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Review article

Relation between rheumatoid arthritis and Interleukin-6

Othman Ali Othman*[1], Al Shimaa Mamdouh[2], Nada Hussein Abdelhakim[1].

1-Chemistry Department (Biochemistry Division)-Faculty of Science- Minia University- 61519 ElMinia –Egypt.

2-Rheumatology, Rehabilitation and Physical Medicine Department -Faculty of Medicine -Minia University- ElMinia-Egypt

***Corresponding Authors**: **Othman Ali Othman** - Chemistry Department (Biochemistry Division), Faculty of Science, Minia University, 61519 El-Minia, Egypt- (Tel: 00201099632168)

Email: osman.mouftah@mu.edu.eg-ORCID: http://orcid.org/0000-0003-4061-6929

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ABSTRACT

Joint and cartilage inflammation is a hallmark of rheumatoid arthritis (RA), an inflammatory disease that can develop into osteoarthritis and a range of symptoms and impairments. The prognosis of RA has been drastically altered by the availability of several therapy alternatives, even though its development and progression are still not fully understood. The microbiota has long been recognized as an important regulator of inflammation and immunity due to its ability to either stimulate or dampen systemic inflammation and alter the host's cytokine production pattern. Interleukin 6 (IL-6) is the most abundantly expressed cytokine in rheumatoid synovium. In particular, IL-6 mediates acute-phase protein synthesis and terminal B-cell differentiation. Increased serum levels have been previously reported in patients with rheumatoid arthritis (RA). In this study, serum IL-6 levels were measured in a well-defined cohort using a bioassay (B9 cells), and levels were correlated with conventional clinical and laboratory indices of disease activity. Increased IL-6 blood levels were associated with rheumatoid arthritis, suggesting that this biomarker may be useful for diagnosing the disease at an early stage. There was no statistically significant correlation between disease severity and IL-6 levels in the serum. The cytokine interleukin 6 (IL-6) has been proposed as a biomarker and possible player in the etiology of rheumatoid arthritis.

Key Words: Rheumatoid Arthritis, IL-6, ESR, inflammatory arthritis.

INTRODUCTION

Rheumatoid arthritis definition and symptoms:

Rheumatoid arthritis (RA) is defined as a systemic autoimmune pathology associated with a chronic inflammatory process, which can damage both joints and extra-articular organs, including the heart, kidney, lung, digestive system, eye, skin, and nervous system [1, 2].

Joint swelling in RA reflects synovial inflammation due to immune activation. The cellular composition of RA synovitis is characterized by the accumulation of innate and adaptive immune cells (e.g., T cells, dendritic cells, B cells, macrophages, and osteoclasts). Pro-inflammatory and bone-destructive factors of the immune response led to the loss of bone or cartilage with synovial thickening, angiogenesis, and muscle wasting [3].

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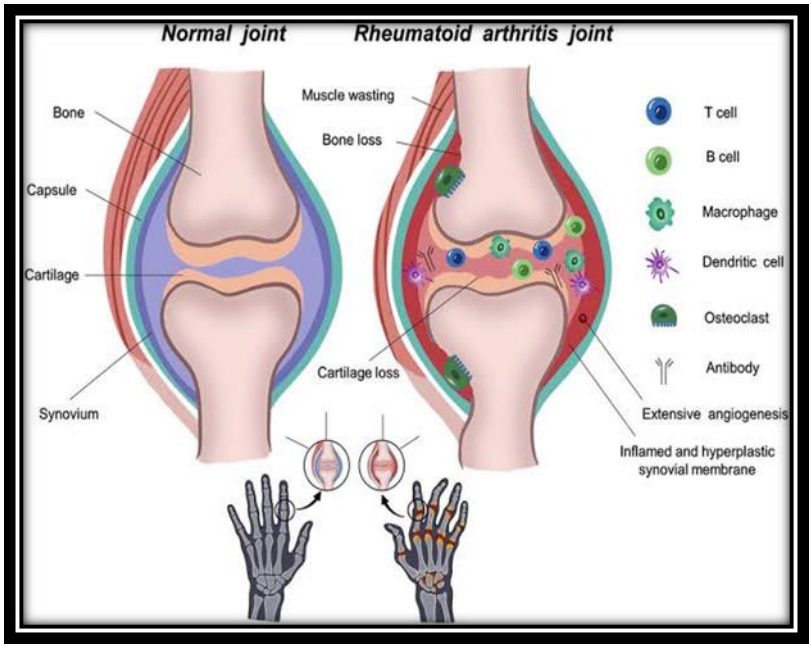

