Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 9 Issue 1 January 2025

Perspective

ABATACEPT as a Modulator of the T and B Cellular Immune Response Against Severe COVID 19

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DOI: 10.31080/ASMS.2025.09.2000

Received: November 26, 2024

Published: December 27, 2024

Abstract

The activation of the immune response to antigens is initiated by the molecular recognition of pattern associated to pathogens and pattern of recognition receptor son antigen presenting cells (macrophages and dendritic cells (PRRs), leading to antigen processing and peptide presentation to T lymphocytes through the interaction of MHC I/II to TCR receptor. The overcome of the induction of the immune response is the lymphocyte proliferation, differentiation of T and B cells for cytokines and antibodies production. Importantly the expression of costimulatory molecules as CD80/CD86, CTAL-4, CD28. CD40/CD40L. Interestingly, ABATACEPT chimeric protein formed by the extracellular domain of the antigen 4 associated to cytotoxic lymphocytes T and a fragment of the Fc portion of the Immunoglobulins constant region, resulting in a modulation of the activation of the B and T cellular immune response, and thus, inhibition of inflammation, and therefor in an amelioration of the physical function of the patients with arthritis rheumatoid Therefore, in based on this, herein it is analyzed the potential of Abatacept, a commercial drug as a modulator of the immune response against SARS-CoV2.

Keywords: Abatacept; COVID-19; SARS.CoV2; innate and adaptive immune response; costimulatory molecules. B and T cell llymphocytes

Introduction

Coronavirus SARS-CoV-2, called COVID-19, discovered in 1960, ir is a beta coronavirus virus belonging to the family of Coronoviridae [1,2], the largest of order Nidovirales and possess the largest genome, of 26 to 32 kb. COVID 19 began in December 2019, spreading rapidly throughout the world, causing a collapse in health services in many countries, which due to the epidemiological and clinical characteristics of patients with COVID -19, generated confusion among doctors and scientists, involving them in a race against time to try to understand and find an effective way to

control this disease. Currently, the risk factors for mortality and its detailed clinical course have been described. However, many cases of COVID-19 will suffer mild to moderate respiratory symptoms, but the real problem is in those patients who develop severe disease, which can evolve into severe systematic inflammation [3], and potentially lead to acute respiratory distress syndrome. (ARDS) [4] and die despite all efforts. This phenomenon of severe inflammation, also called "hyper inflammation", has been shown to trigger various immune mechanisms, which cause significant tissue damage due to the infiltration of macrophages into inflamed tissues, as well as the production of multiple cytokines that cause great damage to the immune system. Endothelium [5], which favors a pro coagulant state [6]. This generates a high risk of thromboembolic complications [7] which together predispose the patient to a state of disseminated intravascular coagulation, increasing the risk of death. Autopsy reports of deaths from COVID-19 mention the presence of a large number of macrophages in the alveolar lumen and a few CD45+ lymphocytes located mainly in the interstitial space, showing great damage with necrosis in the alveolar pneumocytes, as well as; endothelial damage, and fibrin platelet thrombi in small arterial vessels [8,9]. The role of mononuclear phagocytes could represent the effector mechanism of tissue damage, contributing to endothelial injury or responding to that caused by viral infection of endothelial cells, causing cellular damage, fibrin deposition and formation of micro thrombi, potentially generating damage. Progressive [10-15]. Although the site of clinical attention has been pulmonary where alveolar inflammation is evident early through computed axial tomography (CT), whose images will soon be classic; ground glass infiltrates, which with greater severity evolve to crazy pavement lesions, faithful evidence of lung damage, which is related to the level of hypoxemia and dyspnea in patients [10-15]. Furthermore and besides respiratory infection, tissue injury and endothelial injury are occurring in other organs such as; kidney, liver, heart and intestine [10-15]. The systemic damage secondary to this hyper inflammation process play a role in the severity of the disease and not only that pneumonia becomes complicated [10-15]. In this systemic and progressive damage, various immunity mechanisms are involved, however; how to explain the systemic activation of macrophages? Perhaps the presence of the SARS- CoV-2 virus in all tissues stimulates and activates macrophages locally, until causing a systemic effect of hyper stimulation of macrophages, also generated by the massive release of cytokines, with the consequent systemic damage in parallel (Figure 1A). The intensity and severity with which this infection develops in seriously ill patients is clearly related to the pathophysiological phenomenon called: "CYTOKINE STORM" 8 which has acquired great importance and interest, because it is similar to have a monster of thousand heads of the COVID-19 infection [8-10] (Figure 1A).

