ARTÍCULO DE REVISIÓN

https://doi.org/10.36677/medicinainvestigacion.v%vi%i.20348

Monoclonal antibodies in the treatment of autoimmune diseases

Anticuerpos monoclonales en el tratamiento de enfermedades autoinmunes

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Recibido: 9 de enero de 2023
Aceptado: 4 de agosto de 2023

Abstract:

Autoimmune diseases are a group of pathologies characterized by the presence of autoantibodies and the loss of immunological tolerance towards self-antigens. Although it is difficult to establish the incidence and prevalence, it is estimated that only 3 % of the population in the United States suffers from any of them.

There are different therapeutic routes to tackle this class of diseases, highlighting biological therapies, one of them being monoclonal antibodies (MAbs). There are different therapeutic routes to address this class of diseases, highlighting biological therapies, one of them being monoclonal antibodies (MAbs). These are therapeutic agents with additional advantages in selectivity, availability and function related to small molecules and peptides. MABs are developed and approved for the treatment of diseases related to different systems such as nervous, cardiovascular, immunology, among others. This mini review summarizes the applications of monoclonal antibodies in autoimmune diseases with affections in the nervous system, focusing mainly on fda approved monoclonal antibodies products that are currently available in the mar ket.

Key words:

monoclonal antibody; immunotherapy; nervous system; rheumatoid arthritis; lupus; myasthenia gravis; belimumab; anifrolumab; eculizumab; rituximab; efgartigimod; infliximab

Resumen

Las enfermedades autoinmunes son un grupo de patologías caracterizadas por la presencia de auto-anticuerpos y la pérdida de tolerancia inmunológica hacia los auto-antígenos. Aunque es difícil establecer la incidencia y prevalencia, se estima que sólo el 3% de la población en Estados Unidos padece alguno de ellos.Existen diferentes rutas terapéuticas para abordar esta clase de enfermedades, destacando las terapias biológicas, una de ellas son los anticuerpos monoclonales (MAbs). Existen diferentes rutas terapéuticas para abordar esta clase de enfermedades, destacando las terapias biológicas, una de ellas son los anticuerpos monoclonales (MAbs). Se trata de agentes terapéuticos con ventajas adicionales en selectividad, disponibilidad y función relacionadas con moléculas pequeñas y péptidos. Los MAB están desarrollados y aprobados para el tratamiento de enfermedades relacionadas con diferentes sistemas como el nervioso, cardiovascular, inmunológico, entre otros. Esta mini revisión resume las aplicaciones de los anticuerpos monoclonales en enfermedades autoinmunes con afecciones en el sistema nervioso, centrándose principalmente en los productos de anticuerpos monoclonales aprobados por la FDA que se encuentran actualmente disponibles en el mercado.

PALABRAS CLAVE

Anticuerpo monoclonal; inmunoterapia; sistema nervioso; artritis reumatoide; lupus; Miastenia gravis; belimumab; anifrolumab; eculizumab; rituximab; efgartigimod; infliximab

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Introducción

The immune system's main objective and purpose is to provide protection against infectious agents, it has a highly regulated system known as immune tolerance that allows it to distinguish between self and foreign antigens. If this tolerance fails, autoimmune diseases develop which can be caused by hypersensitivity reactions to external agents and hypersensitivity reactions against the body itself. Many components are involved in the loss of tolerance mechanisms, such as genetic susceptibility, environmental, and immune factors.

Autoimmune diseases are considered one of the main causes of morbidity and mortality in women in industrialized countries.[1] In the last 25 years in the US, the prevalence of antinuclear antibodies (autoimmunity biomarker) has increased from 11% to 16 %[2] and they represent one of the main causes of disability and mortality.[2]

Given the high numbers in cases presenting autoimmune diseases, new diagnostic and therapeutic tools have been developed to seek an adequate diagnosis and better management of the disease. In recent years, in addition to drugs that seek immunosuppression, so-called biological therapies have been developed, which are directed at specific target molecules related to the immune response, such as anti-TNF-α, some cytokines, and monoclonal antibodies. The latter have been very relevant, so the objective of this review is to expose the importance and results of treatments aimed at autoimmune diseases, focusing mainly on rheumatoid arthritis, myasthenia gravis and systemic lupus erythematosus (SLE).

