ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Severe infections by SARS-CoV-2 with the use of tocilizumab

Infecções graves por SARS-CoV-2 com uso de tocilizumabe

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ABSTRACT

SARS-CoV-2 causes the COVID-19 infectious disease that affects the respiratory tract. From the beginning of the infection, the immune system starts to produce pro-inflammatory cytokines and chemokines. The main cytokine involved is IL-6 and is linked to the severity and prognosis of the disease, as it provokes a storm of cytokines and severe inflammatory responses. Due to the association of high levels of IL-6 with severity and mortality in COVID-19, the use of Tocilizumab (TCZ), a humanized anti-human IL-6 receptor monoclonal antibody, which binds to IL receptors, is being investigated. -6 and blocks intracellular signaling reducing cytokine storm and hyperinflammatory state. The aim of this review is to assess the effectiveness of using TCZ in the treatment of patients with severe COVID-19. Searches were performed using the Science Direct and PubMed databases in May 2021. Randomized clinical trials with patients in a single stage of COVID-19, severe cases and without age restriction, who received TCZ as medication for treatment, were included. Intervention was combined with treatments protocoled by each hospital and associated with corticosteroids. The analysis of these studies showed significant results regarding the use of TCZ in severe cases of COVID-19. The use of TCZ associated with glucocorticoids led to a reduction in the rate of mortality and compliance with mechanical ventilation and a significant improvement in relation to the "WHO-endorsed 7-point ordinal scale". However, there was no evidence of relevant improvement when using TCZ alone.

Keywords: COVID-19, monoclonal antibodies, Systemic Inflammatory Response Syndrome.

RESUMO

O SARS-CoV-2 é causador da doença infecciosa COVID-19. A infecção estimula o sistema imunológico a produzir citocinas pró-inflamatórias. A principal citocina envolvida é a IL-6, e está ligada à gravidade da doença. Devido à associação dos altos níveis de IL-6 com a mortalidade na COVID-19, investiga-se sobre o uso de tocilizumabe (TCZ), um anticorpo monoclonal humanizado antirreceptor de IL-6 humana. O objetivo desta revisão sistemática é avaliar a eficácia do uso do TCZ em pacientes com COVID-19 grave. As buscas foram feitas através das bases de dados Science Direct e PubMed em setembro de 2021. Foram incluídos os ensaios clínicos randomizados com pacientes em um único estágio de COVID-19, casos graves e sem restrição de idade, os quais receberam o TCZ como medicação de intervenção combinado a tratamentos protocolados por cada hospital e associado a corticosteroides. A análise desses estudos demonstrou resultados significantes sobre o uso de TCZ em casos severos de COVID-19. O uso de TCZ associado a glicocorticoides levou a uma redução no índice de mortalidade e de submissão a ventilações mecânicas e a uma melhora expressiva em relação à escala "WHO-endorsed 7-point ordinal scale". Entretanto, não houve melhora relevante quanto ao uso do TCZ de maneira isolada.

Descritores: COVID-19, anticorpos monoclonais, Síndrome de Resposta Inflamatória Sistêmica.

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Introduction

The new coronavirus (SARS-CoV-2) causes the infectious disease named COVID-19, which started in the city of Wuhan, China, in November 2019 and has spread throughout the world.[1]

So far, there are seven types of coronavirus, of which four are related to common colds, which infect only the upper respiratory tract. The other three (SARS-CoV, MARS-CoV and SARS-CoV-2) are responsible for more aggressive infections, affecting the lower respiratory tract and can progress to extremely severe acute respiratory distress syndrome (ARDS).[1]

SARS-CoV-2 is an RNA virus belonging to the ß-coronavirus group, which acts directly on human ACE-2 receptors. For this to occur, a pico protein (S protein) projects itself as a viral envelope that binds to the ACE-2 receptor, causing the viral genome to enter the cell and thus initiate the COVID-19 infection. The fact that ACE-2 receptors are present mainly on alveolar epithelial cells explains the more aggressive action of the virus in the lower respiratory tract. However, such receptors are also expressed on the surface of heart cells, vascular endothelium, gastrointestinal tract and kidneys.[1]

From the onset of infection, the innate immune system is activated and begins to produce and release pro-inflammatory cytokines such as IL-6, IL-1ß, IL-8, TNF-α and other chemokines, which increase inflammatory responses. In the case of COVID-19, inflammatory responses are exacerbated, causing what is called a cytokine storm. This excessive inflammatory response causes several abnormalities in the human organism, such as clotting abnormalities, development of excessive oxidation, mitochondrial permeability transition and immune system failure. This condition causes central nervous system disorders, renal failure, liver failure, and ultimately, multiple organ failure.[1]

