents that alter the natural history of the disease and reduce mortality.
10	Management of Rheumatoid Arthritis: An Overview	Radu e Bungau/ 2021	There is interest in controlling the autoimmune disease in order to improve the patient's quality of life. There are treatments capable of controlling it, but many patients do not respond to treatment.
11	A Public Health Approach to Addressing Arthritis in Older Adults: The Most Common Cause of Disability	Hootman et al./ 2012	Arthritis has a serious impact on older patients, and brings functional impairment, which is why a multidisciplinary approach, with the support of public health, can delay disability.
12	Economic burden of rheumatoid arthritis: a systematic review	Cooper/2000	There is a complication when estimating the costs of rheumatoid arthritis, because it is not possible to generalize due to the socio-economic conditions of each country. For this reason, there is a need for better global studies to specify better treatments and the size of the costs.
13	Rheumatoid Arthritis: Review of Immunological Aspects	Morais et al./ 2014	In recent years, significant progress has been made in understanding the immunopathological basis of RA, which has led to the development of therapies using blockers of inflammatory cytokines (tnf, IL-1, IL6) and B and T lymphocytes to treat the disease.

14	Interleukin 6 and Rheumatoid Arthritis	Yoshida e Tanaka/2014	As the evidence shows, biologics are recommended as the first line of treatment. However, the mechanism that makes interleukin-6 blockade effective and therefore leads to a better understanding of the pathogenesis still needs to be clarified.
15	Smoking increases rheumatoid arthritis susceptibility in individuals carrying the HLA-DRB1 shared epitope, regardless of rheumatoid factor or anti-cyclic citrullinated peptide antibody status	Bang et al./ 2010	Smoking is associated with rheumatoid arthritis (RA) in individuals with the HLA-DRB1 shared epitope (SE). We demonstrate that the combination of SE alleles and smoking is associated with RA susceptibility, regardless of anti-CCP antibody or RF status, but that the combination shows stronger effects in anti-CCP positive/FR RA patients than in anti-CCP negative/FR negative RA patients.
16	The Immunopathogenesis of Rheumatoid Arthritis	IMBODEN/2009	Rheumatoid arthritis (RA) may represent a T-cell dependent immune response to a restricted antigen(s) within the joint, with inflammatory pathways reflecting secondary recruitment. The nature of the triggering antigen is unknown - the stimulus may be an infectious agent or a host constituent. In patients with RA, the centrality of anti-self and immunogenetic repercussions is apparent. Further clarification of these mechanisms would result in the potential for antigen-specific immunosuppressive therapy.
17	Immunological and molecular factors in rheumatoid arthritis	Neves/2017	Immunological evidence indicates that the HLA-DRB1 marker and the anti-citrullinated peptide antibody are responsible for the onset of rheumatoid arthritis. However, more research is still needed to better understand its pathogenesis.
18	Medicines incorporated into the single health system for the treatment of rheumatoid arthritis	Felice et al./2019	Patients with rheumatoid arthritis need to change their medication constantly. However, without the support of the Ministry of Health to provide treatment, long-term treatment is not possible. In order for this to be available, criteria must be met and what is evidenced can be made available.
19	Pathogenic implications, incidence, and outcomes of COVID-19 in autoimmune inflammatory joint diseases and autoinflammatory disorders.	Ruscitti et al./ 2021	Patients with autoinflammatory diseases or musculoskeletal diseases who have been infected with COVID-19, if treated with biological or synthetic targeted DMARSD, are not at risk of developing the severe form of the disease.
20	The Role of IL-1β in the Bone Loss during Rheumatic Diseases	Ruscitti et al./ 2015	In autoimmune and autoinflammatory bone diseases, despite different treatments to reduce inflammation, continuous bone loss is still observed. However, interleukin 1 beta antagonism was shown to reduce bone loss.
21	Immunology, immunopathogenesis and immunotherapeutics of COVID-19; an overview	Khrosroshahi et al./ 2021	COVID-19 manifests itself as a respiratory disease, and is best explained as a virus-induced immunopathology.