Monoclonal antibodies

The evolution of science and technology in health sciences has allowed scientists to investigate and create new forms of therapy and diagnosis for an array of human disorders. The development of human monoclonal antibodies has provided the solution for many biological problems since the hybridoma technique of Köhler and Milstein was introduced in the late 1970's.[3]

Antibodies circulate throughout the body until they bind to an antigen and mount a specific response with the goal of destroying it. Under this premise Köhler and Milstein developed a technique for obtaining antibodies with known specificity that would allow them to be identified and cloned as many times as necessary, for this great advance in science they received the Nobel Prize in 1972.[4]

Monoclonal antibodies are glycoproteins produced by the clone of hybrid B cells (fusion between a single stem cell of the immune system and a tumor plasma cell).[5] This means that monoclonal antibodies are monospecific and homogeneous, have controlled manufacturing procedures, specificity for antigens and reproducible affinity, making them highly better in the treatment of autoimmune diseases than polyclonal antibodies.[6] Allowing monoclonal antibodies to be a powerful tool for laboratory diagnosis and an instrument constantly used for various diseases.

Structure and Isotypes

Antibodies are formed by two pairs of chains (light and heavy) which are composed of different domains with different functions. There is a domain called the "Fab" which serves as the antigen-binding site. CDRS (Complementary Determining Regions) are the ones that determine the complementary structure of the epitope on the antigen which can be bound by the antibody; the great diversity of antibodies is given by the variations in the aminoacids sequences of the CDRS.[3]

The effector functions of antibodies are determined by de "Fc" domain due to its interactions with effector cells and the activation of the complement cascade; it also takes part in the structure of antibodies and therefore in their isotypes (IgG, IgD, IgA, IgE, IgM).[7]

Therapeutic activity and obtaining process

Various studies have pointed out that monoclonal antibodies are clinical options for diagnosis and treatment of numerous diseases, allowing scientists to study pathogen-host interactions, marking, detecting and quantifying various molecules involved in the pathological process. Nowadays there are different technologies used to obtain monoclonal antibodies:[8]

Generation of hybridomas

The base of this procedure lies in the fusion of a B lymphocyte from a previously immunized animal with the antigen of interest (provides the ability to produce antibodies against the specific antigen) and a myeloma tumor cell that does not secrete antibodies (supply unlimited cell division).

Transgenic animals

This technique was created to reduce adverse effects and increase therapeutic effectiveness of monoclonal antibodies tested. It is based on the creation of hybrid descendants from the cross of two mice whose genes have been modified.

Recombinant DNA

There are 2 different approaches:

Phage-display: the bacteriophage are viruses capable of infecting bacteria, by introducing their genetic material in the bacterial genome. The M13 is a type of bacteriophage widely used for monoclonal antibody production.

Ribosomal-display: is an in vitro monoclonal antibodies fragment production/ synthesis technology. In this procedure, antibody gene libraries are generated based on the synthesis of monoclonal antibody fragments.

Transgenic plants

The use of this type of plants lies in the expression of monoclonal antibodies, either in plants or in plant cell culture. With this technology, the complementary DNA of the IgG heavy and light chains is first cloned from a hybridoma.

Fusion proteins

Two or more genes which are linked in a reading frame and their translation originates polypeptides in order to produce a single protein.

Clinical uses

The constant growth and development of new monoclonal antibodies technology woke up pharmaceutical and medical interest around the world. It is said that at least a quarter in all the lines of treatment and diagnosis investigations are based on monoclonal antibodies.