Studies of the immunological profile of patients with severe COVID-19 demonstrate that there is a high number of activated T lymphocytes and monocytes. These defense cells are responsible for synthesizing pro-inflammatory cytokines, such as interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α) and interleukin-12 (IL-12). Research shows that, in this pathogenesis, the main cytokine involved is IL-6, which is directly linked to the severity and prognosis of the disease, as it causes a storm of cytokines and severe inflammatory responses in the lungs and other organs and tissues.[2]

The IL-6 receptor has two presentations: membrane-bound IL-6 receptor (mIL-6R), and soluble IL-6 receptor (sIL-6R). There is binding of IL-6 with sIL-6R to form a complex, which is coupled to the transmembrane protein gp130 so that signal transduction occurs and the pro-inflammatory function is performed.[2] The IL-6 bound to its receptor, by generating this cytokine storm, can aggravate the immune disorder and, thus, prevent the hematosis process, which makes it possible for a wide range of dysfunctions to occur, from respiratory failure to failure cardiovascular disease and multi-organ dysfunction, thus contributing to the mortality of critically ill patients with COVID-19.[3]

This storm can be controlled through monoclonal antibodies that act on the IL-6 pathway, as they are able to bind to sIL-6R and mIL-6R, thus preventing this signal transduction.[2] Due to this association of high levels of IL-6 with severity and mortality in COVID-19, the use of tocilizumab (TCZ), which is a humanized anti-human IL-6 receptor monoclonal antibody of the immunoglobulin subclass (Ig) IgG1, used in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis and giant cell arteritis.[4] This drug binds to IL-6 receptors and blocks intracellular signaling permeated by the sIL-6R and mIL-6R2 complexes, thus making it possible to reduce the cytokine storm and, consequently, the hyperinflammatory state.

The aim of this study is to evaluate the effectiveness of using tocilizumab in the treatment of patients with severe COVID-19.

Method

Search strategies for published studies such as randomized clinical trials were carried out for such a narrative review. They investigated the effectiveness of using the monoclonal antibody tocilizumab as a therapy for severe cases of COVID-19, that is, use as an additional therapy to conventional medical center therapy. The searches were performed through searches in the following databases: Science Direct and PubMed in September 2021, with no date or language restrictions. The search strategy used was: ("Coronavirus Infections" OR "COVID-19") AND (Tocilizumab) AND ("Randomized Controlled Trial" OR "Randomized Controlled Clinical Trial").

In this review, studies that used the drug without association with any other treatment, unless recommended by the medical center itself, or in association with corticosteroids, in patients in severe

cases of Coronavirus infection were considered as the use of tocilizumab in this review.

Publications of randomized clinical trials of severe cases of patients with a single stage of COVID-19 and without age restriction, who received tocilizumab as an intervention medication, combined with treatments protocoled by each hospital and also associated with corticosteroids, were included in this work. , in some works.

The outcomes of interest were the "WHO-endorsed 7-point ordinal scale" and Pao_2/Fio_2 ratio.

Selection of studies

A priori, searches using the search strategy found 413 works on May 7, 2021. Titles and abstracts were read by independent reviewers (RAP and ACM), and duplicates were removed from these. So, after reading the titles and abstracts, 90 articles remained. After reading the full articles and applying the inclusion and exclusion criteria, 2 articles were included in this narrative review, both randomized clinical trials (RCTs). The inclusion criteria are related to people with active infection by the Coronavirus in a serious condition, using tocilizumab, associated or not with corticosteroids and medications instituted by the hospital, as long as there are no antivirals in the treatment. Another inclusion criterion was RCTs. Exclusion criteria were: use of antivirals, case reports, bibliographic reviews, expert opinions and retrospective, prospective studies other than RCT's. The evaluation of articles according to the PEDro Scale is described in Table 1.

Results

In the search strategy, 413 references were identified. After removing duplicates, analyzing titles and abstracts, applying inclusion and exclusion criteria, 11 potential articles remained for the study. Of the potential 11, 9 were excluded. The main exclusion criteria from these potential studies were no RCT and the use of antivirals. All study results were obtained using tocilizumab. The outcomes found are described in Tables 2 and 3.

All studies portrayed were published between July 2020 and January 2021. People of both sexes, without age restriction, and all diagnosed with COVID-19 by PCR tests or by computed tomography of the lung area were included in this review. It is worth mentioning that all subjects in the studies were in a serious condition.