22	Interleukin-6 in Rheumatoid Arthritis	Pandolfi et al./ 2020	Patients showed improvements in quality of life after treatment with different IL-6 antagonists combined with different DMCDs.
23	Innate Immune Response and Inflammasome Activation During SARS-CoV-2 Infection	Islamuddin et al./ 2022	The pathogenic action of SARS-CoV-2 that acts through binding with ACE2, activating innate immune sensors and generating a massive stimulatory response of inflammatory cytokines, and which may involve the NLRP3 inflammasome.
24	NLRP3 inflammasome activation contributes to the pathogenesis of rheumatoid arthritis	Guo et al./ 2018	It was shown that the NLRP3 inflammasome was activated in the synovium of mice with rheumatoid arthritis.
25	COVID-19 and Rheumatoid Arthritis Crosstalk: Emerging Association, Therapeutic Options and Challenges	Dewanjee et al./ 2021	The immunological/inflammatory pathogenesis of COVID-19 and RA have similarities, but different mechanisms. However, the use of antirheumatic drugs in RA patients with COVID-19 should be analyzed individually for greater benefit and control of COVID-19.
26	Older age, comorbidity, glucocorticoid use and disease activity are risk factors for COVID-19 hospitalisation in patients with inflammatory rheumatic and musculoskeletal diseases	Hasseli et al./ 2021	Patients with current or previous glucocorticoid treatment are at risk of hospitalization. And moderate to high musculoskeletal disease activity is an independent risk factor for hospitalization.
27	Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry	Gianfrancesco et al./ 2020	The use of glucocorticoids greater than or equal to 10 mg/day is associated with a greater chance of hospitalization. Patients who use or have previously been exposed to DMARDs are not associated with a greater chance of hospitalization.
28	Post-COVID-19 arthritis: is it hyperinflammation or autoimmunity?	Taha et al./ 2021	The mechanism of post-COVID-19 arthritis is inflammatory, not autoimmune. Therefore, the increase in interleukin-6 discovered before the manifestation of symptoms allows for early treatment.

DEVELOPMENT

In December 2019, the first cases of infection with the novel coronavirus (COVID-19), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), were documented in Wuhan, China (Rahman et al. 2021). The World Health Organization (WHO) characterized the situation as a public emergency of international concern on January 30, 2020, but declared the COVID-19 pandemic in March.

Covid-19 has approximately 770,437,327 million confirmed cases worldwide. As the disease is highly contagious and infectious, there have been more opportunities for it to mutate and present variants, the Omicron, Alpha, Beta, Gamma and Delta of which are in circulation (Pan American Health Organization).

The view on COVID-19 infection is that 80% of the disease is mild to moderate, 13.1% severe (presence of tachypnea, oxygen saturation <93% at rest, more than 50% of the lung impaired on imaging tests) and 6.1% present with critical severe disease requiring intensive care support (presents with respiratory failure, septic shock or onset of organ failure) (Adil et al 2021). The typical symptomatology is dry cough, fever, myalgia, anorexia, however, anosmia and dysgeusia are often seen, and are not exclusive to COVID-19. It is important to note that around the 5th day, 30% of patients may start with dyspnea and from the second week onwards, there may be a critical worsening of the disease, which is common in patients who have the most severe form of the disease (Salian et al., 2021).

The virus is transmitted through respiratory droplets (Jin et al., 2020). The host's angiotensin-converting enzyme 2 (ACE2) protease is the main gateway to the virus, due to the S protein that does not signal the immune response and increases its affinity to the enzyme (Perico et al., 2021). The

combination of these factors causes sequelae in the body, including atrophy, fibrosis, inflammation and vasoconstriction, causing damage (Umakanthan et al., 2020).Therefore, when the virus enters the body, inflammation is triggered, causing the immune system to activate and release cytokines in a disorderly manner, causing a "cytokine storm" (Singh et al., 2021). Interleukins (IL-1, IL-6, IL-8, IL-10, IL-12), tumor necrosis factor alpha (TNFα), interferon gamma and beta (IFN-γ and IFN-β) are recruited, followed by chemotaxis of neutrophils, CD4 and CD8 cells and B cells. The cells that arrive by chemotaxis are there to fight the virus, but they cause inflammation and persistent lung damage, which culminates in acute respiratory distress syndrome (ARDS) (Parasher 2020).

