

To Analyze the Immunomodulatory Effects of Anti-IL-6 Receptor Drug Tocilizumab in Giant Cell Arteritis (GCA)

Yanyan Zhang*, Tianqian Jia, Xiaojuan Li, Yueyan Wang

School of Medical Engineering, Haojing College of Shaanxi University of Science & Technology, Xi'an, Shaanxi, China.

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***Corresponding author:** Yanyan Zhang, School of Medical Engineering, Haojing College of Shaanxi University of Science & Technology, Xi'an, Shaanxi, China.

Abstract

Giant Cell Arteritis (GCA) is an inflammatory symptom that affects blood vessels in middle-aged and elderly people. The disease involves large and medium-sized arteries in patients, especially the temporal arteries. The appearance of diseases affects the physical health of patients to a certain extent. Interleukin-6 plays an important role in a variety of immune responses and inflammatory responses. Tocilizumab is a kind of humanized monoclonal antibody that can bind and block the IL-6 receptor in a specific way, inhibit the IL-6 mediated signal transduction, alleviate inflammatory responses, and reduce inflammatory damage. This article is divided into four parts and describes the research progress of the immunomodulatory effects of anti-IL-6 receptor drug tocilizumab in giant cell arteritis. Firstly, the basic characteristics and mechanism of tocilizumab were analyzed, including chemical structure and biological activity, pharmacokinetic characteristics, and safety of tocilizumab. Secondly, the application of tocilizumab in the treatment of giant cell arteritis was discussed, including the efficacy analysis, dosage, and course of treatment. The challenges and limitations of tocilizumab in the treatment of giant cell arteritis were discussed again. Finally, the prospect of the proposition is summarized, hoping that this paper can provide reference materials for related personnel's research work.

Keywords

Anti-IL-6 receptor drugs, Tocilizumab, Giant cell arteritis, Immunomodulatory effects, Research progress

Giant Cell Arteritis (GCA) is a common chronic and progressive vascular inflammatory disease in clinics. The disease mainly occurs in the head and neck arteries and large vessels. After the onset of the disease, there will be an inflammatory reaction of the arterial wall, intimal hyperplasia, lumen stenosis, or even occlusion, which will show complications such as tissue ischemia, decreased vision, and blindness. At present, many scholars have pointed out that interleukin-6 (IL-6) and its receptor play an important role in the occurrence and development of GCA. The overexpression of IL-6 not only promotes the infiltration and activation of inflammatory cells, but also participates in the pathological remodeling of the arterial wall [1]. Tocilizumab is a humanized monoclonal antibody. After entering the human body, tocilizumab can bind to IL-6 receptors, block IL-6 mediated signal transduction, and inhibit inflammatory response and immune cell activation. At present, there are not many studies on the immuno-pharmacological effects of anti-IL-6 receptor drug tocilizumab in giant cell arteritis. Based on this, this paper analyzes the above propositions and reviews them as follows.

1. Basic characteristics and mechanism of action of tocilizumab

1.1 Chemical structure and biological activity

Tocilizumab is a recombinant humanized, anti-human immunoglobulin G1k subclass monoclonal antibody against soluble and membrane-bound IL-6R. When it enters the human body, it can form IL-6/IL-6R/gp130 hexameric complex with related receptors to achieve signal transduction. This product has a wide range of biological activities, it is involved in the regulation of inflammation, cell proliferation, blood diseases, and tumor formation. It can improve the viability of lacrimal gland epithelial cells by inhibiting the activation of NLRP3 inflammasome and reducing the JAK/STAT3 signaling pathway. The application of this product in the treatment of dry eye can achieve remarkable results. Drugs can reduce the activation rate of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome, which can reduce the maturation and cleavage of GSDMD by pro-inflammatory cytokines IL-1 β and IL-18 and alleviate the inflammatory response [2]. Tocilizumab blocks IL-6 signaling and reduces the production and release of inflammatory factors. The use of drugs in the treatment of rheumatoid arthritis (RA) can achieve satisfactory results. It can reduce the JAK/STAT signaling pathway mediated by NLRP3 inflammasome, and fully activate and regulate the injury of lacrimal gland epithelium.

