

Progress of monoclonal antibodies in the treatment of autoimmune diseases

Tong Xu*

School of Woosuk University, Jeollabuk-do, North Korea

*Corresponding author: xut0622@stu.woosuk.ac.kr

Abstract. Autoimmune diseases are a hot issue in today's society, and some researchers have found that monoclonal antibodies can be used to treat autoimmune diseases. Autoimmune diseases are a class of diseases caused by abnormal attacks of the immune system on its own tissues, and monoclonal antibodies, as a kind of targeted therapy, have high specificity and selectivity. This article analyses the etiology and pathology of autoimmune diseases, as well as the therapeutic principle and preparation of monoclonal antibodies. Through the comprehensive analysis of the research, it is found that monoclonal antibodies can effectively target the key molecules or cells of autoimmune diseases, reduce inflammatory response and improve the condition. However, challenges faced by monoclonal antibodies, such as drug resistance and adverse reactions, were also pointed out. Further research on the mechanism of action of monoclonal antibodies is needed in the future to optimize the treatment regimen in order to improve its therapeutic efficacy and safety.

Keywords: Autoimmune disease; Immune system; Monoclonal antibody.

1. Introduction

In today's society, with the increasing improvement of medical standards, medical treatment for many diseases has been developed and matured, but there is still a need to continue to make efforts in the treatment of certain diseases. The immune system is an important system that keeps the body safe from outside bacteria, but a dysregulated immune system is the main cause of various immune diseases. In autoimmune diseases, the body's immune system attacks the body's cells, and the immune system's attack on itself is known as autoimmunity. In recent years, more and more people are suffering from autoimmune diseases, which to date have affected 250 million people worldwide, with prevalence rates ranging from less than 5 per 100,000 people to more than 500 per 100,000 people, and continuing to rise [1]. Most autoimmune diseases cause inflammation that results in redness, fever, pain and swelling, and many autoimmune diseases affect multiple parts of the body. Historically, autoimmune diseases have been extremely rare, and through epidemiological studies, the most common of these are autoimmune thyroid disease and type I diabetes (T1D). However, more importantly, the number of autoimmune diseases is much larger than that, with rheumatoid arthritis, ankylosing spondylitis, psoriasis, systemic lupus erythematosus, and osteoporosis among the currently prevalent autoimmune diseases. These diseases share a common feature, which is that they are chronic diseases caused by problems with the immune system [2]. Autoimmune diseases can affect a single organ or the entire body. In the past, treatment options have included anti-inflammatory drugs to alleviate inflammation and pain, corticosteroids for acute symptom flare-ups, and immunological drugs to suppress immune system activity. Pain relief can also be achieved through the use of paracetamol and codeine. It is important to note that all treatments should be prescribed by a medical professional. Over the past decades, other therapeutic modalities have been introduced internationally, the most representative of which are monoclonal antibodies, which, through their development and extensive clinical laboratory testing, have led to significant advances in diagnosis and classification of the disease, including improvements in the aftermath of the disease. The body's immune system is stimulated by antigens and antibodies are produced by plasma cells differentiated from b-lymphocytes, and each b-lymphocyte bead can only produce one monoclonal antibody against the determining cluster of specific antigens, which can attack a specific target, as if it had precision-guidance function, and can carry out a targeted elimination of pathogens such as viruses [3]. These

include adalimumab, skutumumab, tolizumab, desutumumab, etc. This thesis will show the principles of autoimmune diseases and how monoclonal antibodies are used to treat them, as well as the outlook for the future, and hopefully this thesis will help in the future of monoclonal antibodies in the treatment of autoimmune diseases.

2. Principles of autoimmune diseases

In the state of immune tolerance, all individuals have a certain amount of autoreactive T cells and autoantibodies in the peripheral immune system, and autoreactive T cells and autoantibodies are physiologically important for assisting in the removal of senescent degenerative self-components and for maintaining immune self-stabilisation, a process known as autoimmunity [4]. An autoimmune disease is a condition where the immune system attacks the body's own cells or tissues, causing damage or dysfunction. This occurs when autoimmunity becomes abnormal and autoantibodies or autoreactive T-lymphocytes are produced.