For diagnosis, the standard is reverse transcription (RT-PCR) of oropharyngeal and nasopharyngeal swabs, chest tomography and serum antibody tests (IgM and IgG) (Adil et al., 2021). And after diagnosis, watch out for complications such as acute respiratory distress syndrome (ARDS), cardiovascular complications (arrhythmias, heart damage) and advanced stages of collagulation (Salian et al., 2021).

COVID-19 has been shown to be a disease that disadvantages the body, affecting the system and causing a considerable increase in inflammation. Therefore, considering the clinical picture of patients with rheumatoid arthritis, it is necessary to understand them and the way they are affected, in order to consider the appropriate treatments.

Rheumatoid arthritis is an inflammatory, systemic and autoimmune disease, characterized by chronic and progressive evolution, causing damage to the synovial membrane (McInnes and Schett, 2011). There is joint damage, functional loss and pain (Radu and Bungau, 2021). A study carried out in Brazil showed a prevalence of 0.2% to 1% of rheumatoid arthritis in adults, but some factors increase the chances of its development, including age (higher incidence between the third and fifth decade of life) and gender (more frequent in women) (Radu and Bungau, 2021).

With regard to rheumatoid arthritis, statistical studies and interpretation of quantitative data have shown that the disease represents not only a medical pathology, but also a public health issue, since it is the most common medical cause of loss of mobility-related functionality among adults in the United States (USA) (Hootman, J. M et al, 2012). In addition, several health economic studies have measured the economic impact of the burden of RA and, as a result, have shown that the costs of preventing RA by reducing risk factors or treating incipient cases are much lower than those generated by hospitalizations and surgeries (Cooper, N., 2000).

According to Morais et al, individuals who are genetically predisposed and exposed to environmental factors develop the disease as a result of immunological alterations that lead to the activation of subpopulations of T and B cells and macrophages, resulting in the production of cytokines and pro-inflammatory mediators. These components promote an amplified inflammatory response in the joint tissue and culminate in bone and joint damage (Yoshida and Tanaka, 2014). In addition, the combination of exogenous factors, such as smoking, favors an increase in the inflammatory response (Bang et al., 2010; IMBODEN, 2009).

The immune process can occur many years before any symptoms of joint inflammation are considered by the individual, and is called the pre-phase of rheumatoid arthritis. This involves epigenetic alterations and interactions in the genomic structure associated with environmental factors that can cause modifications in immunoglobulin G (IgG), type II collagen and vimentin (structural protein) (Radu and Bungau, 2021).

In rheumatoid arthritis, autoreactive T and B cells lead to inflammation of the synovial membrane (synovitis), becoming a source of pro-inflammatory cytokines enabling joint destruction and affecting its entire structure, forming pannus (inflammatory thickening), which is characteristic of arthritis. B lymphocytes with altered expression, with a low level of IgG inhibitory receptor (FcyRIIb) and a high level of co-stimulatory molecule. T lymphocytes, on the other hand, produce pro-inflammatory cytokines TNF, IL-1 and IL-6, which cause and promote the worsening of the joint (Neves, 2017).

The diagnosis, in addition to signs and symptoms, should be based on laboratory and radiographic findings. According to the American College of Rheumatology, the main symptoms are related to areas of inflammation, nodules, serum rheumatoid factor, radiographic changes (erosions or decalcifications) and arthritis in the joints of the hands or wrists (Felice et al., 2019).

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Therefore, the consequences of COVID-19 infection, open questions about the impact on rheumatic musculoskeletal diseases, mainly because there is evidence that demonstrates the pathological mechanisms that stand out in autoimmune and autoinflammatory conditions are involved in the defense and response of the host against SARS-CoV-2, and in more severe cases, following with a cytokine storm syndrome (Ruscitti et al., 2021).