Fig. (1): Normal and rheumatoid arthritis joints.

RA characterization:

RA is characterized by synovial tissue inflammation, which can cause long-term disability and irreversible structural damage if left untreated. In addition to joint damage, RA has a significant epidemiological impact as it in terms of population, RA is the most prevalent type of inflammatory arthritis, affecting between 0.5% and 1.0% of people worldwide. Its economic burden is similar to that of coronary artery disease [4].

Because approximately 90% of RA patients have some kind of disability within 20 years of the disease's beginning, it is critical to diagnose and treat RA as soon as possible. However, there are barriers to early diagnosis and treatment, including the patient's initial delay in seeking medical attention, which is followed by a delay in primary care, and we do not forget the fact that early RA symptoms are occasionally unspecified and ambiguous [5].

RA affects many joints as a model of immune-mediated inflammatory disease. The presence of autoantibodies in a patient's blood causes a higher incidence of extra-articular symptoms, a higher death rate, and more aggressive articular illness. Even with major improvements in antirheumatic treatment, rheumatism is still associated with early mortality and chronic morbidity, which contributes to early death from cardiovascular disease similar to type I diabetes mellitus [6, 7]. Due to better use of disease-modifying antirheumatic drug and the introduction of biologics so it has slowed the progression of radiographic joint damage over the past few decades but a significant percentage of patients are still unable to achieve disease remission which can lead to disability, a decline in quality of life, a diminished capacity to work, and improved health [8].

Causes of RA:

When talking about its etiology, it is well acknowledged that RA primarily affects the

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synovium, resulting in chronic hypertrophic synovitis and inflammation of synovial fluid (SF), which causes connective tissue degradation and functional impairment to bone and cartilage components [9, 10]. The pathophysiology of RA begins with an unidentified antigen attacking the synovial membrane, then starting a local inflammatory response that swiftly progresses to chronic inflammation by the production of cytokines and the recruitment of cellular infiltrates. Finally, the joints sustain irreversible damage and abnormalities. The chronic inflammatory process doesn't happen alone; at the same time, the SF experiences an acute inflammatory process that draws activated phagocytes, especially primarily polymorphonuclear leukocytes, to the region [11 - 12].

In established RA, the inflamed synovial membrane forms a pannus, due to infiltration of peripheral blood cells and proliferation of fibroblast-like synoviocytes. These cells are highly activated, releasing pro-inflammatory mediators and autoantibodies within the joint, sustaining the inflammatory process. This is accompanied by cartilage damage and osteoclast-mediated bone erosion, leading to invasion of the pannus tissue and irreversible deformation of the joint [13].

RA begins before the appearance of clinically apparent inflammatory arthritis (IA):

There is established and growing evidence that RA develops in a series of stages, as outlined in the Figure. In general, it appears that the natural history of RA begins before clinical RA during a period that can be termed “pre-RA,” where genetic and environmental factors interact to drive early breaks in immune tolerance that have been best identified through blood elevations of autoantibodies, including RF and ACPA [14-15].

Genetic and environmental risk factors combine to trigger initial autoimmunity, potentially at mucosal sites. This autoimmunity may then progress to clinically apparent IA, which can be termed “clinical RA.”