There are more than 100 autoimmune diseases, including rheumatoid arthritis, ankylosing spondylitis, psoriasis, systemic lupus erythematosus, and osteoporosis. They can affect one organ or the entire body. Eighty per cent of people diagnosed with autoimmune diseases are women, but it is not known whether this is due to hormonal or genetic differences between men and women [5]. Autoimmune diseases have a multifactorial aetiology, with genetic and environmental factors playing a role. Environmental factors include viruses, bacteria, drugs, and diet, all of which can increase the risk of developing autoimmune diseases [6].

In our immune system there are many cells that have a role to play, including white blood cells, there is a very important type of white blood cell called a macrophage, the macrophage can recognize a non-self cell, such as a bacterium, and then go to phagocytose him, the bacterium is slowly phagocytosed in the macrophage, and then finally turns into a very small remnant, these bacterial remnants are excreted by the macrophage to the outside of the cell, so that the rest of the cells in the immune system will be able to recognize that bacteria have entered the body. In addition, during the phagocytosis of bacteria by macrophages, inflammatory substances are produced, which are called cytokines, which bind to cellular receptors and subsequently inflammation occurs [7]. During inflammation, the number of macrophages increases to combat bacterial infection. However, it is important to note that macrophages are only able to eliminate some of the bacteria, not all [8].

Lymph nodes are the site of cellular communication in the immune system. macrophages, after destroying some of the bacteria, come into contact with T and B cells in the lymph nodes. bacterial fragment antigens outside the macrophage are recognized by the T cells. the T cells become activated when they bind to these bacterial antigens, a process known as activation. At the same time, the activated cells are also B cells, and the activated T cells and B cells divide to produce large numbers of T cells and B cells. The T and B cells will migrate to the site of inflammation. The T cells will then attack the bacteria, aiding the macrophages in producing more cytokines or inflammatory substances. Once all the bacteria are eliminated, the inflammation will cease. [8]

When self-cells are attacked as if they were foreign bacteria, but in this case, macrophages still produce cytokines. Therefore, in the case of autoimmune diseases, the own cells are attacked and receive damage. Autoimmune diseases are characterized by the continuous regeneration of cells and the presence of cytokines, macrophages, T-cells, and B-cells at the site of the disease. These cells react in combination, causing damage to the body. It is important to note that subjective evaluations have been excluded from this description.

In the process of autoantibody production, there are cells called regulatory cells, or Tregs, which prevent the body from being harmed, but IFN- α downregulates the level of Tregs [9]. IFN- γ , which is secreted after antigenic stimulation, accelerates the production of autoantibodies, thereby accelerating the victimisation of the body [10]. At the same time, effector T cells secrete large amounts of IL-17A, which not only reduces the number of Tregs, but also induces further T cell activation, including IL-6, which accelerates the secretion of autoimmune antibodies, and promotes

the differentiation of T cells, which produce more IL-17A [11]. Finally, there is IL-10, which strongly reduces the level of Tregs and leads to an immune imbalance [12]. By this point, the organism's immune regulation has failed. Interferon induces T-cell activation and reduces the level of Tregs, IL-17A and IL-6 activate each other, accelerating autoantibody production, and IL-10 finally amplifies the above reaction further, thus increasing the severity of the disease.