Nowadays, monoclonal antibodies have proven to be more convincing in the use of diagnosis and therapies for medical conditions. The FDA has approved at least a hundred different kinds of monoclonal antibodies for the treatment of numerous diseases such as cancer and various autoimmune disorders.[3]

Systemic lupus Erythematosus

The etiological factor of Systemic Lupus Erythematosus (SLE) is unknown, however it has been observed that in the development of the disease there are diffe-

rent genetic, hormonal and environmental factors that interact, giving rise to a loss of tolerance of the organism to its own constituents.[9]

Epidemiology

SLE is a rare disease around the world. It has a worldwide distribution with a prevalence of 40 cases per 100,000 inhabitants in Europe; while in Asia and North America it is 200 per 100,000 individuals, prevailing mostly in black people. It is estimated that more than 100,000 new cases are diagnosed each year, being a disease that affects about five million people worldwide.[9] Systemic lupus erythematosus is observed in all races, of any age (predominance between 15 and 30 years of age) and presents more in females, being more frequent and severe in black women. The disease is more common in 90 % of cases that correspond to women of reproductive age.[10]

Physiopathology of SLE

It is related to the multiorgan deposition of circulating antigen-antibody complexes, and activation of the complement system, which leads to inflammation mediated by humoral and cellular mechanisms.[11]

T cells have been the main ones identified in the development of the disease due to their ability to communicate with other cells of the immune system, being unique and strictly regulated. Many studies show that in the absence or alteration of helper T lymphocytes, B cells are capable of generating pathogenicity. Compared to healthy individuals, several studies have shown that T cells isolated from SLE patients are abnormal in number and function compared to samples from healthy individuals.[11]

Activation of T lymphocytes is initiated through the presentation of endogenous or exogenous antigens by antigen-presenting cells through the major histocompatibility complex, which binds to a specialized receptor present on T lymphocytes. This recognition triggers a cascade of intracellular signaling that leads to an increase in the expression of integrins, modifications of the cytoskeleton and production of transcription factors involved in the release of cytokines and inflammatory mediators.[12] The high expression of CD40L detected in the T cells of patients with SLE was pointed out as being responsible for the stimulation and signaling of CD40 in B lymphocytes, triggering the production of autoantibodies as a consequence.[12]

In most patients, the disease begins slowly, with symptoms appearing progressively over an indefinite period of time; sometimes it takes months or years to diagnose the disease. Once diagnosed, it goes through periods of remissions and exacerbations.[9]

Despite being a serious disease, if diagnosed early, survival is prolonged and increases the individual's quality of life. With disease control and proper treatment, most patients lead normal lives.[13]

Myasthenia gravis

Etiology

The cause of this disease remains a mystery, it is important to mention the different factors that are involved in the initiation of certain responses to autoantigens that are present in striated muscle and the role played by the thymus. This disease can be broadly divided into 3 different forms depending on the age of onset, thymus pathology, MHC associations, and the presence of antibodies specific for nonacetylcholine receptor (AChR) antigens.[14]

The thymus has a special role in this pathology, as it has been observed in young patients (less than 40 years at the onset of the disease) that anti-AChR T lymphocytes are cloned in this organ.[14]

Epidemiology

It is estimated that this disease affects approximately 15 people per 100,000. It affects men and women, but mainly women under 40; it affects men and women equally after the age of 50. About 10% of patients are children and adolescents.[14]

Physiopathology of Myasthenia gravis

In myasthenia gravis, the neuromuscular junction is affected by autoantibodies against the nicotinic acetylcholine receptor or against proteins that play a role in acetylcholine binding. This neuromuscular junction does not have a blood-brain barrier, which is why antibodies can easily attack.[14]

It has been observed that AChR antibodies belong to subclasses of IgG1 and IgG3, they activate complement, which will result in the loss of AChR from the neuromuscular junction. To compensate for this loss, an increase in ACh with positive antibodies will be seen. Similarly, MuSK antibodies, which are antibodies against muscle-specific kinase, decrease the postsynaptic density of AChRs and will alter their position between the nerve terminal and the postsynaptic membrane.[14]