Background

Cytokine storm corresponds to an inflammatory mechanism that we are increasingly making progress towards understanding. This storm is characterized by the sudden and massive release of cytokines such as; gamma interferon (IFN-γ), tumor necrosis factor alpha (TNF-alpha), interleukins; (IL): 1, 2, 6, and 18 among others [11-15]. The activation of inflammatory cells, of which macrophages are relevant, due to its presence in affected tissues and organs. This process culminates in a serious systemic inflammatory phenomenon, which can lead to conditions as serious as disseminated intravascular coagulation, multiple organ failure with a high risk of death. It is important to mention that this phenomenon can occur in the pathophysiology of different conditions, such as heme phagocytic syndrome (HFS), also known as heme phagocytic lymphohistiocytosis (HLH); macrophage activation syndrome (especially related to systemic juvenile rheumatoid arthritis); acute respiratory distress syndrome; septic shock, even within the same phenomenon, the events called: "Hyperferritinemic Syndromes", also considering the systemic manifestations of toxic shock syndrome [11-15]. Therefore, if the systemic activation of multiple cytokines is the pathophysiological explanation of all these diseases, the question that arise from this is, what is the source of such a high and sudden release of cytokines? This is key for understanding the phenomenon, with perspective of better and straightforward treatments. A possible answer to this question based on a phase 1 clinical trial carried out by Suntharalingam., *et al*. 2006 [11]. The authors described a series of events that occurred after the administration of monoclonal antibody; anti-CD28 (TGN1412) intravenously, applied to six young and apparently healthy subjects, participants of the trial, and ninety minutes after administration of the drug, the patient developed data of systemic inflammatory response, characterized by a rapid induction of pro inflammatory cytokines, headache, myalgia, nausea, diarrhea, fever, erythema, vasodilation and hypotension [11]. Later at 12 and 16 hours they were seriously ill with pulmonary infiltrates and lung injury, renal failure and disseminated intravascular coagulation, with intense and unexpected depletion of lymphocytes and monocytes, within the first 24 hours. The six