3. Therapeutic modalities: overview of different monoclonal antibody applications

3.1. Introduction to monoclonal antibodies

Antibodies are actually cells secreted by B cells during the formation of effector B cells in the plasma, both in mice and humans, which undergo an immune response when stimulated by certain antigens. This antibody molecule consists of a Y-shaped structure, and this Y-shaped cell specifically has four peptide chains, one of which is symmetrical and has a longer form and a larger molecule called the heavy chain. The other peptide chain is called the light chain, the heavy chain is denoted by VH and the light chain is denoted by VL. The molecular weight of the heavy chain is around 55-75, while the light chain is only around 25. The VH contains 450-550 amino acid residues, and the VL consists of roughly 214 amino acid residues. The heavy chain consists of one variable region and three constant regions, while the light chain consists of one variable region and one constant region. IgG, IgA, and IgD in antibodies also contain three constant regions, but IgM and IgE will contain four constant regions. The constant region, as the name implies, is basically unchanged in terms of species and properties. The most specific region is called the variable region, and the main function of the variable region is to recognize and bind to the antigen, and the most important part of the binding process is the antigen binding site, called CDR. there are three CDRs in the heavy chain, and three CDRs in the light chain. the CDRs are complementary determinants, and the CDRs are the sites that bind directly to the antigens. The binding between the light and heavy chains is via disulfide bonds, and the upper and lower portions of the antibody are connected at a site called the hinge region, which functions to adjust the binding of the antigen to the antibody so that the antigen binds more tightly to the antibody [13].

Historically, the first antibodies were extracted from mice, but the immunogenicity of mouse antibodies was particularly high. Later, with the advancement of time and technology, mouse antibodies were used in the variable region, but the constant region was replaced with human antibodies, which belonged to the chimeric type of antibodies, and the immunogenicity of chimeric type of antibodies was reduced in comparison with that of mouse antibodies. Later on, there were cases in which the CDRs were mouse antibodies and the other regions were replaced with human antibodies, so that the immunogenicity of the antibodies could be weakened to the greatest extent possible. In the present society, all-human antibodies, called all-humanised antibodies, have also appeared [14].

For the preparation of antibodies, mice are usually injected subcutaneously with an antigenic drug, and an adjuvant is used while the antigenic drug is administered to the mice. The role of adjuvants is to assist the antigenic drug to produce a stronger immune response in the mice, which results in a higher concentration of antibodies. Generally, the adjuvant of choice is between complete and incomplete Freund's adjuvant. The most direct difference between these two is that incomplete Freund's adjuvant contains liquid paraffin and lanolin, which is a water-in-oil mixture. In this way, the incomplete Freund's adjuvant can continue to release the antigen even after we have extracted it. The complete Freund's adjuvant is the addition of dead Mycobacterium tuberculosis, or BCG, to the incomplete Freund's adjuvant. The purpose is to stimulate the Toll Like Receptor to produce a stronger immune response in mice because Mycobacterium is a ligand for TLR2,TLR4,TLR9. Generally, when injecting, we choose 3-4 subcutaneous sites to inject, the first time of injection will use complete Freund's adjuvant, then every two to three weeks for booster immunisation, when booster immunisation we choose incomplete Freund's adjuvant, after 3-4 times of booster

immunisation, and the last time without any adjuvant, so that the effector plasma cells will be produced [15].

Most of the B cells are found in the spleen and myeloma cell lines have a characteristic of infinite multiplication. Then B-cells are combined with myeloma cell lines to form a hybrid tumour, which retains its ability to secrete antibodies and also grows indefinitely in vitro [16]. And there are three general methods of fusion, the first with Sendai virus, the second with electrofusion, and the third with chemical method. After the fusion, HAT medium is needed to screen the cells, then the living cells are used in the limited dilution method, and finally compared with the B cells to select the needed cells, and after selecting the cells, they are cultured and expanded, and finally the needed monoclonal antibody can be obtained.

With the progress of time, we can do Phage Display Library with B cells after immunisation, and we can also get genetically engineered antibodies, but the affinity and specificity of the antibodies obtained in this way are not stable, and the main reason is that the heavy chain and light chain in them are formulated in vitro, which is not the real natural conception, so the stability is not as good as the natural antibodies.