Notably, detectable autoimmunity and/or subclinical arthritis in the absence of clinical RA may be termed “pre-RA.” Some individuals may not progress through all stages. [16]

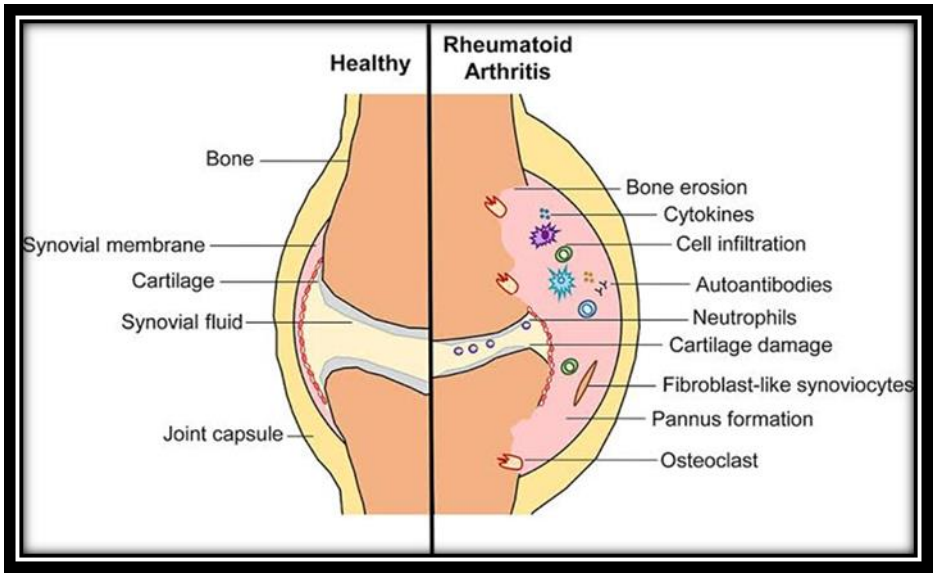

Fig. 2: Pathological changes in a rheumatoid arthritis joint.

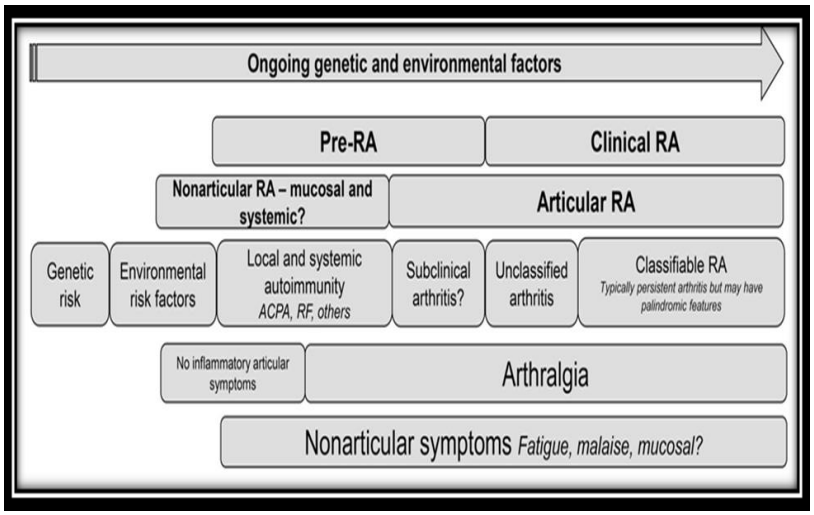

Figure. (3) Model of seropositive RA development.

