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The Genetic Polymorphism of TNF-α Associated with the Anti-TNF-α Therapy Used for COVID-19 Patients – Another Possible Approach

O Polimorfismo Genético do TNF-α Associado com a Terapia Anti- TNF-α Usada para Pacientes com COVID-19 – Outra Abordagem Possível

El Polimorfismo Genético TNF-α Asociado con la Terapia Anti-TNF-α Utilizada Para Pacientes Con COVID-19: Otro Enfoque Posible

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Abstract
Objective: This work aimed of to review the implications of anti-TNF-α therapy in COVID-19 patients associated with the genetic polymorphism (TNF-α polymorphisms in the region-308) of this pertinent cytokine Methodology: Electronic searches were carried out on PUBMED Central, BVS/BIREME, Web of Science and The Cochrane Library with the aid of key-words. Results: Twenty-six articles were collected. Anti-TNF-α therapy was interpreted and evaluated. Conclusions: Although scarce information is available in the current literature, anti- TNF-α therapy seems to be a viable clinical approach for hospitalized COVID-19 patients who do not need oxygen supply. The genetic polymorphisms, although relevant, may be useful for further researched to assess the clinical response in different research groups.
Keywords: Cell-free nucleic acids; Genetic polymorphism; Polymorphism, single nucleotide; DNA.

Resumo
Objetivo: Este trabalho teve como objetivo revisar as implicações da terapia anti-TNF-α em pacientes com COVID-19 associada ao polimorfismo genético (polimorfismos TNF-α na região-308) desta citocina pertinente. Metodologia: As buscas eletrônicas foram realizadas no PUBMED Central, BVS / BIREME, Web of Science e The Cochrane Library com o auxílio de palavras-chave. Resultados: Vinte e seis artigos foram coletados. A terapia anti-TNF-α foi

interpretada e avaliada. Conclusões: Embora informações escassas estejam disponíveis na literatura atual, a terapia anti-TNF-α parece ser uma abordagem clínica viável para pacientes com COVID-19 hospitalizados que não precisam de suprimento de oxigênio. Os polimorfismos genéticos, embora relevantes, podem ser úteis para pesquisas futuras que avaliem a resposta clínica em diferentes grupos de pesquisa.
Palavras-chave: Ácidos nucleicos livres; Polimorfismo genético; Polimorfismo de nucleotídeo único; DNA.

Resumen
Objetivo: Este trabajo tuvo como objetivo revisar las implicaciones de la terapia anti-TNF-α en pacientes con COVID-19 asociado a polimorfismo genético (polimorfismos TNF-α en la región-308) de esta citoquina pertinente. Metodología: Se realizaron búsquedas electrónicas en PUBMED Central, BVS / BIREME, Web of Science y The Cochrane Library con la ayuda de palabras clave. Resultados: Se recolectaron veintiséis artículos. Se interpretó y evaluó la terapia anti-TNF-α. Conclusiones: Aunque se dispone de escasa información en la literatura actual, la terapia anti-TNF-α parece ser un abordaje clínico viable para los pacientes hospitalizados con COVID-19 que no necesitan suministro de oxígeno. Los polimorfismos genéticos, aunque relevantes, pueden ser útiles para futuras investigaciones que evalúen la respuesta clínica en diferentes grupos de investigación.
Palabras clave: Ácidos nucleicos Libres de células; Polimorfismo genético; Polimorfismo de nucleótide simple; ADN.

1. Introduction

The process of inflammation in more complex and developed animals imply in the due communication of leucocytes and their communication, accomplished by cytokines and chemokines. The 2019 pandemic caused by SARS COV-2 has caused an unprecedent evolution in the immunological approach in search of the cure, or at least a way to halt the infection all over the world.

Tumor Necrosis Factor alpha (TNF-α) is known to play significant roles during theacute phase reaction of inflammation, but can also be found in a large number of chronic and degenerating diseases, including endodontic lesions, such as periapical granulomas, radicular cysts, and apical abscesses (Nair, 2004; Oliveira, 2001).The genetic profile of TNF-α has been extensively explored in the last fifteen years, and the use of new approaches in molecular biology has made it possible to identify several polymorphisms in the promoter region of this gene (Swardfager, 2010), enabling the prevision of the inflammatory response of the host according to its genetic profile. In this sense, different individuals may be low, intermediate or high producers of TNF-α.

The quality of the immune response depends mostly on the balanced cell-to-cell communication through interactions. Therefore, the intertwinement of the different cell types has many things to do with the general state of health of the host mammal organisms; especially those basic steps responsible for the construction of a well established immunologic system, such as nutrition, exposure to microorganisms that will lead to immune memory. In this sense, TNF-α is responsible for the modulation of the inflammatory, along with other cytokines. In fact, the immune effective response is defined by the genetic profile of proinflammatory cytokines, such as TNF-α, Interleukin -6; counterbalanced by anti-inflammatory ones, such Interleukin-10. The quality of the immune response therefore is directly linked to the genetic profile of the individuals. Nevertheless, due to the importance of TNF-α in promoting expressive proinflammatory response, it is possible that complicated “red zone” cases of COVID-19 be lower in patients with anti- TNF-α treatment other than those who use corticosteroid traditional therapy (Brenner, 2020).

