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Update on The Risk Factors and Treatment Options for Rheumatoid Arthritis

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Abstract. Rheumatoid arthritis (RA) is characterized by inflammation of the surrounding joints and tissue hyperplasia, which affect all joints in the body. Although RA is generally not fatal, extrarthral lesions may have adverse consequences, which should be paid enough attention to. At present, the treatment mainly relies on anti-inflammatory, analgesic and immunosuppressive drugs, but the problems of relapse and the adverse drug reactions are still faced. This paper introduces the different high-risk factors of the disease, and the related drug and non-drug intervention measures. At the same time, it expounds the new targets of current treatment, such as psychological intervention, exercise intervention, diet intervention, traditional Chinese medicine intervention, and non-drug intervention assisted by digital remote monitoring. To further reduce the disease progression of RA, and to provide reference for improving the life quality and carrying out continuous care, the problems of the intervention methods were summarized and the prospects for future research were put forward.

Keywords: Rheumatoid arthritis; risk factors; treatment.

1. Introduction

Rheumatoid arthritis(RA) is kind of the chronic inflammatory disease, although it is called rheumatoid arthritis, but it does not only affect the joints, in some cases, it can damage a variety of systems and organs, such as the skin, blood vessels, eyes and other parts. RA is also an autoimmune disease that occurs when the body's immune system fails to recognize tissue properly and mistakenly attacks its own tissues. Symptoms of RA include, but are not limited to abnormal softness, swelling, or temperature in the joints; Stiffness of the joints, inability to flex and extend normally, especially after prolonged activity; Abnormal fatigue, high fever and loss of appetite [1]. Early RA often affects the joints first, such as those in the fingers and toes. will appear in the knee, shoulder and other places as the disease reaches the middle and late stages. About 40% of RA patients also experience the signs and the symptoms unrelated to the joints, include the skin, the eyes, the kidneys, and other organs that are not directly related to the joints.

In recent years, the concepts of early treatment, ladder medication, and standard treatment have significantly improved the prognosis of RA patients. However, at present, the rate of compliance after RA treatment in China is still less than 30%, and the overall prognosis is not optimistic. For example, most of the existing drugs cannot selectively target the diseased joint, resulting in the lack of organ and tissue specificity in the treatment of RA. Meanwhile, for some RA patients, there are usually no obvious clinical symptoms in the early stage. It is usually in the late stage of RA, and multiple organs of the whole body are often involved, and there is an urgent need to improve diagnostic techniques and improve existing drugs. This paper reviews the pathogenesis, treatment and new targets of RA in recent years.

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2. Pathogenesis of Rheumatoid Arthritis

2.1. Genetic Factors

It has a crucial role in the progress of this disease. These factors include the general prevalence of RA in families has inhanced, result in estimates of familial disease, serologically positive RA has a risk contribution of ~ 40-50%, with the first group at greatest risk. Furthermore, this element in onset of RA may increases, whose performance is common [2].

With the penetrate to the study on RA, it has been shown to be associated with the human leukocyte antigen. At now, 278 alleles have been officially named, HLA-II genes, including the DR, DQ and DP genes, have a variety of forms and are the main part of the body's specific recognition and the immune response, which have been found to the pathogenesis of RA. From another perspective, many nucleotides genotyping studies have identified lots of popular genetic variants associated with RA risk, and these associated variant projects continue to expand rapidly as genotyping techniques advance [3].

2.2. Cytokines of Rheumatoid Arthritis

Under the influence of genetic and environmental factors, susceptible individuals lose immune tolerance to autoantigens, leading to the formation of autoimmunity and autoantibodies. This lack of immune tolerance is the first step towards autoimmunity. Both innate and adaptive immune responses lead to an increase in cytokines and are closely associated with RA pathogenesis.

Cytokine is an important regulator of synovial inflammation. For example, some cytokines, such as tumor necrosis and interleukin can play a role by promoting the rate of inflammation and inducing cartilage degradation. Inhibiting the effect of proinflammatory cytokines through the use of specific cytokine inhibitors or anti-inflammatory cytokines is currently the most basic testing method in RA patients. The application of neutralizing anti-TNF-α monoclonal antibody in RA treatment has also achieved corresponding results [4].

