The Role of IL-6 in Rheumatoid Arthritis: Mechanisms, Tocilizumab Efficacy, and Challenges in Treatment

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Abstract. Rheumatoid arthritis (RA) is a systemic autoimmune disease that primarily affects small joints and soft tissues. Currently, several effective drugs, such as tocilizumab (TCZ), are used in clinical practice to control disease progression and alleviate symptoms. While these treatments offer significant benefits, adverse effects remain a challenge. This article explores the molecular mechanisms of IL-6 in RA pathology, emphasizing its role in disease development and symptom manifestation. Additionally, it reviews the efficacy of TCZ, highlighting both its therapeutic advantages and associated risks, such as increased susceptibility to infections and cardiovascular complications. The study suggests that future research should focus on minimizing these adverse effects while maintaining treatment efficacy. Moreover, multi-drug combination therapy is proposed as a potential strategy to improve patient outcomes. However, this article does not cover other cytokines involved in RA, such as IL-2 and IL-8, nor does it address all potential adverse effects. Further research is necessary to enhance treatment strategies and better manage RA-related risks.

Keywords: TCL, IL-6, rheumatoid arthritis, adverse effect.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent joint inflammation, leading to pain, swelling, and progressive damage. Several studies reveal the incidence rate of RA in adult populations around 0.5%-1%, they also explain middle-aged women prevalence may be lower than before [1]. RA mainly affected tissue called pannus and destroyed its local basial structure at the same time. Indeed, the cure for RA is almost impossible with nowadays` levels of medical science although some medicine could slow down the disease progression.

The pathogenesis of rheumatoid arthritis (RA) is mainly driven by antibodies and the immune system. Anti-citrullinated protein antibodies (ACPAs) are key in triggering disease symptoms. Post-translational modifications also contribute, where the calcium-dependent enzyme PAD converts arginine to a polar residue, increasing ACPA production [2]. Besides, smoking environment and daily diet are also the causes of the disease. Several medical treatments help manage RA by reducing inflammation, relieving symptoms, and preventing joint damage. These include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), biologics, and TNF inhibitors [3]. While effective, these treatments pose risks such as osteoporosis, hypertension, increased infection risk, and, in rare cases, malignancies. These challenges suggest the need for continued research into safer and more effective RA therapies. Tocilizumab (TCZ) is a recombinant humanized anti interleukin-6 receptor (IL-6R) monoclonal antibody (mAb) mainly utilized in RA treatment .IL6 is a cytokine which may lead to the symptoms of RA. The mechanism of the drug is that TCZ could compete both the soluble and membrane-bound forms of the human IL-6R which could inhibit the binding of IL6 and its receptors. After that the cytokine`s pro-inflammatory activity will be reduced [4]. TCZ has passed pre-clinical and clinical efficacy. Studies shows this drug can not only bind to IL-6R dependent but also displace IL6 already bound to its receptors. However, it also has some adverse effects. One of the most common problems were infections. Some of the patients suffered from skin infections, gastrointestinal disorders. If they take TCZ by a mistake, there are gradual increase in the risk of spontaneous abortion death and the risk of malformations in women. It will bring about danger to both pregnant women and newborn. This article focuses on the mechanism of TCZ in Rheumatoid Arthritis treatment and provide some novel

therapy of the disease. Another critical purpose is giving more methods to get rid of the adverse effects which causes plenty of patients are in danger. Furthermore, this article will show more suggestions of application of TCZ in RA treatment.

2. IL-6 in RA Pathogenesis

Although the mechanism of RA is not fully clear, plenty of evidence has shown IL-6-plays an important role in its pathogenesis. It is a cytokine which could lead to a serious of immune response, inflammation, and hematopoiesis [5]. Signal transduction is a crucial step in release of biological activities. IL-6R and gp130 are the key elements in this process. When IL6 binds to its receptors on the membrane, homodimerization of gp130 will be formed. Then with the combination of cell membrane and gp130, membrane bound

gp130 (mgp130) also appeared which is expressed in patient`s body [5]. A series steps above may lead to the symptoms of RA. TCZ is an antibody which is able to block both classic-signaling and trans-signaling, which is useful to stop IL-6 bind with its receptors. If the signaling is blocked, the symptoms will ease possibly. Several studies have illustrated IL-6 could produce autoantibodies. For instance, IL-6 may become regulator of CD4+ T cell differentiation and activation. IL-6 impacts T-cell development by promoting the proliferation and differentiation of T lymphocytes into TH-17 cells which subsequently produce IL-17. Some T cell effector functions are also affected by IL-6 due to Th2 cell differentiation. IL-6 could activate the production of T-helper 17 cell over Treg in the effector CD4+ T cells subset, which plays a crucial role in the development of RA and other disease of immune system [6]. In terms of joint damage, there are multiple reasons. One of the most important reasons is IL-6 is engaged in local inflammation and induced endothelial cells, which could lead to the production of IL-8 and recruit leukocyte. These two molecular will involve joints and cause the destroy of the joints [6]. All of these contents above could be the causes of the RA, which has great implications for drug discovery and disease therapy.

3. TCZ in RA Treatment with its Efficacy and Safety

TCZ a recombinant humanized antibody is useful to relieve symptoms of Rheumatoid arthritis. It can block the bounding of interleukin6 and its receptors (IL-6R). It firstly comes out as an orphan drug for the Castleman`s disease in Japan in 2005 [7]. There are multiple molecular mechanisms of the RA therapy. Generally, IL-6 is the most abundant cytokine in the serum and synovial fluid of RA patients correlates with disease activity and joint destruction, making its receptor an important treatment target. TCZ is a mAb inhibitor of the IL-6 receptor by blocking both classic-signaling and trans-signaling. TCZ is a drug with a relatively good efficacy.