3.2. Treatment of ankylosing spondylitis using adalimumab

3.2.1. Introduction to the pathology of ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic autoimmune disease, mainly manifested by invasion of the sacroiliac joints, spinal bony prominences, paraspinal soft tissues and peripheral joints, and with the progression of the disease, spinal deformity and ankylosis can occur in severe cases. Clinical manifestations include inflammatory low back pain with morning stiffness, peripheral arthritis and uveitis or iritis. Cases of ankylosing spondylitis are characterised by attachment point inflammation, which progresses through the stages of attachment point inflammation, to bone erosion, to bony encumbrance formation and finally to ankylosis as the pathology progresses. As the bone structure progresses, ankylosing spondylitis gradually leads to calcification of the paravertebral ligaments, formation of bony bridges, fusion of the bones, loss of joints, and then complete or incomplete ankylosis of the spine and limitation of movement. In the advanced stage of the disease, vertebral body squaring, ligament calcification, and spinal dendritic degeneration may occur, leading to dysfunction and a high rate of disability, which seriously affects the quality of life of the patients [17].

3.2.2. Therapeutic principle of adalimumab

Adalimumab is a novel monoclonal antibody that is widely used in the field of tumour therapy. The mechanism of action of adalimumab is through recognition and binding to HBR2/neu receptors. It inhibits signalling at the HER2/neu receptor, a cholesterol-based tyrosine kinase receptor found on the surface of normal cells and some cancer cells, thereby preventing the normal growth and multiplication of tumour cells. When the HER2/neu receptor is activated, it triggers tumor growth and promotes cancer cell infiltration and metastasis. Adalimumab is able to recognize specific external structural domains on the surface of the HER2/neu receptor, thereby inhibiting the proliferation of tumor cells [18,19,20].

As adalimumab acts against tumors, it is considered a common targeted therapy. This targeting allows adalimumab to attack tumor cells with greater precision, reducing damage to normal cells and improving the efficacy and safety of treatment. By specifically binding to and inhibiting the HER2/neu receptor, adalimumab offers a promising strategy for tumor treatment and helps to improve patients' quality of life.

3.2.3 Preparation of adalimumab

Firstly, in the cell culture stage, we need to select the cell line, the cell line for adalimumab preparation is Chinese Hamster Ovary. CHO cells have good growth characteristics and high stability, which is suitable for mass production. After selecting the cell line, the culture medium needs to be prepared, and the culture of CHO cells requires the use of culture medium containing sufficient nutrients. Commonly used media include DMEM (Dulbecco's Modified Eagle's Medium) and F-12

(Ham's F-12 Nutrient Mixture), and the addition of serum and other nutrients to the media at appropriate concentrations can promote cell growth. nutrients can promote cell growth. Secondly, the culture conditions of the cells also need more attention. CHO cells need to be cultured at 37°C, 5% CO₂, and are usually mass-produced in rolling or stirred culture tanks. In order to ensure the health and stability of the cells, fresh medium needs to be changed regularly, and the cell density and incubation time need to be controlled. To produce adalimumab, CHO cells need to be transfected with a plasmid containing the adalimumab gene. Commonly used transfection methods include electroporation, calcium phosphate co-precipitation and polyvinyl alcohol [21].

The purification stage needs to be carried out after the cell culture is completed, and the cultured cells are first collected when the CHO cells reach a certain density. Firstly, the cell culture needs to be centrifuged and separated, and then the cell membrane is disrupted using salt solution or other methods to release adalimumab. Purification is then carried out, with affinity chromatography being a common purification method that selectively captures the target molecule with a specific affinity agent. For purification of adalimumab, affinity chromatography can be performed using a resin containing Protein A or Protein G.

Finally, there is the quality control of the collected adalimumab, which needs to be identified during the production process to ensure its purity and activity. Common identification methods include SDS-PAGE gel electrophoresis, Western blotting, ELISA and bioactivity assay. Bacterial endotoxin is also a common contaminant, and bacterial endotoxin also affects the quality and safety of adalimumab, therefore, bacterial endotoxin needs to be detected during the production process. Finally, stability test, stability test is the long-term preservation ability of adalimumab and quality stability of the test, commonly used stability test including stress test, light stress test and freeze-thaw cycle test.

3.3. Treatment of psoriasis using secukinumab

3.3.1. Introduction to psoriasis pathology

Psoriasis is a chronic inflammatory skin disease that has a long course and is prone to recurrence, in some cases for almost a lifetime. The patients of this disease are mainly young adults, and it has a greater impact on the physical health and mental condition of the patients. Clinical manifestations are mainly erythematous and scaly, which can occur all over the body, with the scalp and limbs being more common, and mostly aggravated in winter [22].