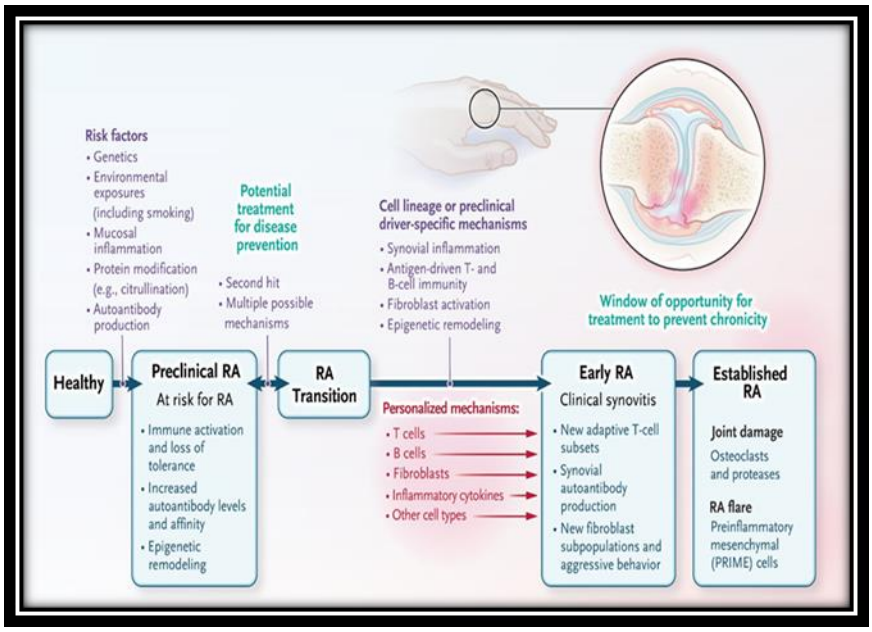

Figure (4): Initiation and Progression of Rheumatoid Arthritis (RA).

The boxes show various stages of the disease continuum and the pathogenic features of each stage. The purple text shows characteristics that affect the transition between disease stages. RA progresses from a healthy state to preclinical RA (at risk for RA) to the RA transition to early synovitis and finally to established, destructive disease. The pathway is not unidirectional, since persons in the disease stage before synovitis who are positive for antibodies against citrullinated peptides (ACPAs) can become ACPA-negative, and in some ACPA-positive persons, disease never develops. The continuum of disease evolution offers potential opportunities for the prevention of RA.

Although each disease state has a characteristic clinical phenotype, multiple pathways and mechanisms can contribute to pathogenesis for an individual patient. This is depicted by the red text and arrows, which indicate a disease that is dependent on a particular cell type or mediator. Therapeutic approaches should ideally be targeted to address the particular pathogenic mechanism in an individual patient. Some patients may have a disease that is characterized by multiple mechanisms, resulting in a partial response or a lack of response to a given targeted therapy [17-19].

Risk factors that affect RA:

Many risk factors that increase the risk of RA or inflammatory arthritis such as infections, vaccinations, hormonal and reproductive risk factors, such as breastfeeding, the timing, number, and outcome of pregnancies, and lifestyle factors, such as diet, smoking, and obesity. Furthermore, a higher prevalence of RA has been linked to periodontitis and silica exposure (20 – 21).

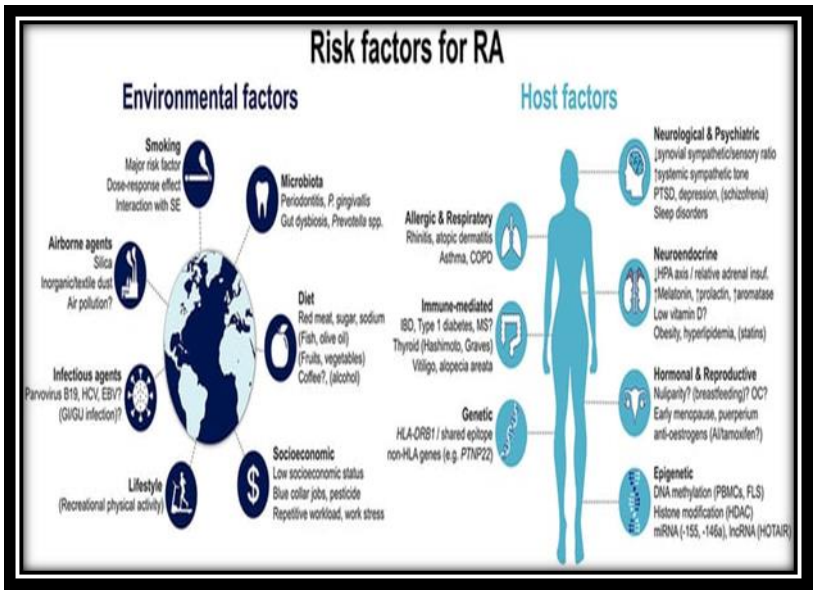

Figure (5): Summary of risk factors for the development of rheumatoid arthritis.