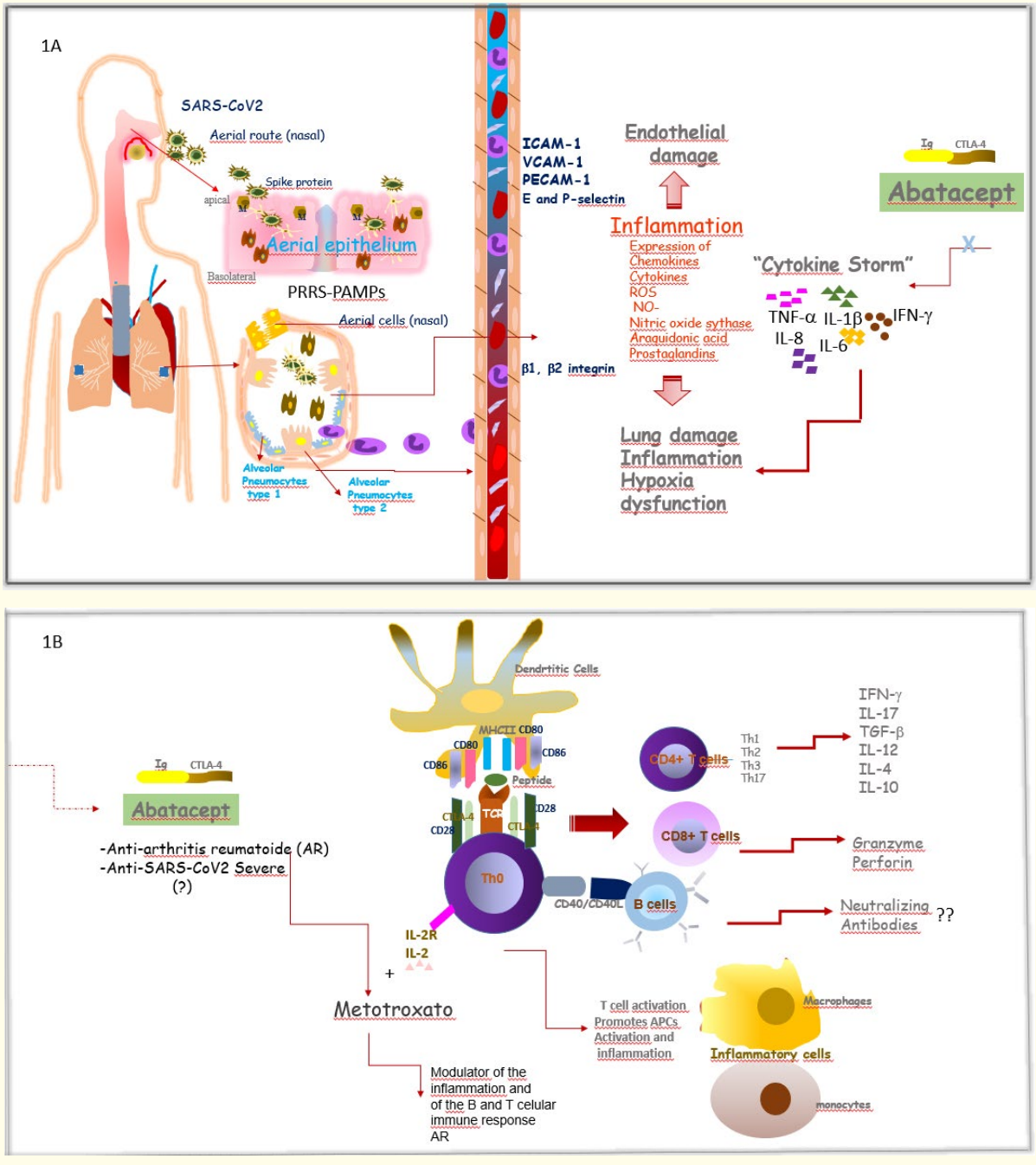

Figure 1: Scheme of the aerial infection by SARS-CoV2. 1. The virus enter via aerosol route and it is uptake by the aerial cells, which transport the virus to the alveolar space in which antigen presenting cells, such as pneumocytes, alveolar macrophages have a molecular interaction with the spike protein of the virus. SARS-CoV2 as an antigen is able to induce an immune response and cause an inflammation which can even cause damage to the lung and provoke a cytokine storm (A). Abatacept is a chimeric protein formed by a fragment of the antigen 4 associated to cytotoxic lymphocytes and by a fragment of the immunoglobulins (Ig) (B). Thus, in AR Abatacept modulate the B and T cellular immune response and due to its structure can also modulate the cellular immune response to SARS-CoV2 which is able also to evade this response and inhibit it.