Psoriasis is generally divided into four categories, the first category is common psoriasis, common psoriasis is the most common category, mostly acute onset. The onset of psoriasis is characterised by well-defined erythematous plaques of varying shapes and sizes, surrounded by an inflammatory red halo. The surface of the skin is covered with silvery-white scales, which are easy to scrape off, and after the scales are scraped clean, there is a translucent film that is reddish and shiny, and small haemorrhages can be seen when the film is scraped. (Auspiz disorder). In the affected area will appear different degrees of itching.

The second category is pustular psoriasis, this kind of psoriasis is more rare, mostly pan-type and palmoplantar type, pan-type pustular psoriasis is in the erythema on the emergence of clusters of superficial aseptic pustules, the whole body can be onset. It is more common on the limbs and folds, and there is also a probability of developing in the oral mucosa. Acute onset or sudden exacerbation is often accompanied by systemic symptoms such as chills, fever, joint pain, general malaise and increased white blood cell count. Episodes tend to be periodic. Palmoplantar pustulosis lesions are confined to hands and feet, occur symmetrically, and are usually stubborn and recurrent.

The third category is erythrodermic psoriasis, also known as psoriatic exfoliative dermatitis. It manifests as diffuse redness, swelling and flaking of the skin all over the body, accompanied by fever, chills and swelling of superficial lymph nodes.

The fourth category is arthropathic psoriasis, also known as psoriatic arthritis. Patients with psoriasis develop joint damage of rheumatoid arthritis at the same time, which can occur in small and

large joints all over the body. Redness and pain in the joints are accompanied by redness and swelling of the skin around the joints [23].

3.3.2. Therapeutic rationale for scucizumab

Skuticizumab is a biologic agent for the treatment of psoriasis, as well as a fully humanised monoclonal antibody with a fast onset of action, good efficacy and a high safety profile. Skuticilumab is an inhibitor against IL-17A (Interleukin 17A) and is a fully humanised antibody. These two characteristics determine its advantages over other biologics. IL-17A is a key cytokine that triggers psoriasis and is mainly produced by two pathways, the intrinsic immune cells and the TNF- α pathway. It is a downstream factor closer to the disease than TNF- α and IL-12/23, and can cause damage to the skin, joints, nails, and scalp. Cosentyx, as an inhibitor of IL-17A, on the one hand, is able to maximise the inhibition of IL-17A from any source pathway and, on the other hand, reduces the scope for side effects. In addition, the fully humanised antibody has a higher affinity and can reduce the development of resistance [24,25].

Some side effects can also occur during the treatment of psoriasis with stuccizumab. Common side effects include upper respiratory tract infections and oral herpes, and occasionally oral candidiasis, tinea pedis, otitis externa, and lower respiratory tract infections. Side effects of gastrointestinal disorders can also occur and commonly include diarrhea and inflammatory bowel disease [26].

3.4. Treatment of systemic lupus erythematosus using belimumab

3.4.1. Introduction to SLE pathology

SLE is a chronic disease in which the autoimmune system attacks the body's tissues, and the factors responsible for its development are currently unknown. The pathogenesis of the disease is currently reflected in four aspects. Firstly, there are immune abnormalities, in which the patient's own immune system has problems, leading to inflammation and damage. The second is genetic factors, which play a role in the development of SLE. Thirdly, environmental factors, such as ultraviolet light, chemicals and viral infections may also trigger SLE. Lastly, sex hormones, which are significantly more common in female patients than in males, may also be associated with the development of SLE [27,28].