The aim of this article was to research through literature review, whether TNF-α polymorphisms are able to modulate the clinical course of COVID-19 patients.

2. Methodology

For the construction of this review, electronic searches were carried out with the use of Key-words accomplished on PUBMED Central, BVS/BIREME, Web of Science and The Cochrane Library. The articles were scrutinized and used to give

support for the statements offered by this paper. Nevertheless, no article specifically worked as a model to be followed. The information acquired were used to be compared with the clinical findings found in the database researched.

3. Literature Review

TNF-α modulation in COVID-19 patients

As the COVID-19 pandemic infected the whole world, the scientific community soon began to gather information and try to minimize the effects of the disease in the human organism. One of the things that was rapidly observed was the intense inflammatory effects on hospitalized patients, caused by cytokine release. This process was then named cytokine storm syndrome (CSS) that is triggered mainly by infections, although some drugs may also stimulate it (Shimabukuro-Vornhagen, 2018). This cytokine storm is unleashed when proinflammatory cytokines are initially released by white blood cells, which in turn activate and recruit the mass production other cell types, establishing a vicious cycle (Lee, 2014), Cytokine storm may also be triggered by drugs related to immunotherapy for cancer, usually as a side effect (Kroschinsky & Stölzel, 2017).

Tumor necrosis factor-α (TNF-α) is a powerful pro-inflammatory cytokine that amplifies the signs and symptoms of inflammation in more developed organisms, such as mammals. It´s inhibition has opened new possibilities for a vast number of treatments applied for diseases that are modulated by this cytokine. The inflammatory pathways suppression of TNF-α has been applied for rheumatoid arthritis in 1990, and has opened a new era for therapeutic success rate for the bearers (McInnes, 2011). It strongly indicates that the course of inflammatory diseases depends on the balance of interconnected cytokines, especially TNF-α. This possibility is supported by the results of its inhibition among patients with auto-immune diseases, such as ulcerative colitis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis. An exception is multiple sclerosis, which seems to worsen if TNF-α is inhibited (Probert, 2000).

During the beginning of the 2020 pandemic, a particular study noticed that the prevalence of severe cases of COVID-19 was lower in those patients whose treatment involved therapies with anti-TNF-α rather than in those who made use of steroids (Probert, 2000). Additional evidence was given by two case reports that came from Italy which showed the fatal outcome of a COVID-19 patient who had ulcerative colitis and was being treated with steroids, compared to another patient, bearer of Crohn´s ileitis and also affected by COVID-19 who was under treatment with a TNF blocker; adalimumab, who had a rapid discharge from the hospital[11]. Adalimumab has been prescribed to treat specific bowel conditions and eye diseases, such as uveitis. Knowing the proinflammatory effects given by TNF-α, the scientific community began to speculate if there could be a relationship with anti- TNF-α therapy and COVID-19 treatment.

Tumor Necrosis Factor alpha (TNF-α) is a cytokine that acts mainly in the acute phase reaction of inflammation. It has been extensively explored in the last fifteen years and the use of new approaches in molecular biology has made it possible to identify several polymorphisms in the promoter region of this gene. It is believed that their presence leads to the differential function of the gene and regulation of the production of this cytokine, which plays a key role in the inflammatory mechanism, to be explained: TNF-α is produced mainly by macrophages, although they can also be synthesized by other cell types such as CD4+ lymphocytes, natural killer cells (NKs), polymorphonuclear neutrophils (PMNs), mast cells, eosinophils and neurons12.

TNF-α is produced and released in inflammatory processes, playing a significant role in the initiation and coordination of cellular events, which constitute the immune system's response to infection13, and is also pyrogenic, capable of inducing the onset of fever, apoptosis and inflammation, and also inhibits tumorigenesis and viral replication. It also responds to infections via activation of IL-1 and IL6 producing cell, promoting vascular events and diapedesis. Eventual alterations in the regulation of TNF-α have been related to a wide variety of human diseases, such as Alzheimer's disease12, cancer14, and psoriasis15, among others. Its biological effects include activation of T and B leukocytes, macrophages and

natural killer (NK) cells; fever induction, release of acute phase proteins such as C-reactive protein (CRP), and gene expression of cytokines and chemokines, and endothelial cell activation16, significantly contributing to vascular alterations.