According to Ruscitti et al., the triggering of a persistent inflammatory reaction depends on the host's immune response, following with exacerbation in inflammatory diseases. This infection results in the uptake of antigens by antigen-presenting cells and presents them to T cells, initiating the activation of the pro-inflammatory cascade that can cause tissue damage and autoantigen uptake, and molecular mimicry can occur.

When the immune response is activated by the angiotensin-converting enzyme 2 (ACE2), lymphocytes and macrophages are summoned by the link they have with ACE2. Macrophages have been shown to up-regulate interleukin-6 (IL-6), which favors excessive inflammatory involvement and increases the severity of the disease (Riscutti et al., 2021).

Inflammasomes play a vital role in immune regulation, leading to autoimmune diseases due to their dysfunction or hyperactivation, and rheumatoid arthritis is one of them. As previously explained, rheumatoid arthritis is characterized by chronic inflammation, which is exacerbated by

cytokines in its pathogenesis. According to Guo et al., expression of the NLRP3 inflammasome has been shown in patients with RA. It is important to note that the treatment chosen to control RA can directly affect the outcome of the cure in patients who contract COVID-19.

The pharmacological treatment of RA has been expanded over the years, and the strategy being assigned to patients follows the principle of reducing symptoms, slowing down the progression of the disease and avoiding future complications. For this reason, NSAIDs and glucocorticoids are used to reduce symptoms, and disease-modifying therapy (DMARDS) is used to slow down progression, divided into conventional synthetic, biological and targeted synthetic (Radu and Bungau, 2021). According to Dewanjee et al., the use of drugs used in RA treatment can increase the chances of COVID-19 infection, so the use of certain drugs is being discouraged, such as: glucocorticoids, biological DMARDs (except IL-6 inhibitors) and targeted synthetics, and in severe cases of COVID-19, NSAIDs should be discontinued. Now the proposed drugs that have a good prognosis are: Conventional synthetic DMARDs (except leflunomide, methotrexate and sulfasalazine), NSAIDs, IL-6 inhibitors. According to a study by Hasseli et al. of 468 patients infected with COVID-19, 48% were diagnosed with RA and had a high hospitalization rate. In addition to analyzing the pattern of use and dosage of RA symptomatic drugs, the use of glucocorticoids > 5 mg/day was related to the hospitalization rate, and drugs that prevent the progression of the DMARDS disease were not associated with hospitalization. According to Gianfrancesco et al., of 600 patients it was reported that 230 (38%) the most common disease was RA and 104 patients were hospitalized, and that patients on monotherapy treatment with targeted synthetic DMARDs have a low rate of hospital admission.

Taha et al. (2021) showed that the prevalence of post-COVID arthritis was 37%. Ankle, knee and wrist were the most commonly affected joints. Older age, smoking and arthralgia were all associated with post-COVID arthritis. Pre-treatment (baseline) interleukin (IL)-6 levels, as well as 6-month post-COVID C-reactive protein (CRP) and erythrocyte sedimentation rate were significantly higher in patients with arthritis compared to those without.

Thus, even with the end of the pandemic, there are still variants that can cause serious complications, which is why it is important to follow therapeutic lines that aim to avoid the cytokine storm and that there is no loss of treatment, and it is important to be aware of the clinical picture and the proposed treatment of the patient with RA, so that changes can be made that do not cause complications due to the COVID-19

FINAL CONSIDERATIONS

This study made it possible to understand both pathogens and how rheumatoid arthritis worsens after infection with SARS-COV-2, as well as analyzing the therapeutic similarities for treatment. By analyzing the mechanism of pathogenesis, it was possible to come to the conclusion that the clinical picture of post-COVID-19 arthritis is inflammatory and not autoimmune, as shown by the fact that there is an increase and persistence of pro-inflammatory cytokines. It is therefore essential to evaluate the treatments associated with autoimmune diseases individually, as they can change the course of exacerbation. Thus, based on this analysis, a suggestion for new therapy mechanisms could be the management of NLRP3 inflammasome activation, allowing early management and preventing the patient from reaching the hyperinflammatory state responsible for worsening the clinical condition.

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