Factors that are associated with decreased risk are represented in brackets. Factors for which evidence is conflicting and uncertainty remains are followed by a question mark.

AI, aromatase inhibitors; COPD, chronic obstructive pulmonary disease; EBV, Epstein-Barr virus; FLS, fibroblast-like synoviocyte; GI, gastrointestinal; GU, genitourinary; HCV, hepatitis C virus; HDAC, histone deacetylases; HLA, human leukocyte antigen; HPA, hypothalamic-pituitary-adrenal; IBD, inflammatory bowel disease; lncRNA, long non-coding RNA; miRNA, micro RNA; MS, multiple sclerosis; OC, oral contraceptives; PBMCs, peripheral blood mononuclear cells; PTSD, post-traumatic stress disorder; SE, shared epitope [22].

Classification of risk factor:

We can classify risk factors that affect RA into two general groups: the first group is host factors, and the second is environmental factors.

Host factors:

Host factors may be divided into genetic, epigenetic, hormonal, neuroendocrine, reproductive, and comorbid host factors.

Genetic Factors:

The initial evidence for a genetic component to RA came from twin and family studies. Indeed, a monozygotic twin of a patient with RA has a 9–15% chance of getting RA, which is up to four times the risk for dizygotic twins and much greater than the general population. Similarly, the RR of RA for first-degree relatives ranges from 2 to 5 and is comparable for both men and women [23 - 24].

Epigenetic Factors:

Over the past ten years, the significance of epigenetics in the development of RA has begun to be uncovered. Heritable differences in gene expression are caused by epigenetic mechanisms, which do not actually alter the deoxyribonucleic acid (DNA) sequence. This could help explain the low concordance rate between monozygotic twins (9–15%) and the partial role of genetic factors in the disease [24 - 23].

Monozygotic twin couples dissimilar for RA had differently varied methylation profiles, according to a recent large epigenome-wide association study. Furthermore, epigenetic alterations may serve as the connection between the genome and environmental interactions because they can be activated by external stressors, such as medicines, tobacco, or nutrition. DNA methylation, post-translational histone modifications, and non-coding RNAs are the main epigenetic alterations that have been linked to an increased risk of RA [25 - 26].

Hormonal and sex-related factors:

There have long been studied as predisposing factors to RA, given the female majority in the disease's spread. In contrast to the anti-inflammatory effects of progesterone and androgens, which are reduced in both male and female RA patients, the sex imbalance is frequently ascribed to estrogens, which are generally characterized as pro-inflammatory. But their functions are much more intricate, and estrogens have anti-inflammatory qualities in a variety of tissues and cells. The reproductive stage, the major cell types and estrogen receptors implicated, serum and tissue levels, and other variables are likely to influence the overall net effect [27 - 28].

Psychiatric conditions:

There seems to be a particularly stimulating connection between RA and psychological conditions. Post-traumatic stress disorder has been linked to a higher risk of RA in both males and females [29 - 30].

Comorbid Host Factors:

This is not the same as comorbidities that affect individuals with established RA, such as cardiovascular disease, infection, cancer, and osteoporosis. These conditions are more common than in the general population and significantly impair the prognosis of the disease [31 - 32].

Environmental risk factors:

On the other hand, environmental risk factors include smoking and other airborne exposures, such as germs and microbes, in addition to diet, such as eating red meat, sugar, and drinking alcohol.

Smoking: It is the most important of such exposures and has been established as one of the main risk factors for the development of RA [33].

