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JAK2 INHIBITOR AND NSAIDs combined use as a treatment proposal for COVID-19: A literature review

Uso de INIBIDOR de JAK2 combinado con AINE como propuesta de tratamiento para a COVID-19: Una revisión de la literatura

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ABSTRACT

The search for drugs protocols to the COVID-19 treatment had been severely studied, considering the inflammation states and the thrombotic events. Objective: Propose, through a literature review, the combined use of baricitinib and aspirin for patients with moderate to severe COVID-19 disease. .METHODS: An integrative literature review was carried out on Google Search and Pub Med, analyzing observational and clinical intervention studies Results: The average mortality between the studies with the aspirin was 13.25%, it was observed a lower necessity for mechanical ventilation and rate of admission to the ICU. While the baricitinib studies had an average of 6.25%, decrease in plasma concentrations of IL-6, CRP and neutrophils and an increase in the number of lymphocytes. Conclusion: The association of these two drugs shows antiviral, anti-inflammatory and antithrombotic activity, acting on JAK2 and NF-kb simultaneously.

DESCRIPTORS: COVID-19; Aspirin; Baricitinib; Treatment.

RESUMEN

La búsqueda de protocolos de fármacos para el tratamiento del COVID-19 había sido estudiada de forma rigurosa, considerando tu estado inflamatorio y los eventos tromboticos. Objetivo: Proponer, a través de una revisión de la literatura, el uso combinado de baricitinib y aspirina en pacientes con enfermedad COVID-19 de moderada a grave. Método: Se realizó una revisión integradora de la literatura en las plataformas Google Search y Pub Med, analizando estudios observacionales y de intervención clínica. Resultados: La mortalidad media entre los dos estudios de aspirina fue del 13,25%, fue observado menor necesidad de ventilación mecánica y menor tasa de ingreso en UCI. Mientras, los estudios con baricitinib tienen una media de 6,25%, disminución en las concentraciones plasmáticas de IL-6, PCR, número de neutrófilos y un aumento en el número de linfocitos. Conclusión: La asociación de los medicamentos muestra actividad antiviral, antiinflamatoria y antitrombótica, actuando sobre JAK2 y NF-kb simultáneamente.

DESCRIPTORES: COVID-19; Aspirina; Baricitinib; Tratamiento.

RESUMO

A COVID-19 induz a um processo inflamatório e de eventos tromboticos que geram danos ao organismo. A busca por novos protocolos medicamentosos tem sido severamente pesquisado como meta de combate à doença. Objetivo: Propor, por meio de uma revisão de literatura, o uso combinado do baricitinib e da aspirina para pacientes com doença moderada a severa da COVID-19. Métodos: Foi realizada uma revisão integrativa da literatura nas plataformas Google Search e Pub Med, analisando estudos observacionais e os clínicos de intervenção. Resultados: A média da mortalidade entre os estudos da aspirina foi de 13,25%, foi observado menor necessidade de ventilação mecânica e menor taxa de admissão em UTI. Já com o baricitinib, a mortalidade foi de 6,25%, houve diminuição na concentração plasmáticas de IL-6, CRP e de neutrófilos e aumento do número de linfócitos. Conclusão: A associação dos dois medicamentos mostra atividade antiviral, antiinflamatória e antitrombótica, atuando sobre o JAK2 e NFkb simultaneamente.

DESCRIPTORES: COVID-19; Aspirina; Baricitinib; Tratamento.

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INTRODUCTION

The SARS CoV-2 virus is the causative agent of COVID-19 disease. It is responsible for causing severe respiratory illnesses. However, it is also able to target several other systems. Greater susceptibility to thrombotic events has already been reported in patients with severe disease, especially in small blood vessels. The clinical evolution of the disease may be associated with the individual's immune dysregulation, and may come from a protective response to the organism to an uncontrolled production of inflammation mediators and cells. Inflammation caused by the virus is the main cause of mortality in people affected by the disease.^{1,2}

Due to these inflammatory events, several drugs, such as anti-inflammatory and antiviral drugs, have been tested at COVID-19³ among them, the inhibitors of the JAK-STAT signaling route stand out for their remarkable activity in controlling the production of cytokines involved in the inflammation process.⁴ The Acetyl Salicylic Acid (ASA) classified as Non-Steroidal Anti-inflammatory (NSAID) has been considered promising for acting on the mediators of inflammation and preventing thrombotic events.⁵

Considering the antiviral and anti-inflammatory activity of baricitinib

and AAS as well as the promising results in the treatment of COVID-19⁶, an integrative literature review was carried out to seek data on the effectiveness of each treatment individually. Proposing a possible clinical study using these two associated drugs to control inflammation, viral load and thrombosis caused in severe patients for COVID-19.