With the further investigation of the pathogenesis of RA, other related cytokines have gradually come into public view. If IL-15 activates neutrophils and delays FLS and endothelial cell apoptosis in locally inflamed synovium, it can also increase the water level of the phase capacitant complex (MHC) -II on macrophage cells, thereby enhancing the proliferation of CD4+ T cells. IL-23 enhanced the pathogenicity of Th17 cells in RA, induced the proliferation of Th17 cells and IL-17 production. IL-32 collaborates with TNF-α and IL-1β to induce the synovial inflammation. IFN-γ promotes osteoclast differentiation and inhibits Treg cell differentiation to induce RA immune reaction and can also induce VCAM-1 expression on endothelial cells to facilitate lymphocyte migration to tissues [5].

2.3. Disruption of Intestinal Flora

Under normal physiological conditions, the human intestinal microbiota is in a stable state and has a number of functions and interrelationships important to host health, such as helping the human body to carry out nutrient absorption, synthesis, energy conversion and metabolism, and regulating the body's immune response to resist the invasion target external pathogenic bacteria also the immune response of the body to its own pathogens. Once this balance is disrupted, the gut microbiota environment is disrupted, increasing the risk of disease. In the last few years, the description and understanding of the gut microbiome has also gradually improved, the broad field of research has been formed, especially in autoimmune diseases such as rheumatoid arthritis, where there has been renewed interest in studying the microbiome as a potential candidate for autoimmune development [6].

Current findings also support the possibility that the beginning of RA is in connection with the gastrointestinal follow up. In one study, it showed that early RA patients had a different microbial composition than controls and a significant rise in species of the prevotella. Also, the mouse model, the parenteral injection of cell wall fragments of various gut bacteria caused arthritis in this case,

reproduction under sterile conditions did not develop arthritis; Otherwise, it appears when gut bacteria species are introduced

The dysfunctional flora may affect the firm connection between intestinal epithelial cells, destroy the mucosal barrier, and lead to the translocation of pathogenic bacteria to intestinal lamina propria, which causes immune response, produces pro-inflammatory cells and factors, and reaches the joints through the blood circulation, triggering RA.

2.4. Unhealthy Lifestyle

Unhealthy living habits like smoking, may cause inflammation and damage in the lungs and stimulate the immune system to produce rheumatoid factors. When combined with IgG, rheumatoid factors can activate the complement system and cause inflammation in joint tissues. The deposition of this immune complex can lead to persistent inflammation in the joint cavity, which in turn can cause joint damage. Smoking can lead to osteoporosis, this is because nicotine inhibits the activity and differentiation of osteoblasts, which are the cells responsible for building new bone. When the rate of new bone formation decreases, bone mass decreases. Nicotine can also constrict blood vessels and reduce blood flow to bone. This impairs the delivery of oxygen, nutrients, and other essential factors needed for bone health and repair, which can compromise bone strength and density. Weak bones are more likely to aggravate RA. An unhealthy diet can also exacerbate rheumatoid arthritis. Long-term high carbohydrate intake makes people obese. Obesity not only increases the burden on the joints, but also produces chronic inflammation [7].

3. Treatment of Rheumatoid Arthritis

3.1. Non-drug Therapy

Non-drug therapy of RA usually plays a role in controlling, it is difficult to heal. Traditional physical treatment such as wax therapy, massage and acupuncture can relieve pain, eliminate inflammation, and help restore joint function. Electrotherapy is another way of treatment. It is a kind of physiotherapy method commonly used in clinical practice. Infrared radiation is used to irradiate diseased joints, promote blood circulation around joints through thermal effect, help local inflammation absorption, thus reducing joint adhesion, joint pain, and promoting the gradual recovery of joint function. In addition, exercise coupled with a healthy diet, is more conducive to recovery. Consuming foods rich in vitamins, high in protein, and high in calcium helps boost immunity and promote bone health. Foods's high in fat and stimulant foods should be avoided or reduced. However, non- drug therapy alone may not work as well, it is necessary to combined with medication, which may achieve the desired effect more quickly. Rheumatoid patients need to follow the doctor's advice and return to the doctor on time, which can reduce the treatment cycle and unnecessary consequences.

