

THE RHEUMATOLOGIST IN THE COVID-19 SCENERY

O reumatologista no cenário da covid-19

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Abstract

Amid the pandemic of the new SARS-CoV-2 coronavirus, some clinical and pathophysiological aspects of this disease are associated to immune disorders that are well known in rheumatology. In this scenario, the rheumatologist is faced with some uncertainties and the need to face this pandemic associated with immune-mediated diseases and their peculiarities. The cytokine overuse, the use of immunomodulatory and immunobiological medications, the therapeutic recommendations given due to the presence of COVID-19 and the emerging need for social isolation directly impacting the assessment of rheumatological patients are essential aspects that should be valued in this period.

Keywords: COVID-19, Rheumatology, Rheumatic diseases.

Resumo

Em meio à pandemia do novo coronavírus SARS-CoV-2 alguns aspectos clínicos e fisiopatológicos desta doença estão associados a distúrbios imunes bastante conhecidos na reumatologia. Nesse cenário o reumatologista se vê diante de algumas incertezas e necessidade do enfrentamento desta pandemia associada às doenças imunomediadas e suas peculiaridades. A tempestade de citocinas, a utilização de medicações imunomoduladoras e imunobiológicas, as recomendações terapêuticas diante da presença do COVID-19 e a necessidade emergente do isolamento social impactando diretamente na avaliação do paciente reumatológico são aspectos essenciais que devem ser valorizados nesse período.

Palavras-chave: COVID-19, Reumatologia, Doença Reumática.

1. INTRODUÇÃO

Approximately 20% of COVID-19 cases are more severe, from this 5% are in critical condition, requiring (in majority times) intensive care support. Scientific documented evidence suggests that patients with a more severe clinical presentation develop a state of hypercytokinaemia, triggering an exacerbated inflammatory response responsible for severe organic dysfunction in patients with SARS-CoV-2 (SBD, 2020).

The cytokine release syndrome, usually known as “cytokine storm”, is characterized by the systemic inflammatory response triggered by several factors, among which stand out: infection, neoplasia and / or autoimmune disorders. The dynamic changes that occur in the immune system associated with the increase of certain cytokines in patients who express COVID-19, appear to be crucial for the development of severe acute respiratory failure.

Current studies suggest that the cytokine profile in severe forms of COVID-19 is similar to the Macrophage Activation Syndrome (MAS), characterized by: fever, cytopenias, elevated ferritin and respiratory distress syndrome; analogous picture identified in the clinical presentation of the cytokine storm (Huang, Wang, Li, Ren & Hu, 2020). A study published in “The Lancet” journal observed cytokine changes similar to those found in MAS in patients with the new coronavirus, characterized by an increase in of: interleukins IL 2 and 7, granulocyte colony stimulating factor, protein 10 inducible by interferon- γ , monocyte-chemotactic protein 1, macrophage inflammatory protein 1- α and tumor necrosis alpha factor (Mehta et al., 2020). Two predictors of mortality were identified in a retrospective, multicenter study of 150 patients confirmed with COVID-19 in Wuhan, China, they are: ferritin (mean 1297.6 ng / ml in non-survivors vs 614.0 ng / ml in survivors; $p < 0.001$) and IL-6 ($p < 0.0001$), suggesting that mortality may be secondary to hyperinflammation caused by the virus (Mehta et al., 2020).

Chinese cohort shows that patients with severe disease and the need for intensive care generally have leukopenia, lymphopenia, thrombocytopenia, hypoalbuminemia and significantly higher levels of C-reactive protein (CRP), thrombin time, fibrinogen, glucose, lactic dehydrogenase (LDH) and transaminases. In addition, higher levels of IL6 (> 24.3 pg / mL) and D-dimer (> 0.28 μ g / L) were predictive for the development of severe pneumonia in patients with COVID-19, with 93.3 % of sensitivity and 96.4% of specificity (Pedersen & Ho, 2020, Zuo et al., 2020).

The pathophysiology is not fully explained, it is believed that the interaction between cytokines and cells of the immune and non-immune system, such as endothelial cells, are responsible for most clinical manifestations. IFN- γ induces the activation of other immune cells, mainly macrophages (Matthys et al., 1993). Activated macrophages produce excessive amounts of additional cytokines, such as IL-6, TNF- α and IL-10. TNF- α causes flu-like symptoms such as fever, malaise and fatigue, but, in addition, it is responsible for watery diarrhea, increased vascular permeability, cardiomyopathy, lung injury and acute phase protein synthesis. IL-6 leads to more severe symptoms, because it enhances vascular leakage in addition to activating the complement and coagulation cascade, inducing disseminated intravascular coagulation (DIC) (Tanaka, Narazaki. & Kishimoto, 2016, Hunter & Jones, 2015). Concomitant with the actions of cytokines, cellular components of the immune system, such as cytotoxic T cells (CTLs) and NK cells, necessary to generate an effective immune response against viruses, are dramatically compromised in SARS-CoV-2 infection. It seems that the virus cancels the host's innate immunity by expressing the inhibitory receptor NKG2A in CTLs and NK cells, resulting in the inactivation of its cellular functions (Zheng et al., 2020).