participants required admission to an intensive care unit (ICU), two of them with signs of severe shock and need for invasive mechanical ventilation. However, all six patients achieved full recovery [11]. Therefore, resuming what represents COVID-19 infection in patients with severe evolution, aimed to find and develop an effective and safe treatment, combinations of two antiviral drugs have been used such as; lopinavir/ritonavir, umifenovir; remdesivir; with immunomodulatory properties similar to those described for chloroquine/hydroxychloroquine, azithromycin [16-20], for anti- interleukin drugs such as; anakinra and canakinumab against Il-1β; sarilumab, siltuximab and tocilizumab against IL-6; and cytokine signaling pathway inhibitors such as; baricitinib and ruxolitinib; JAK pathway inhibitors; B cell signaling inhibitors such as; acalabrutinib, ibrutinib, rilzabrutinib; and Bruton's tyrosine kinase (BTK) inhibitors. Systemic corticosteroids and plasma therapies for convalescent patients were also used; ivermectin as an inhibitor of viral replication; low molecular weight heparins for thrombotic complications, and many other possibilities that have been considered (Figure 1A). There have been a variety of alternatives, with encouraging results [21], and which should not be discarded. Since it is possible that a treatment for COVID-19 does not depend on a single drug, a combination of two or more therapeutic options may be necessary. An important observation in this infection has been the behavior of lymphocytes during the initial stages, where almost pathognomonic patients develop lymphopenia, and some authors also mention its correlation with the severity of the disease, and even associate it with the risk of death. What it has been observed is that if lymphopenia is severe, the prognosis is usually poor for that patient [11-13]. Meanwhile, the race continues, since the possible causes of lymphopenia in COVID-19 infection are still not entirely clear. One of the hypothesis is that the lymphocytes could be failing to maintain their immune function or they may be hyper activating, favoring a phenomenon of hyper inflammation. Another possibility is that lymphocytes that play a fundamental role in the cellular immune response goes unnoticed. Moreover, the antiviral immune response would depend on the presence of cytotoxic CD8+ T lymphocytes (Tc) and Natural Killers lymphocytes, which would eliminate virus-infected cells, which apparently occurs in COVID-19; On the other hand, the main role of CD4+ T helper lymphocytes (Th); will be to organize the immune response through the release of cytokines, which in turn would activate other inflammatory cells, to contain the viral infection. It is worth to highlight the role that Th1 lymphocytes should have in the production of INF-g and factor TNF-alpha, which would activate macrophages to (IFN-γ) eliminate microorganisms. In SARS-CoV2 infection, the role of this lymphocytes could be exacerbated [22-24]. For the lymphocytes to be activated, the fiist ste p in the recognition of the pepiide on the major histocompatibility complex (MHC II) by the TCR T cell receptor, resulting in the produciton of cytokines. The complete activation of the lymphocyte will only occur if the antigen-presenting cell stimulates the lymphocyte molecules through its B7 molecules (CD80/CD86); CD28, that is, the activation of the lymphocyte will only be completed until CD28 is activated, generating the specific immune response of the lymphocytes [18-20]. As an example, it is a clinical trial reported by Suntharalmgam, *et al* ery [11] (Figure 1A) in which a super agonist antibody against CD28 was used, causing a sudden phenomenon of hyper inflammation, due to a cytokine storm in six healthy volunteer subjects 18-21. Likewise, current immunotherapy treatments such as; monoclonal antibodies (mAbs); bispecific T cell coupling antibodies (BiTe) and T cell therapy with chimeric antigen receptors (CAR-T), which seek to overstimulate lymphocytes to destroy tumor cells and lymphocytes, are overstimulation therapies which action is often complicated, presenting clinical symptoms of the cytokine storm syndrome [11-16]. The hyper inflammatory event and the systemic activation of macrophages and monocytes could be the cause or secondary effect of lymphocyte hyper activation, a similar and comparable phenomenon to the effect of staphylococcal toxins in toxic shock syndrome, and to the super antigen mechanism or CD28 over activation, which leads to a probable explosion of lymphocytes and the massive release of cytokines, causing all the damage mentioned in severe cases of COVID-19 [25-32].

In the light of these studies and based on this theory, it can be thought that the hyper activation of lymphocytes is related to the level of intensity of the disease secondary to the cytokine storm. Considering then that the origin of the cytokine storm is the lymphocyte, and that the hyper activation of macrophages; tissue and endothelial damage are secondary to the storm. However, what could be the treatment that would help contain this hyper

inflammation? remember that, just as CD28 must be stimulated by the B7 molecule (CD80/CD86) on antigen-presenting cells (APC) for lymphocyte activation. The activated lymphocyte with the CTLA-4 molecule binds to the same B7 molecule (CD80/CD86) of the CPA, will generate the signal to turn off the same lymphocyte. This dual crosstalk between receptors and ligand son APCs and B and T lymphocytes, One question that has been the subject at least from 2020 to date is how to fight against severe coronavirus disease 2019 (Covid-19) caused by the acute respiratory syndrome coronavirus 2 (SARS- CoV-2) infection: Current antiviral therapies are limited and challenged due to drug-drug interactions and the effectiveness monoclonal antibodies, by viral evolution [33,34]. However, one important target would be protein translation. For this, drugs as metformin, could have action against proteins involved in virus translation, and in fact it has been shown *in vitro* activity against SARS-CoV2 and other RNA viruses. Moreover, Metformin has also shown anti-inflammatory properties, such as decreasing production of Il-1β, and IL-6. In addition, it is able to reduce the risk of thrombosis and inflammasome activation. In mice, administration of Metformin has shown protection against liposaccharide induced lung injury after SARS-CoV2. Indeed, it has been observed in patients with Covid-19 less severe and acute disease with Metformin administration [35-43]. Another drugs that has been evaluated against acute severe SARS-CoV2 are Fluvoxamine which has anti-inflammatory properties mediated by the sigma-1- receptor. This participate in the virion assembly as for example viral proteins transfer from the cytoplasm to the endoplasmic reticulum. The treatment of patients with this, in randomized trials have showed a reduction in hospitalization or prolonged medical care visits. The positive effect of this drug is much better at lower (50 mg) doses than at high doses (100 mg) [35-43].