1.2 Pharmacokinetic characteristics

Tocilizumab transporters play a key role in the process of ADME. The distribution and gene polymorphism of tocilizumab transporters in various tissues and organs can lead to differences in the absorption, distribution, metabolism, and excretion of related drugs. The pharmacokinetics of this drug is affected by individual genetic differences. Relevant literature shows that many drugs can affect drug distribution and metabolism after binding to plasma proteins. Only part of the unbound drug can enter the cell membrane and reach the site of action. It can be seen that the drug-protein binding rate can affect its distribution and bioavailability in the human body. The absorption, distribution, metabolism, and excretion of drugs are greatly affected by gastric acid secretion, gastrointestinal blood flow, gastric transit time, intestinal microorganisms and enzymes, and the action of "transporter" proteins. These factors collectively determine the oral bioavailability and plasma concentration-efficacy relationship of tocilizumab. It is also worth noting that the plasma concentration of the drug decreases exponentially over time, with the detailed rate of decrease and the steady-state plasma concentration level ultimately achieved depending on the half-life and dose profile of the drug.

1.3 Safety of tocilizumab

Common side effects of this product include abnormal diastolic blood pressure, abnormal systolic blood pressure, rubella, abnormal erythrocyte sedimentation rate, etc. Relevant staff needs to strengthen the degree of attention to hepatobiliary system diseases, ear and labyrinth diseases, reproductive system, breast diseases, and heart organ diseases. Studies have confirmed that the adverse reaction liquid involved in this product involves the skin, accessories, and blood system.

Before the application of drugs, the staff needs to do a good job of patient assessment, implement the configuration and injection process, and dynamically grasp the emergency treatment measures for adverse reactions. As an immunosuppressant, tocilizumab is likely to interact with some drugs after entering the human body, which is mainly reflected in drugs that affect the function of the immune system [3]. Staff need to be aware of patient medication history to prevent potential drug interactions. One study showed that RA patients treated with TCZ had a high rate of reaching the target. After discontinuation of TCZ, RA patients should still take DMARDs according to the needs of the disease and follow the doctor's advice to achieve good disease control. The patient's safety and tolerance were satisfactory after half a year of drug treatment.

2. Application of tocilizumab in the treatment of giant cell arteritis

2.1 Efficacy analysis of treatment for giant cell arteritis

Studies have confirmed [4] that drugs can improve the clinical symptoms and laboratory test results of GCA patients. The erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (CRP) levels were significantly reduced, and the common carotid artery wall thickness and subclavian artery thickness were reduced. The patient was able to use fewer doses of glucocorticoids to treat the disease and was less dependent on hormonal drugs. In

addition, it has been reported that it can reduce the inflammatory response mediated by IL-6 and alleviate the inflammation of blood vessel wall. Imaging studies confirmed that the vascular involvement of GCA patients was significantly improved after drug treatment. It is worth mentioning that although the drug treatment of GCA has shown satisfactory results, the adverse reactions caused by drugs deserve attention. In addition to the major adverse events mentioned above, some patients experienced pain response to drug treatment.

The study showed a significant decrease in hs-CRP and wall thickness of the common carotid and subclavian arteries in the 18 patients treated with TCZ, and all patients had a reduction in glucocorticoid use during treatment. The efficacy of TCZ in the treatment of GCA was also confirmed in a multi-center real-world study, in which 231 patients achieved long-term remission after TCZ treatment. In terms of optimization of TCZ treatment, studies have shown that once GCA patients have achieved complete remission, TCZ treatment can be further optimized by reducing the dose or extending the dosing interval. In a study comparing patients who received optimized therapy (TCZOPT group) with those who did not (TCZNON-OPT group), similar long-term remission rates were observed in the two groups, but serious infections were more common in the nonoptimized group. This suggests that by optimizing the TCZ regimen, the risk of adverse effects can be reduced while maintaining efficacy.