METHODS

An integrative literature review was carried out to identify the scientific production related to the use of AAS and baricitinib for the COVID-19 treatment. The bibliographic survey was carried out in the databases: PubMed and Google Search, carried out from September to October 2020. The language used for search was the English language. Descriptors present in the Health Sciences Descriptors (DeSC) were used. Thus, for the works on the use of AAS in COVID-19, the descriptors "Aspirin" were used; "COVID-19". Those related to the therapy of baricitinib in the disease, the descriptors "Baricitinib" were used; "COVID-19". Articles from observational studies (case-control, cross-sectional and cross-sectional) were included, as well as intervention studies (controlled, uncontrolled clinical trials and blind trial), using these two drugs in patients positive for COVID-19.

The articles excluded for the analysis were the literature review (systematic, integrative review, meta-analysis) on the applicability of these drugs for the treatment of the disease.

Data were collected from the studies on the number of people investigated in each job, the state of the disease they had at the time of admission to the hospital (mild, medium, moderate and severe), mortality rate of patients after using these drugs, improvements symptoms and blood count data on the increase / reduction of mediators and inflammatory cells after. At the end, the results of the studies were compared with each other and an analysis of the behavior of these parameters mentioned above was carried out at the end of the treatment with the drugs.

RESULTS

The total number of studies found on the platforms was 136 studies (78 from baricitinib and 58 from aspirin), of which 6 were selected, in which 4 were clinical studies using baricitinib and 2, aspirin.

The total number of patients studied in the studies analyzed with the use of Acetyl Salicylic Acid (ASA) totaled 133. Most had medium to severe disease with an average mortality rate between studies of 13,25%. As shown in table 1.

In the study by Florêncio et al. (2020) atorvastatin or with rusorvastatin. All patients had a significant remission of symptoms, and became symptomatic or oligosymptomatic, and there were no hemorrhagic events with the application of this medication. The comparison between the use and non-use of aspirin as a treatment for COVID-19 was described by CHOW et al. (2020), there was less precision in mechanical ventilation, admission to the ICU for the first group.

The total number of straightened patients was 180, distributed among the cases, moderate and severe. With an average mortality rate between studies of 6,25%. In the 4 studies, patients were treated with 2 to 4mg of baricitinib with a treatment time ranging from 1 to 2 weeks (Table 2).

In the group of 15 people from Ti-

tianji and collaborators (2020), 86,7% of the participants had a significant reduction in body temperature in the first 5 days of therapy, in the CRP and IL-6 levels. In Cantini's work (2020), the decrease in plasma levels of C-reactive protein (CRP) in mg / ml in 2 weeks of treatment, a decrease in the number of neutrophils in $\times 9 / L$ and an increase in the number of lymphocytes at $\times 9 / L$. As for cytokines, the study by Bronte et al. (2020) showed a decrease in pro-inflammatory cells, IL-1 β , IL-6 and TNF, in the first 7 days of treatment (t_0 - t_7), as well as in CRP. There was an increase in the number of circulating lymphocytes, CD4 + T cells, memory cells (CD3 + CD4 + CD45RA-CD27-), and B cells. Regarding the plasma levels of IgA and IgG antigens, there was an increase in the number of IgG.

DISCUSSION

The association of drugs in COVID-19 was observed in the analyzed articles. In the works of Cantini and collaborators^{6,7} used baricitinib with lopinavir / ritonavir and in the control group used hydroxychloroquine with these antivirals, Titanji et al.⁸ used a combination of hydroxychloroquine and baricitinib. Florêncio and collaborators⁹ used AAS with atorvastatin or rusorvastatin.