Table 1
Evaluation of studies by Ramiro et al. and Salvarani et al. according to the PEDro scale

PEDro criteria	Ramiro et al.[5]	Salvarani et al.[6]
Eligibility	Yes	Yes
Random allocation	No	Yes
Hidden allocation	No	Yes
Similar groups at baseline	Yes	Yes
Blind participants	No	No
Blind therapist	No	No
Blind researcher	No	No
< 15% dropouts	Yes	Yes
Intent to treat analysis	Yes	Yes
Difference between groups reported	Yes	Yes
Point estimate and reported variability	Yes	Yes
Total (0 to 10)	6	8

Source: prepared by the authors based on the PEDro Scale, 2021.

Table 2
Outcomes of the study by Ramiro et al.[5]

Ramiro et al.[5]		
	Risk Ratio or Treatment Effect Coefficient versus Control*	**Interval**
Primary outcome		
Clinical improvement (2 points) WHO scale	2.31	1.45 - 3.68
Main secondary outcomes		
Hospital mortality	0.26	0.13 - 0.52
Mechanical ventilation	0.22	0.10 - 0.52
Other secondary outcomes		
Clinical improvement (1 point) WHO scale	2.26	1.44 - 3.54
Independence from oxygen support	2.36	1.45 - 3.83
Duration of mechanical ventilation in survivors	-6.83	-21.45 - 7.79
Duration of hospitalization in survivors	-6.65	-10.93 - 2.37

* Adjusted for age, sex, body mass index (BMI), smoking, hypertension, diabetes, cardiovascular disease, and arrhythmia.

Table 3
Outcomes of the study by Salvarani et al.[6]

Salvarani et al.[6]			
	Clinical Outcome Ratio in Intention-to-Treat Population (TCZ versus Standard Care)	**Interval**	**p value**
Primary outcome (on the 14th day)			
Clinical improvement	1.05	0.59 - 1.86	0.87
General outcomes on the 14th day			
ICU admission	1.26	0.41 - 3.91	
Deaths	1.05	0.07 - 16.4	
Hospital discharge	0.99	0.73 - 1.35	
General outcomes on the 30th day			
ICU admission	1.26	0.41 - 3.91	
Deaths	2.10	0.20 - 22.6	
Hospital discharge	0.98	0.87 - 1.09	

TCZ = tocilizumab, ICU = intensive care unit.

Two RCTs were selected. The first was performed by Ramiro et al.[5] who selected a sample of 172 patients and divided them into an intervention group and a control group, both with 86 people with a mean age of 67 years. Both groups received some form of treatment. The control group received immediate treatment with methylprednisolone (MP) 250 mg intravenously on day 1, followed by MP 80 mg intravenously on days 2-5, with an option for a 2-day extension if deemed necessary and safe, in addition to to receive Ceftriaxone 2g daily for seven days and chloroquine 300mg every 12 hours after a loading dose of 600mg. The intervention group received tocilizumab (TCZ) between day 2 and day 5 (TCZ in a single dose, 8 mg/kg of body weight intravenously, max. 800 mg).

In turn, in the other RCT, according to Salvarani et al.,[6] a sample of 126 patients was selected, 60 destined for the group that would receive the monoclonal antibody and another 60 that would be the control group. The mean age of these patients was 60 years, and both the control and intervention groups received treatment. The intervention group received intravenous tocilizumab within 8 hours of randomization (8 mg/kg up to a maximum of 800 mg), followed by a second dose after 12 hours. The control group in turn received supportive care, which was guided by the protocols of each hospital center. It is noteworthy that all patients were followed up for 14 days according to the study protocol and an additional 30 days for analysis of secondary outcomes.

Ramiro et al.[5] aimed to evaluate an intensive course of glucocorticoids with or without tocilizumab to analyze whether there is an acceleration of clinical improvement in patients with cytokine storm syndrome (CSS) associated with COVID-19, using the "WHO-endorsed 7-point ordinal scale".

The study by Ramiro et al.[5] also sought to assess the mortality rate and the need for ventilation.

The study by Salvarani et al.[6] aimed to evaluate the effect of early administration of tocilizumab versus standard therapy in preventing clinical worsening in hospitalized patients with COVID-19 pneumonia, through the PaO_2/FiO_2 ratio, and through secondary outcomes that are mortality and hospital discharge.

At the end of the evaluation of the selected works, relevant results were obtained on the use of tocilizumab in relation to COVID-19 in severe cases. It was noticed that in the study by Ramiro et al.[5] there was a significant improvement with the use of glucocorticoids and tocilizumab associated, reducing the mortality rate, submissions to mechanical ventilation and, therefore, showing a significant improvement in relation to the primary outcome.

However, the work carried out by Salvarani[6] did not show a significant improvement. There were no significant differences in the outcomes when comparing the control groups and those submitted to treatment with tocilizumab.