Diet: The relation between diet factors and RA development has been studied over a wide range. Although it is difficult to limit patients' behavior in nutrition before RA onset and isolate the effect of a given diet [34 - 35]. Studies also provide clues on RA etiology and pathogenesis, as shown by the influence of the modulation of the intestinal microbiome by diet on the risk of developing RA. Similarly, general healthy eating behaviors have also been associated with decreased risk of RA. They have also shown that drinking alcohol in low

and moderate amounts is protective from RA development [36].

Clinical RA:

The presence of symptoms and indicators of active joint inflammation (such as a swollen joint on physical examination that is consistent with synovitis), in addition to biomarkers like autoantibodies and imaging results that can show joint inflammation and/or damage, are the usual criteria used in clinical care to diagnose RA. One phrase for this diagnosis is "clinical RA." Furthermore, there are established classification criteria for RA, such as the 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) criteria and the 1987 American College of Rheumatology (ACR) criteria.[18,19] Additionally, there are two types of clinical RA known as "seropositive" and "seronegative," which are characterized by the presence or lack of serum elevations of autoantibodies, which at the moment comprise anticitrullinated protein antibodies (ACPA) and/or rheumatoid factor (RF).

In addition to elevated levels of inflammatory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), circulating antibodies like rheumatoid factor (RF) and anti-cyclic citrullinated antibody (anti-CCP) are frequently found in high titers in the serum of RA patients. These antibodies aid in the diagnosis and assessment of disease activity [37].

Laboratory markers for RA:

Autoantibodies are among the laboratory markers that have been linked to RA disease activity and/or prognosis. [38].

Although RF is present in up to 80% of RA patients, it has limited specificity because it can also arise in a variety of other inflammatory conditions that result in persistent antigenic stimulation. These comprise different rheumatologic illnesses (e.g., Sjogren’s syndrome, systemic lupus erythematosus), infectious diseases (e.g., Epstein-Barr virus, hepatitis C virus, and subacute bacterial endocarditis), cancer (e.g., B-cell neoplasms), and healthy people. Additionally, smoking has been linked to a higher incidence of RF [39].

Treatment of RA:

Once confirmation of diagnosis is obtained, treatment is usually started with DMARD therapies that have been shown in controlled clinical trials to be helpful in treating inflammatory arthritis (IA) [40].

Most patients who are diagnosed with a clinical RA benefit from DMARD medication, which reduces joint impairment and improves function and well-being, while a small group of patients achieve disease remission and a very small group of patients achieve DMARD-free remission [41]. But for most people who get clinical RA, their disease will take lifetime treatment with continuous negative impacts on their health and finances, and lasting remission is rare (less than 50% of patients in some studies) [42].

Methotrexate is frequently started as monotherapy for RA and is typically effective at doses between 15 and 25 mg. It is also compatible with sulfasalazine and hydroxychloroquine, two other DMARDs medications. When methotrexate is ineffective, a biological DMARD is often used in conjunction with it for improved outcomes. It should be mentioned that the absorption of oral methotrexate varies greatly; this can be increased by utilizing a subcutaneous delivery route or by splitting the weekly dose [43].

Oral methotrexate is primarily eliminated by the kidneys by glomerular filtration and active tubular secretion, and it is typically absorbed through the small intestine's protein-coupled folate transporter. About 10% of the drug's excretion is biliary, with some enterohepatic recycling, and the remainder is processed in the liver [44].

Interleukin-6 in Health and Disease

Interleukin (IL)-6 is a prototypical cytokine, featuring pleiotropic and redundant functional activity. IL-6 belongs to a family of cytokines, which includes IL-6, IL-11, IL-27, IL-31, oncostatin M (OSM), leukaemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), and cardiotrophin-like cytokine factor 1 (CLCF1); all these cytokines use the common IL-6 signal transducer gp130 [45]. IL-6 production can be induced by both infection and other types of inflammation. Indeed, IL-6 is promptly produced, mainly by macrophages, in response to pathogens or inflammation-related damage-associated molecular patterns [46] and performs a protective function by removing infectious agents and healing damaged tissue via induction of acute-phase and immune responses. IL-6 is crucial for both innate and adaptive immunity. Several cell types produce IL-6, including monocytes, T-lymphocytes, fibroblasts, and endothelial cells, and production is strongly enhanced at sites of inflammation [47].