The main metabolite of AAS is salicylic acid, it is a non-selective inhibitor of cyclooxygenases COX-1 and COX-2, responsible for the production of mediators such as: prostaglandins (PG) and tramboxane A2 (TXA2). The acetylation of COX-1 in serine residue 530 or COX-2, in ser 516, thus reducing the synthesis of deprostanoids like PGG2 and PGH2 and TXA2. The inhibition of TXA2 decreases the generation of platelets and the infiltration of neutrophils in the lung. However, at high doses, this effectiveness is not maintained, as there is an interaction between AAS and PGI2, which, in turn, plays a role contrary to TXA2.^{5,10,11}

Other mechanisms would be: suppression of the intracellular NF-kb signaling pathway, inactivating the IKKb protein, which is related to a large part of the production of pro-inflammatory cytokines and the consequent recruitment of inflammation cells and with the differentiation of CD4 + T cells.^{12,13} In addition, there is the acetylation of the iNOS molecule, the induction of da heme oxygenase (HO) expression, and fibrogen acetylation, promoting fibrolysis. The antiviral activity by salicylate, which can inhibit viral replication by blocking the production of prostaglandin E2 (PGE2) in macrophages and increases the regulation of interferons, is also due to the inhibition of the intracellular route NF-kb.⁵

Baricitinib has a broad spectrum of cytokine inhibition, it acts in inhibiting the JAK2 intracellular route, playing a role in inhibiting proinflammatory cy-

Table 1: Data on studies using AAS in patients positive for COVID-19

STUDY	INDIVIDUALS	DISEASE STATUS	ADMINISTERED DOSE	MORTALITY
Florêncio et. al (2020)	35	Average	200 to 300 mg followed by daily doses of 100 mg until the 15th or 21st day	0%
CHOW et. al (2020)	98	Moderate to severe	Single dose (unspecified)	26,5%

Source: Author

Table 2: on studies using baricitinib in patients positive for COVID-19

STUDY	NUMBER OF PEOPLE ¹	DISEASE STAGE AT ADMISSION	ADMINISTERED DOSE AND COMP	MORTALITY (%)
Bronte et. al (2020)	20	Uninformed	Baricitinib 2- 4 mg/day (7 days) ¹	5%
Titanji et. al (2020)	15	Moderate to severe	Baricitinib 2- 4 mg/day (7 days)	20%
Cantini et al. (2020)	113	Moderate	Baricitinib 4 mg/day +lopinavir/ritonavir 250 mg (14 days)	0%
Cantini et al. (2020)	12	Moderate	Baricitinib +lopinavir/ritonavir- 250 mg (14 days)	0%

Source: Author
¹ in the first two days, baricitinib was administered twice daily

tokines, and it shows to act in preventing SARS-cov-2 viral endocytosis in host cells.¹⁴ It prevents the activation of Th17 cells by the cytokines IL-6 and IL-23, which lead to the production of inflammatory proteins such as IL-1, G-CSF, IL-17, IL-1 β , IL-6, TNF α ; chemokines KC, MIP2A, IL-8, IP10, MIP3A and the activation of metalloproteinases.¹⁵ Baricitinib also acts to inhibit the production of angiotensin II (ANG II), responsible for vasoconstriction, hypertension and chronic damage to the lung and increased infiltration of immune cells with its production of pro-inflammatory cytokines.^{15,16} However, RICHARDSON and collaborators¹⁷ argue in their studies that the use of this medication should be given to patients with moderate to severe illness.

The antiviral mechanism of this inhibitor is the result of the chemical interaction of baricitinib with the AAK1 protein (AP2-associated protein kinase), this molecule is part of the NAK family, as well as BIKE, GAK and KTK16, which, notably AAK1 and GAK are linked to ACE2 receptors, which allows the endocytosis of SARS-CoV-2 through the virus S protein. Baricitinib shows affinity for the protein AAK1 (8.2 nM), BIKE (20nM) and GAK (120 nM).^{14,15}

CONCLUSION

Clinical trials with baricitinib and AAS have obtained promising results in patients with medium to severe disease. In the NSAID group, the variables: less need for mechanical ventilation, lower rate of admission to the ICU and there

were no hemorrhagic events with use. The treatment with baricitinib showed, in general, a lower plasma concentration of IL-6, CRP, number of neutrophils and an increase in the number of lymphocytes, being more effectively added with lor. In view of the results of each group of drugs studied and considering the theoretical approaches developed by several authors in the discussion about the mechanism of action of these substances on the infection by SARS-CoV-2, a promising path was found for the association of drugs for presenting activity antiviral, anti-inflammatory and anti-thrombotic, for acting together in the inhibition of intracellular routes JAK2 and NF-kb, which may increase the spectrum of cytokine inhibition, allow non-platelet aggregation and block the entry and replication of the virus. ■

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