There are great number of evidence for a significant changing on RA patients. Most of them feel their disease activities are reduced after using TCZ. This result come from American College of Rheumatology (ACR). The details of this are 8mg/kg TCZ could show remarkable clinical benefit. Compared with the methotrexate monotherapy, TCZ is more effective. The SAMURAI studies from Japan illustrate TCZ monotherapy could provide more protection to damage joints. Besides, TCZ monotherapy could also reduce the bone erosion. It’s a good idea for patients to choose TCZ monotherapy if they do not respond to treatment with methotrexate [8]. There are some safety profiles below which should be noticed comprehensively. TCZ is forbidden during pregnancy which may lead to increase the risk of spontaneous abortion even death, although the risk is only found in animal experiments. On top of that, although several studies indicate TCZ could not lead to increase the risk of cancer, it is still necessary to do more research to find the answer to this question The reason for this is the incidence rate ratio is still 0.79 which become a threat to the patients` health [9]. In terms of hypersensitivity, the incidence rates of hypersensitivity are relative rare in RA patients only 1/2000 per year [10]. However, people still must deal with it. Therefore, these contents above indicated the

application status, which is generally effective to a great number of patients and introduced some possible risk of using TCZ.

4. Adverse Effect and Risk Factors of TCZ in RA Treatment

Generally, TCZ as a novel drug for treating RA, can be administered subcutaneously once a week by patients themselves and has the same effect as intravenous injection, making it more convenient and efficient for patients. However, safety and ethical considerations should be considered in administration, first thing that should be mentioned is safety profile. There are some effective methods to cope with these adverse effects. Firstly, a full physical examination should be conducted before using TCZ, especially for patients with cardiovascular disease and those who suffered from other basic disease. On top of that, doctors are responsible to know patients' basic information of their health. It will bring about danger to both pregnant women and newborn. After that, the most common adverse effects are infections]. It should be noticed when patients are utilizing TCZ to treat RA. After that, the most common adverse effects are infections [11]. It should be noticed when patients are utilizing TCZ to treat RA. Skin infections are relative more common. Besides, patients and doctors need to pay attention to the Cardiovascular safety [12].

4.1. Cardiovascular Disease (CVD)

CVD is one of the biggest adverse effects of taking TCZ for RA treatment. Moreover, even directly leads to the death of the patients with a great reaction. The reason for this is TCZ could increase lipid levels and decrease the quantity of C-reactive protein. The level of total cholesterol, high-density lipoprotein cholesterol and triglycerides will increase due to the utilization of the TCZ. On top of that, total cholesterol (>6.2mmol/L) and low-density lipoprotein cholesterol (>4.1mmol/L) increase continuedly in 24% and 15% patients in clinical trials. Another interesting observation is that patients with early RA experience a rapid increase in total cholesterol. However, the patients with a long-standing RA exhibit no change in total cholesterol levels, although they receive TCZ (8mg/kg) [13]. Whereas, some examples still indicate there are risk of CVD after using TCZ. A Japanese patient with long-standing RA has been treated by TCZ 8mg/kg monotherapy for more than 5 years, his blood cholesterol increases every year [14]. Therefore, patients still need to pay attention to blood lipids and cholesterol levels, which could lead to the CVD.

4.2. Infections

Some effective therapies including TCZ have the risk of serios infections or infestations according to some reports. Some research gives some valuable data. The overall rate of infections in long-term patients` groups is 108/100PYs`, and 4.7/100PYs is the rate of serious infections [15]. British society for rheumatology biologics register finishes an experiment about the incidence of serious infection by different drugs. The TCZ is within the scope of the study. It is a drug with high rate of infection [16]. The rate of gastrointestinal perforations is also an obvious adverse effect. The average rate was 0.26/100PYs`, and the data of long-term patients is almost similar (0.28/100PYs`). Most of the gastrointestinal perforations exits in the lower gastrointestinal tract [17]. Compared with other drugs such as TNFi, csDMARDs, rituximab, the TCZ is easier to lead to the lower gastrointestinal perforations [17].

5. Conclusion

This article indicates the mechanism of the RA pathology. It contains the gene factors and environment factors. Mostly focus on the gene and molecular. Besides, IL-6 plays an important role in the mechanism of the disease and some of the paragraph introduce how IL-6 leads to symptoms. Next, the article gives the information on the how TCZ treat with the RA and its efficacy. However also has some adverse efficacy which could impact patients a lot, such as infectious and

cardiovascular disease. At the same time, article also gives some suggestions on how to deal with the risk and adverse efficacy. Finally, muti-drug combination therapy is also a good choice for RA. It is beneficial to specific groups. These contents above could promote the research on how to eliminate the adverse efficacy, which means minimize the adverse effects while relieving symptoms. On top of that, it is also beneficial to develop the methods of dealing with the emergency (CVD and infections).

However, this article could not indicate other factors or cytokines which could lead to RA, such as IL-2 IL-8, etc. Many other adverse effects are not listed. I hope that there are more and more research and projects which could help doctors and patients dealing with the adverse effects effectively. What's more, scientists could find more factors which could lead to RA.

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