In infections, toll-like receptors (TLRs) directly recognize the bacteria, virus, or fungi and can directly or indirectly, depending on the type of stimuli, induce the production of IL-6 and other inflammatory cytokines, such as IL-1 or tumor necrosis factor (TNF), through the nuclear factor-kappa B (NF-kB) signaling pathway. Interestingly, the production of IL-1 and TNF also stimulates the production of IL-6 [48]. Overall, dysregulated IL-6 production leads to persistent inflammation [49]. IL-6 demonstrates its biological activities only by binding to its specific receptor, IL-6R. Neither IL-6 nor IL-6R has affinity for gp130 (also known as CD130). However, as a complex, IL-6 and IL-6R can bind to and activate the IL-6R-subunit, gp130, leading to its dimerization and intracellular.

Interleukin-6 in Rheumatoid Arthritis

The IL-6 pathway is involved in different inflammatory diseases and could be a potential target in a vast array of clinical conditions in different branches of medicine [48], spanning RA, cytokine release syndrome in CART cells [49], or COVID-19 infection [50,51]. IL-6 blockade has been successfully used in Castleman's disease, a lymphoproliferative disorder with a wide spectrum of manifestations, and juvenile idiopathic arthritis (JIA). In some countries, it has also been used with various degrees of success in other rheumatologic diseases, such as giant cell arteritis (GCA), Takayasu arteritis (TA), and cytokine-releasing syndrome (CRS).

In the past few months, IL-6 has gained visibility because of its effects on COVID-19 infection. COVID-19 is a disease caused by a novel coronavirus, and it can cause a vast array of symptoms, ranging from mild, flu-like symptoms to severe respiratory failure [52,53]. Many different therapeutic approaches have been tried, mostly anti-inflammatory therapies, ranging from steroids to antimalarial drugs; even non-conventional therapies, such as ozone therapy, have been tested [54]. The most severe symptoms seem to be caused, at least in part, by an autoinflammatory reaction, with characteristics of a cytokine storm [52]: Binding of the novel coronavirus to TLRs causes an increase in the levels of IL-1, which mediate fibrosis and inflammation of the lung [50].

The role of IL-6 in promoting fibrosis has been studied in other pathologies, particularly in the liver [55]. Blocking IL-6 in this context has proven useful: Patients have been treated with tocilizumab (TCZ), a monoclonal antibody against IL-6R, and results have been encouraging [51]. The role played by IL-6 in COVID-19-related inflammation is confirmed by the fact that patients with higher circulating levels of IL-6 and other inflammatory cytokines, such as persons suffering from Down syndrome, are at a higher risk of developing more severe forms of COVID-19 infection [56]. In the treatment of RA, IL-6 blockade has proven to be very useful for those patients who do not respond to

conventional therapy or even less standard ones. For instance, TNF had been a promising target in patients with severe RA, but up to two-thirds of patients do not have a full response; in this group, targeting IL-6 is not only useful, but even improves the overall response to therapy of these patients [57].

An increase in serum IL-6 and IL-21 levels is associated with markers of B cell activation, and IL-6 is associated with radiographic progression in patients with RA [58]. Based on studies emphasizing the critical role of IL-6 in the development and progression of RA, targeting IL-6 has been proposed as a tool to add to the armamentarium to treat RA. Targeting IL-6 can be achieved by either direct targeting of the cytokine or targeting of its receptor. Targeting the receptor (instead of the cytokine itself) may have the advantage of blocking other cytokines of the IL-6 family.

Conflict of interest: NIL

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