SLE is a systemic autoimmune disease characterized by the production of autoantibodies against self-antigens (Ags) B-cell stimulating factor promotes loss of B-cell tolerance and drives autoantibody production. In 1997, HGS discovered and rapidly characterised the function of the B-lymphocyte stimulating factor (BLyS) protein. BLyS, also known as BAFF (B-cell activating factor from the TNF family of B-cell activating factors), is a type II transmembrane protein that exists in both membrane-bound and soluble forms. BLyS is expressed on the surface of a wide range of immune cell types (monocytes, activated neutrophils, T-cells, and dendritic cells), and its secretion can be increased by a wide range of inflammatory cytokines [29,30].

The clinical presentation of SLE is heterogeneous, ranging from mild skin disease to catastrophic organ failure and obstetric complications. When lupus occurs, it may result in redness and swelling in some areas, as well as butterfly-shaped rashes on the cheeks and nose, and small ulcers may form inside the nose or mouth. A maculopapular rash and a scaly papular rash may also appear after sun exposure. When the fingers become white or purplish in colour after being exposed to cold, this condition is known as Raynaud's phenomenon. In the chest area, it may also lead to pleural effusion and pericardial effusion, a phenomenon known as plasmapheresis.

3.4.2. Physiotherapy principles of belimumab

Beliumab is a fully human IgG1 λ recombinant monoclonal antibody specifically directed against BLyS. It prevents soluble BLyS from binding to receptors on B cells, thereby inhibiting the survival of B cells, including autoreactive B cells, and reducing the differentiation of B cells into immunoglobulin-producing plasma cells. The target of belimumab, BLyS, also known as BAFF (B-cell activating factor, belonging to the tumour necrosis factor family), is a type II transmembrane protein that exists in both membrane-bound and soluble forms [31].

The specific binding of belimumab to soluble BLyS prevents its interaction with three receptors, indirectly reducing B cell survival and autoantibody production. Although TACI and BCMA also bind APRIL, BLyS is the only ligand for BR3, and the interaction of BLyS with BR3 is critical for the survival of both naïve B cells and mature primary B cells. This makes the effects of belimumab more pronounced on early B cells (e.g. naïve B cells) and less so on memory and plasma B cells [31].

4. Conclusion

The use of monoclonal antibodies to treat autoimmune diseases is characterized by many features. Monoclonal antibodies can target specific autoantigens or immune cell surface markers, reducing non-specific damage to normal tissues and reflecting the high specificity of monoclonal antibodies. Monoclonal antibodies bind to target antigens with high affinity, effectively causing an autoimmune response. Monoclonal antibodies also have the characteristics of individualized treatment. By detecting the patient's autoantibodies, monoclonal antibodies targeting specific autoantigens can be selected for individualized treatment to improve the therapeutic effect. Secondly, in terms of efficacy, monoclonal antibodies have lower toxicity and relatively fewer side effects than traditional immunosuppressive drugs. Moreover, monoclonal antibodies are usually able to act quickly, rapidly suppressing autoimmune reactions and relieving symptoms. Monoclonal antibodies can also be used in combination with other immunosuppressive drugs to improve the therapeutic effect.

Treating autoimmune diseases with monoclonal antibodies is not always easy, and there are shortcomings and side effects. High cost is a major problem with monoclonal antibodies, and the high cost of monoclonal antibodies can make them potentially unaffordable for some patients. Secondly, some patients may develop resistance to the use of monoclonal antibodies, resulting in reduced or ineffective treatment. In terms of use, monoclonal antibodies need to be administered by injection, which may be inconvenient or unacceptable to some patients. Some side effects can also occur during use. The most common side effect is an allergic reaction, which may occur as a rash, itching, shortness of breath, and other allergic symptoms. Other side effects such as infections, haematological abnormalities, vomiting, diarrhoea, abnormalities in liver and kidney function sometimes occur.

In the future, there are many aspects of using monoclonal antibodies to treat autoimmune diseases that need to be improved. These include lowering the cost of development and production so that more patients can afford to use them. Developing more monoclonal antibodies for different autoimmune diseases to provide more treatment options. On the efficacy side, the long-term safety and efficacy of monoclonal antibodies need to be further investigated to ensure that patients continue to benefit from their use. And corresponding studies on their side effects need to be conducted to minimize or eliminate them as much as possible.

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