Discussion

The novel coronavirus (SARS-CoV-2) acts on ACE-2 receptors, which are present mostly in alveolar epithelial cells. This fact increases the action of the virus in the lower respiratory tract, but it is possible to find these receptors on the surface of heart cells, vascular endothelium, gastrointestinal tract and kidneys.[1] The phenotype of this infection ranges from the absence of symptoms to severe pneumonia, leading to respiratory distress syndrome (ARDS).[7]

Cytokine storms often happen in the most severe cases of COVID-19. This fact is linked to the genesis of aberrant T cell immunophenotypes associated with a deregulated secretory profile of pro-inflammatory drugs, cytokines and chemokines. SARS-CoV-2 can influence CD4+ T lymphocytes towards a pathogenic TH1 lineage, which leads to overproduction of IL-6 and GM-CSF. These cytokines contribute to the activation of CD14+ CD16 monocytes, which secrete interleukin-6 (IL-6) and can travel to the lung, where eventually there is differentiation into alveolar macrophages or dendritic cells.[7]

When IL-6 binds to its receptor (IL-6R) it performs classic cis signaling, an action that affects the functions of T and B cells, macrophages, natural killer cells and neutrophils. Interleukin also contributes to the pathogenesis of cytokine storms. When there is interaction with sIL-6R, transinalization occurs, which has an effective role in the cytokine storm, as it stimulates the production of IL-6, IL-8, MCP-1 and endothelial growth factor (VEGF). It also regulates in favor of the expression of the adhesion molecule E-cadherin, which, together with VEGF, intervenes in the marked increase in vascularization, permeability and leakage, a fact of relevance to generate damage to the lungs. When IL-6 signaling is mediated by dendritic cells that express IL-6R, transpresentation occurs, which compromises T cells and generates an immunophenotype capable of destroying tissues[7].

Based on this assumption, an interesting therapeutic strategy to mitigate the dangerous effects of the cytokine storm associated with COVID-19 is the inhibition of IL-6. There is a humanized monoclonal antibody approved for the treatment of rheumatoid arthritis, tocilizumab, on the pharmaceutical market. Its pharmacological effect interacts with the IL-6 binding epitope, thus preventing IL-6 fixation, a fact that prevents cis-signalization, transsignalization and trans-presentation. Therefore, tocilizumab has anti-inflammatory properties. Wang et al.[11] concluded that tocilizumab can improve oxygenation, symptoms and reduce disease worsening with an acceptable side effect profile. Tleyjeh et al.[8] concluded that high-certainty cumulative evidence showed that tocilizumab reduced the risk of mechanical ventilation in hospitalized patients with severe COVID-19.

Ramiro et al.[5] showed a beneficial effect in relation to the use of tocilizumab associated with glucocorticoids, as such use together would generate a decrease in general and specific pro-inflammatory factors, thus causing a decrease in CSS and, as a consequence, generating a decrease in mortality and a decrease in of submissions to mechanical interventions. In this sense, the use of tocilizumab associated with methylprednisolone generates a beneficial effect.

However, according to Salvarani et al,[6] there was no significant improvement in the outcome, which is the Pao_2/Fio_2 ratio, thus showing that the isolated use of tocilizumab does not generate significant improvements, due to the fact that it inhibits in a specific isolated way. That is, due to the action of the drug, the need to use it associated with other drugs is perceived, because, in fact, the SARS-CoV-2 acts on IL-6 but also affects other pro-inflammatory cytokines. For this reason, tocilizumab alone does not generate the expected improvement.

Through the analysis of the outcomes and the results obtained, it appears that tocilizumab can provide some improvement, but this result is not obtained if used in isolation. Furthermore, it was understood that the use of a drug with an intense generalized inhibitory effect on the inflammatory response, associated with a drug with a specific inhibitory effect on IL-6, in this case tocilizumab, generates significant improvement effects, such as decreased mortality, decreased of interventions for the use of mechanical ventilation and change of WHO-endorsed 7-point ordinal scalefavorable to improvement.

Conclusion

The use of tocilizumab in patients with COVID-19 results in an improvement in the inflammatory condition due to its inhibitory effect on the IL-6 pathway, thus reducing the cytokine storm, which is one of the main causes of aggravation of COVID-19. However, by acting only on the IL-6 pathway, the use of tocilizumab alone did not offer significant improvements in the severe clinical conditions of patients with COVID-19. Those who received a combination of tocilizumab and drugs that have generalized inhibitory effects on the inflammatory response had a decrease in mortality and the need for mechanical intervention. Thus, it is concluded that the use of tocilizumab associated with other drugs that also interfere with the inflammatory response can contribute to an improvement in the clinical picture of patients with severe COVID-19.

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