Interestingly the chimeric protein, Abatacept¨, formed by the constant fraction (CF) of immunoglobulin G1 (IgG1) and an analogue of Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) produced by the company Bristol-Myers as a commercial medicine OHRENCIA®, has been indicated for the treatment of rheumatoid arthritis in adults and young people. As an immunotherapy against COVID-19, Abatacept binds to the B7-1 and B7-2 (CD80/CD86) molecule of CPA, preventing the activation of CD28, and therefore the activation of lymphocytes, an action that could help among several effects: to attenuate the explosion of lymphocytes, reduction of the cytokine storm, inhibition of the hyper activation of macrophages, stopping tissue damage and preventing serious progression in patients with COVID-19 (Figure 1A-B).

Mechanism of action of Abatacept

The mechanism of action of Abatacept that has been proposed is the selective modulation of a co stimulation signal required for the activation complete of T lymphocytes, which express CD28. It inhibits signals to the B7 molecules of antigen-presenting cells, through blocking the activation of CD-2812 T lymphocytes, inhibiting the release of cytokines such as TNFα, IFN-γ- and IL-2 [14-16]. Some effects observed *in vitro* of CTLA-4-Ig have been the suppression of the expression of TNF-α and IL-6, as well as that of CD80 and CD86, in human B lymphocytes; after stimulation with *Staphylococcus aureus*, according to the report by Po-Chun Liu *et al* [15] (Figure 1B).

Perspective for the use of Abatacept as immunotherapy against severe SARS-CoV2

Based on the aforementioned immune action mechanism of Abatacept, we are proposing the implementation of a controlled clinical trial to; evaluate the effect of abatacept in patients with moderate to severe COVID-19 at the Zacatecas General Hospital (HGZ). With the following working hypothesis: "The CTLA-4 analogue (Abatacept) inhibits the co-stimulation of antigen presentation to T lymphocytes, attenuating cytokine storm effects." The research protocol to determine the effectiveness of Abatacept in the treatment of moderate to severe COVID 19 in the HGZ is being reviewed by the HGZ Research Ethics Committee for approval. Briefly, a controlled clinical trial (double-blind, randomized) in patients diagnosed with moderate to severe COVID-19 disease, who are hospitalized, and who show poor prognosis data such as: lymphopenia less than 800/μL, hypoxemia with; PaO2/FiO2<150, elevation of ferritin > 400mg/L, and D-dimer >1,000 ng/ml, ideally the intervention should be before being intubated and connected to invasive mechanical ventilation. At the beginning, a blood sample (4 ml) and nasopharyngeal fluid will be collected to evaluate the profile of pro inflammatory cytokines in the blood and mucosal fluid, through flow cytometry analysis. The intervention will consist of administering; 10 mg/kg of Abatacept OHRENCIA®, intravenously, these patients would correspond to group A, and we would also generate a second group B, in whom it would not be administered; the drug. Basal inflammation markers will be

evaluated as already mentioned; before the administration of the drug, and subsequently at 24 and 48 hours. In addition, C-reactive protein levels will be determined; troponin I; procalcitonin; white blood cell count; lactate dehydrogenase; TNF-α cytokines; INF-γ and IL-2, IL-1; IL-6; IL-10. INF-γ. Other parameters to be evaluated and considered are organ failure and survival data. Some points to be considered with the administration of the drug is that As a prophylactic drug in an acute and severe SARS- CoV2 infection, inhibits the entire cellular immune response, and no differentiation of lymphocytes to Th1 or Th2, resulting in no T helper; for the maturation of B cells into plasma cells and memory B cells. They would also not activate cytotoxic T cells and macrophages. On the other hand, with the administration of Abatacept to patients with SARS-CovV2, once the critical phase begins, it can act by inhibiting hyper inflammation. But, this would be more of a therapeutic effect [44-46].

Acknowledgments

The authors are grateful with the Health Institutes (ISSSTE; Hospital General de Zacatecas), with SNI-CONAHCYT (2023-2027), and with PERFIL-PRODEP. SEP (2023-2025).

Author Contributions

D.C.G. and A.A.C. Theorical and Clinical Proposal, content, writing and discussion, G.G.G: content, writing, schemes, and discussion

Informed Consent Statement

No applicable.

Data Availability Statement

This review was based on search and data from PubMed database without limitation to 2024.

Conflicts of Interest

The authors declare not conflict of interest/the author declare that they have no competing interests.

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