It was found that of the 40 patients treated with TCZ, only 30% met the inclusion and exclusion criteria for the GACTA trial. In addition, the route of administration (e.g., intravenous infusion or subcutaneous injection) may also affect the efficacy and safety of treatment.

2.2 Dosage and course of treatment

Combined with the information on the subcutaneous injection of tocilizumab approved by the FDA in 2017 for the treatment of GCA, and considering the safety of this product in the treatment of GCA, it is speculated that the early dose should be determined based on the actual situation of patients and clinical experience [5]. In general, the frequency of drug use was 1 time/week, 8mg/kg. As for the duration of drug therapy, it has been suggested that after complete remission, treatment can be optimized by reducing the dose or extending the interval between doses. However, the specific situation needs to be determined by the doctor's judgment. If a patient fails treatment, an increase in the dose of tocilizumab or a change in the administration of tocilizumab is recommended.

3. Challenges and limitations of tocilizumab in the treatment of giant cell arteritis

In terms of the challenges and limitations of tocilizumab in the treatment of giant cell arteritis, although many kinds of literature have confirmed the potential efficacy of tocilizumab in the treatment of GCA, and its effect in the treatment of Takayasu arteritis is significant, there are also kinds of literature pointing out that the effect of drug treatment of the disease is not obvious. Relevant literature showed [6] that only 23.00% of patients who used tocilizumab to treat diseases reached the endpoint. The patient underwent 52 weeks of relapse and normalization of erythrocyte sedimentation rate and C-reactive protein. As mentioned above, the safety of drugs deserves attention [7]. It has been documented [8] that 5 patients developed infections requiring antibiotic treatment after using this product. Two of the patients had severe infections, which prompted physicians to pay attention to their health when administering drugs to treat the disease. Compared with tocilizumab, glucocorticoids, and methotrexate are more commonly used for patients with GCA. Tocilizumab is a biologic agent that has shown potential for glucocorticoid-dose reduction. One study [9] showed that the average glucocorticoid dose was significantly reduced in patients treated with tocilizumab. It represents that tocilizumab may help mitigate glucocorticoid-related side effects and the risk of long-term use. It is worth noting that although tocilizumab has shown good efficacy in some patients, there is still limited information on how to optimize its treatment regimen to improve efficacy and reduce adverse reactions [10-13]. After the patient's condition is completely relieved, the treatment plan of tocilizumab can be optimized to reduce the dose or extend the dosing interval [14].

4. Research progress

At present, as an IL-6 antagonist, tocilizumab has shown certain efficacy in the treatment of diseases such as Takayasu arteritis and systemic sclerosis [15]. However, tocilizumab may cause some adverse reactions in clinical application, which suggests that we need to develop safer and more effective new formulations of tocilizumab in future studies. For example, in order to reduce the incidence of adverse reactions, the drug administration method should be improved, the dose should be adjusted, or the long-acting preparations should be developed [16-18].

Although tocilizumab has shown some efficacy in the treatment of Takayasu arteritis, its potential application in other non-giant cell arteritis diseases still needs to be further explored. For example, considering that tocilizumab can

reduce vessel wall inflammation and inhibit neovascularization in patients with vasculitis, its application in other types of vasculitis, such as systemic sclerosis, TAFRO syndrome, and other diseases, can be considered [19-21].

In view of the efficacy and safety of tocilizumab in the treatment of a variety of diseases, as well as its possible adverse reactions, it is necessary to adopt a multidisciplinary cooperation approach for future research. Such cooperation should include not only experts in rheumatology, immunology, endocrinology, pediatrics, but also experts in basic research fields such as pharmacology, medicinal chemistry and biostatistics. Through multidisciplinary collaboration, the efficacy and safety of tocilizumab can be more comprehensively evaluated, and new knowledge about the mechanism of action of tocilizumab can be explored.

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