3.2. Drug therapy:Methotrexate

Methotrexate (MTX) is a classic dihydrofolate reductase inhibitor, originally used mainly to treat childhood leukemia. Since 1980s, it has been used in the treatment of RA at low doses (5-25 mg/ week), showing good efficacy and safety, and has become the first choice for the treatment of RA at home and abroad.

At present, the main explanation for methotrexate is the adenosine signaling pathway. MTX may inhibit the deamination of adenosine in lymphocytes and enhance the vasodilation induced by adenosine. Most adenosine is continuously dephosphorylated in the extracellular space to form adenosine. Intracellular, adenosine may inhibit ATIC, leading to increasing the adenosine levels in the intracellular AICAR and extracellular. AICAR may also inhibits adenosine deaminase, thereby preventing adenosine from breaking down into inosine. When AICAR levels rise, adenosine levels also rise inside the cell and are transported outside the cell via extracellular nucleoside transporters. Most extracellular adenosine is actually formed by transporting ATP from outside the cell via ATP

transporters and cleaved by exonuclide nucleoside triphosphate phosphohydrolase, which dephosphorylates the ATP and ADP to produce AMP. Exo-5 'ribosidase then cleaves the AMP to adenosine, then converted to inosine by activating intracellular signaling through adenosine receptors [8].

Previous studies showed that IL-17, IL-6, IFN-γ levels are lower than before treatment and IL-35 levels are higher in patients taking high and low doses. Patients suffer from adverse reactions such as vomiting. High doses of MTX can improve the clinical symptoms of patients, reduce CRP and ESR levels, increase IL-35 levels, decrease IL-17, IL-6 and IFN-γ levels, and do not increase the occurrence of adverse reactions [9].

The main side effects of MTX include gastrointestinal disorders, pneumonia, and hematological diseases, but due to the low dose of MTX, there are basically no life-threatening side effects in these typical cases, but no matter the dose, there will be some problems such as the liver toxicity, the lung damage, and also the bone marrow suppression [10]. At present, there is still a lack of sufficient prediction and prevention means, and further research is needed.

3.3. New Treatment Target

With the advancement of science and technology, there are new treatment targets for RA. Janus kinase (JAK) inhibitors have emerged as a new treatment option for RA. It works by blocking the activity of Janus kinase enzymes. JAK enzymes are a family of the non-receptor tyrosine kinases which involve in the transduction pathways [11]. When JAK enzyme is activated, the transcriptional activator (STAT) constitutes the JAK-STAT signaling pathway, affecting cell proliferation, differentiation and immune response. By inhibiting JAK-STAT signaling, JAK inhibitors can reduce the production and activity of pro-inflammatory cytokines, leading to a dampening of inflammatory and autoimmune responses. The benefits of JAK inhibitors method involve fast onset of action, enhanced disease control and safety. Even though this method does not cure RA, but its maximum control and relief.

In addition, there are many new drugs in preliminary clinical trials or new drug applications, Examples include glucocorticoid receptor modulator antibody drug binding (ABBV-3373), selective non-steroidal glucocorticoid receptor modulator drugs, and CD40 ligand antagonist fusion eggs White (VIB4920), selective immune metabolism modulator (MBS2320), etc., still need to be further evaluated in future phase II/III clinical trials.

4. Conclusion

Rheumatoid arthritis, as a more common clinical disease of rheumatology and immunology, will cause great obstacles to the patient's joint function, and affect the patient's health. In recent years, the research on the RA treatment has developed very rapidly. So far, rheumatoid arthritis has been transformed from a highly disabling disease to a well-controlled disease. However, the diagnostic technology, new drugs and new therapies have emerged endlessly, they still lack some specificity. Meanwhile, the adverse reactions and the long-term efficacy of commonly used drugs are worrying, affecting patient compliance, in addition, the lack of clinical trials to verify the effectiveness and safety of new drugs under development also limits their scope of use. Therefore, in the future research, on the one hand, people should continue to study the key substances and mechanisms in the development process of rheumatoid diseases; On the other hand, we should start from the pathophysiological basis of disease pathogenesis and use biotechnology to develop biological drugs not only with good efficacy but also the low adverse reactions to treat and prevent rheumatoid arthritis, bringing good news to many patients with rheumatoid arthritis.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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