Since SARS-CoV-2 infection is strongly related to the cytokine storm, it is speculated that immunomodulatory medications already widely used in rheumatology are effective in the treatment

of Covid-19. Evidence is still scarce, incipient studies demonstrate a satisfactory response to medications such as interleukin-6 inhibitors (tocilizumab), interleukin-1 inhibitors (anakinra and canakimumab), anti-malarials (chloroquine and hydroxychloroquine), inhibitors of small molecules for janus signaling. kinase - JAK (tofacitinib, upadacitinib, baricitinib) and corticosteroids in the new coronavirus infection (ACR, 2020).

Tocilizumab, an inhibitor of the interleukin 6 receptor (anti-IL-6R), has been studied to combat the new corona virus. Cohorts with 57 to 63 patients performed in Italy and Spain demonstrate a good safety profile in the use of this medication (ACR, 2020). In most of the evaluated cases, Tocilizumab proved to be effective in patients infected with SARS-CoV-2 with pulmonary impairment associated with biochemical changes suggestive of the cytokine release syndrome (Ferro et al., 2020, Campins et al., 2020). A Chinese study concluded that Tocilizumab effectively improves clinical symptoms and delays the worsening of patients with COVID-19, when used in the appropriate “window of opportunity” (Xua et al., 2020).

Considering the participation of interleukin 1 in the pathophysiology of COVID-19, another drug has also become the target of studies for the control of this pandemic. Anakinra is an inhibitor of interleukin 1 (anti-IL1Ra), however the data obtained from such studies are less encouraging, showing no significant difference in the use of (anti-IL1Ra) versus hydroxychloroquine, lopinavir / ritonavir in patients affected by COVID-19 (Ferro et al., 2020). In contrast, a study published in “The Lancet” confirms the potential role of Anakinra in selected conditions (severe forms of COVID-19 related to pneumonia requiring oxygen therapy or contraindications to other anti-rheumatic drugs), significantly reducing the need for mechanical ventilation in the ICU and mortality in patients with severe disease, without relevant side effects (Ferro et al., 2020, Huet et al., 2020).

Clinical trials have evaluated the efficacy of JAK inhibitors to fight SARS-CoV-2 and propose the use of baricitinib as a potential treatment, considering its inhibitory activity both in the production of cytokines and in endocytosis by Coronavirus (Ferro et al., 2020, Stebbing et al., 2020, Richardson). Despite the small cohort of patients, such studies demonstrate that baricitinib can represent a safe and effective treatment strategy, especially in the initial phase of COVID-19 infection (Ferro et al., 2020).

In addition to the drugs already mentioned, chloroquine (CQ) and hydroxychloroquine (HCQ) has been showing a therapeutic effect on COVID-19 infection. Such medications, initially used for the treatment of malaria, are widely used in Rheumatology to control and maintain autoimmune diseases, such as Systemic Lupus Erythematosus and Rheumatoid Arthritis. These medications interfere with acidification of the medium, increasing the lysosomal pH. Thus, its antiviral effect may be associated with the inhibition of pH-dependent viral replication and the

prevention of glycosylation of the viral envelope glycoprotein, as well as the host receptor protein (Ferro et al., 2020, Yazdany & Kim, 2020). Another mechanism of action that is involved is its ability to prevent the endocytosis of nanoparticles by resident macrophages, mediated by enzymes such as claritin. Studies show that chloroquine decreases the expression of claritin, thus reducing the rate of endocytosis mediated by this enzyme, in addition, SARS-CoV-2 has the same size range (60–140 nm) and (spherical) shape as the synthetic nanoparticles commonly studied, so we can associate the therapeutic effect of this medication to these new mechanisms studied *in vitro* (Yazdany & Kim, 2020). Also other actions related to chloroquine, such as attenuation and expression of pro-inflammatory factors that induce severe acute respiratory syndrome and determine the morbidity and mortality of the disease, are also therapeutic targets for CQ and HCQ, thus contributing to their promising effects. Although the results of *in vitro* experiments provide a justification for the use of QC and HCQ, it is important to note that the clinical efficacy is still very limited and mainly based on non-randomized clinical observation trials and individual, small-cut protocols (Ferro et al., 2020).

The routine use of corticosteroids as an adjunct therapy in COVID-19 infection remains highly controversial (Ferro et al., 2020). Meta-analyses based on the previous literature suggest caution in the use of these drugs in infection with the new corona virus (Ferro et al., 2020, Yang et al., 2020). Despite the evidence derived from retrospective analyzes, currently, corticosteroids have been frequently used in clinical practice, particularly in severe respiratory syndrome (Ferro et al., 2020, Yang et al., 2020). As they control the inflammatory response characteristic of the second phase of the disease, its use can bring therapeutic benefits, limiting the progression of lung damage and has been widely inserted in clinical practice, according to expert consensus (Ferro et al., 2020, Zhao et al., 2020).