One study has associated TNF-α role in virotic infections. TNF-α and beta interferons seem to be the first cytokines to be recruited in infections caused by influenza virus, jeopardizing its replication17. Another one has shown that cells with TNF-α is able to inhibit replication of vesicular stomatitis virus, as well as other virotic infections, including encephalomyocarditis virus, and herpes simplex virus in a dose-dependent way18.

The 2020 pandemic brought to light a new enemy named SARS-CoV-2; a coronavirus extremely transmissible who has left, up to the construction of this article, more than 16 million infected people, and more than 3.5 million deaths. Its pathogenesis is increased when the virus finally reaches the endothelial cells of the lungs, via attaching the ACE2 receptors located in the cell membrane therein; whose immunological reaction acts by hyperactivating macrophages and other immune cells, such as natural killer cells, stimulating cytokine and chemokine production and liberation 19,20. When these cytokine are unleashed, a cascade may me initiated known as cytokine storm, responsible for many of COVID-19 clinical complications; inducing multiple organ damages, sometimes fatal21.

SARS-CoV-2 causes complications in almost every important organ in the human body. The patients who have the severe form of the illness usually develop acute respiratory distress syndrome that evolves to pulmonary edema and progressive lung commitment. Kidneys are usually the second organ involved following lung breakdown, followed by heart and liver. During this process, cytokine storm is the main responsible for the inflammatory devastation installed, manifesting with the increase in the serum levels of many interleukins, including IL-1b, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17 and TNF-α. From them all, IL-1b and TNF-α are known to promote vascular permeability and leakage, promoting edema formation and diapedeses22,23. Therefore, TNF-α began to be considered a main cytokine involved in the inflammatory storm installed. In this sense, TNF-α antibodies were researched; they have been used for more than 15 years to combat inflammatory pathologies such as rheumatoid arthritis, ankylosing spondylitis and bowel disease. Scrutinizing the US Food and Drug Administration (FDA) concerning anti- TNF-α therapy, ten have been reported up to 2020; from them, four indicate that blocking TNF-α in many inflammatory diseases may be a promising clinical approach. As for what concerns COVID-19 pathology, it has been observed that TNF-α plays pertinent roles in virtually all acute reactions, amplifying inflammatory responses24.

So, in anti-TNF-α therapy could be applied in the clinical approach of COVID-19, when would it be best indicated? Obviously as it seems, the answer requires researches and time, but we do believe that the soonest the better in patients who arrive in the hospitals looking for medical assistance for this pathology. It is important to pinpoint that these patients have been infected for nearly 7 days when the come to the hospitals, and therefore their immunity is usually jeopardized. In this sense, we believe that patients who require oxygen support but not intensive care would be eligible for anti- TNF-α therapy. Nevertheless, understanding the genetic profile of TNF-α would be interesting to understand how the genetic programming could produce more or less serum levels of TNF-α, and how this could alter the outcome of the disease.

Depending on the genetic information in the human GENOMA, an individual may produce more or less substances responsible for the immunological response. Genetic polymorphisms take place within the very DNA, and can be conceptually defined as variations in the DNA chain, creating or deleting sites of recognition of certain restriction enzymes. Such sites create variations related only to a certain constituent base. If this variation is observed in frequency higher than 1% of the population, it can be considered a polymorphism[25].

The genetic polymorphisms named single nucleotide polymorphisms (SNPs) are responsible for 90% of the variations that take place in the human genome. They may be located in the coding region, or in the gene regulatory region; generating alterations in the amino acid sequence of the coded protein, or at its production rate. Among the SNPs chosen for the scope of this word, the -308 G/A (rs1800629), in the promoter region, is believed to increase the genetic expression and consequently

the level of production of TNF-α, due to the transition of the wild allele G to the variant allele A. This fact offers three possibilities[26]: The wild genotype G_{-308}/G_{-308} is the most common genetic profile of TNF-α, categorizing the individuals as low producers, and therefore are expected to express a less intense inflammatory reaction when compared to the intermediate profile, G_{-308}/A_{-308}. The high producer profile is the rare mutant A_{-308}/A_{-308}, which produces higher amounts of TNF-α, and therefore the individuals with this genotype are expected to react intensely to inflammation. These genetic polymorphisms may play pertinent roles in the outcome of COVID-19 outcome in high producers or intermediate producers of this cytokine.

4. Conclusion

Anti-TNF-α therapy may be an interesting approach for hospitalized COVID-19 patients who do not need oxygen supply. This clinical approach may diminish or interrupt the cytokine storm responsible for the catastrophic effects on the main vital organs, promoting more chances of survival. The genetic profile of TNF-α, although impractical to be accomplished in all the patients, might be useful for further researches to be carried out comparing the different genetic profiles with the intensity of the symptoms in the different groups.

In this sense, proposing the treatment for the patients with Anti-TNF-α therapy may be confirmed by further studies that may bring light to this new approach. Since vaccination has proved itself partially efficient, all means available proved promising may be useful to take over this pandemic which has taken many lives throughout the planet.

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