In this scenario in which the results are controversial and others are not yet available, it is not possible, until then, to draw firm clear indications (10). The need for further studies and it is evident the need of a concrete scientific basis for the routine use of the aforementioned medications, a real indication for the clinical practice and the management of patients infected with the new corona virus (Ferro et al., 2020, Yazdany & Kim, 2020, ACR, 2020).

Regarding the practice of rheumatologists, the COVID-19 pandemic impacted the routine of doctors and rheumatological patients, directly reflecting on well-being, routine and care. Our patients have chronic illnesses most of the time, and the welcoming profile is to maintain a direct, personal and constant contact with the patients. Our routine demands periodic clinical evaluation, drug dose management, infectious and laboratory surveillance, as well as all psychosocial support. Given this, some obstacles are revealed in the pandemic: how to proceed in the face of social isolation, with ambulatories and clinics with suspended or limited functioning; how to deal with the

distress of “lack of assistance” on both sides, doctor and patient, and at the same time with the risk of exposure to the virus if attendance is maintained as usual?

Many of the rheumatic patients have immune-mediated diseases and, therefore, have the need to use immunosuppressive and immunobiological medications. In addition, they have multiple associated comorbidities, such as Systemic Arterial Hypertension, Diabetes Mellitus and heart disease, which already increase the risk of worsening by the new coronavirus. It was believed that these patients, being immunosuppressed, would be more affected and present more severe forms of the disease caused by SARS-CoV-2 when compared to the general population. However, it has been observed that adequate disease control, keeping it in remission, contributes to a favorable outcome and lower mortality in the face of this infection (SBR, 2020).

Patients with systemic lupus erythematosus, for example, are treated with immunosuppressive therapy to maintain remission and prevent organic complications, in addition to the use of glucocorticoids, medications that induce an immunosuppressive state. However, there are no specific data that suggest a major predisposition to infection or an increase in the severity of COVID-19 when compared to the general population, as seen in a study that evaluated transplant patients using immunosuppressants (Sawalha & Manzi, 2020, D'Antiga, 2020). Studies show that disease control reduces morbidity during infection with the new coronavirus (Sawalha & Manzi, 2020). Therefore, maintaining lupus in remission is essential to avoid unnecessary visits to the doctor's office, emergency room and hospitalizations, increasing the chance of exposure and infection by SARS-CoV-2. That is why it is essential to maintain the current immunosuppressive treatment without reducing the doses of these drugs, unless there is a clear clinical indication (Sawalha & Manzi, 2020). Due to the controversial effects of the use of glucocorticoids in Covid-19, we must maintain a lower effective dose to maintain remission of the disease, being adjusted when necessary (Misra, Agarwal, Gasparyan & Zimba, 2020).

It is recommended that immunosuppressive therapy is frequently interrupted during active infection processes, and until validated scientific data on the subject is available, the ideal is to follow this guidance even at COVID-19 (Misra, Agarwal, Gasparyan & Zimba, 2020).

Regarding immunobiological therapy, the intention of the Brazilian Society of Rheumatology at the present time is to educate and guide patients, with a focus on preventive measures and guidance on not interrupting this treatment, as there is no evidence that the suspension will result in less contamination or severity by SARS-CoV-2 (SBR, 2020). We must consider the risk of exacerbating underlying diseases when deciding to maintain patients' usual medications. Eventually, in patients with well-controlled diseases, who need to travel to infusion centers to receive treatment with biologicals, we can space out some dose of their medications, in order to decrease the displacement of patients and the greater risk of exposure.

The recommendations that patients receive in clinical care routine need to remain in active, or if possible, adapted. It is necessary to maintain, for example, self-care and follow guidelines of pain management, physical exercise, sun protection, dietary education, saving repetitive movements and avoiding fatigue. In addition, postponing the consultation or using communication resources to answer questions whenever possible is considerable, in order to minimize exposures, knowing that the hospital environment is at greatest risk of contagion (Sawalha & Manzi, 2020).

In our service, measures to facilitate access to medications were necessary, especially those high-cost ones, which started to be delivered at home or through health agents; as well as automatic updating of medical expertise, because the access to new laboratory tests for periodic renewal is now limited. The patients' demands are being met through telephone contacts made with the nursing team, which are then directed to the Rheumatology doctors team. Currently, many countries and services are adding and evolving in relation to virtual consulting.

Stress is a major influence on the activity of rheumatological disease, increasing the need for medical intervention. We understand and share all the anxiety of patients, in the face of numerous news reports and the uncertainties of a pandemic of such magnitude and its impacts, unprecedented in history. Thus, we recognize the importance of emotional vigilance in this context, for the correct identification of the moment when other assistance is needed. Therefore, we, rheumatologists, must maintain good medical practice before the limited evidence in the current scenario and, at the same time, stimulate awareness and the importance of preventive measures, pending new evidence and experiences.

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