Also, it has been described that antibodies bind to the membrane, blocking the interaction of protein 4, which is related to the low-density lipoprotein receptor; this mechanism will inhibit the aggregation of AChR in the membrane.[14]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of articulations. It generally affects the metacarpophalangeal joints and the wrists, causing pain, numbness, and tenderness in or around the joint area.[15]

Etiology

Its cause is still unknown, however, it has been observed that in most cases it is related to a genetic predisposition of the HLA DR4 allele, and/or the related alleles of the class II histocompatibility complex. Furthermore, there is an influence of environmental factors such as infectious agents: Hepatitis C virus, retroviruses, Epstein-Barr virus (EBV), parvovirus B19, *Mycobacterium tuberculosis* and *Mycoplasma proteus*, which trigger the manifestation of the disease.[15]

Epidemiology

The prevalence of RA ranges from 0.3 to 1.2 % worldwide. The highest estimates are for American Indian and Eskimo tribes, above 3 %, and the lowest have been found in Africa and Asia, below 0.2 %. It has been observed that this is more frequent in women than in men (3:1 ratio) and in inhabitants of urban areas. The disease is more likely to occur between 30 and 60 years, with a mean of 41.5 years.[16]

Physiopathology of RA

The initial manifestation is presented as an autoimmune synovial inflammation caused by the infiltration of inflammatory cells (T lymphocytes and macrophages) into the synovial membrane, showing a microvascular injury and an increase in the number of synovial lining cells and perivascular inflammation by mononuclear cells; Subsequently, this inflammatory process spreads to the adjacent cartilage and bone, thus causing joint damage. The mechanism that leads to cartilaginous bone destruction is not clear; From different studies, different causes of this phenomenon have been pointed out, where the enzymes of the synovial fluid have been the most indicated. However, it has been observed that most patients have a positive Rheumatoid Factor, which is an effective agent di-

rected against the Fc part of IgG, this being a possible trigger of pathogenicity.[15]

In the early stages of the disease, it is difficult to establish a diagnosis since its symptoms are very nonspecific. As the disease progresses, more characteristic symptoms appear, such as polyarticular involvement, especially of the hands, wrists, knees, and feet.[15]

Being a multi-organ disease, RA can compromise any system. Rheumatoid nodules can appear in any organ, revealing systemic failures in the body. One of the most important is cardiac involvement, mainly pericarditis, and pulmonary conditions, manifesting more frequently as pleurisy, interstitial pneumonitis, pulmonary nodules, bronchiolitis obliterans, and less frequently pulmonary hypertension.[15]

Monoclonal antibodies in the treatment of autoimmune diseases

In addition to palliative medications prescribed for autoimmune diseases, FDA-endorsed treatments include the following:
For systemic SLE there is a recombinant IgG1 monoclonal antibody known as **Belimumab**, which has resulted in a reduction of anti-dsDANA antibodies, better levels of C3 and C4. This monoclonal antibody is able to reduce BAFF-dependent survival of autoimmune B cells, it also limits B-cell promoted autoimmunity.[17]

Similarly, **Anifrolumab** is an IgG1 monoclonal antibody that targets IFN type 1, blocking their action, since it binds to subunit 1 of the IFN type 1 receptor, presenting high affinity and specificity. This monoclonal antibody is in phase 2 and 3 clinical studies.[18]

Regarding *myasthenia gravis*, **Eculizumab** is an IgG monoclonal antibody which binds to complement protein C5, inhibiting complement activation. It has been approved for generalized myasthenia gravis with antibodies against the acetylcholine receptor. Efgartigmod, manages to reduce the levels of pathogenic IgG antibodies, it has proven to be effective and safe to treat this disease. Similarly, **Rituximab** is an anti-CD20 monoclonal antibody, it has been shown to be effective in certain subtypes of myasthenia gravis, but it may not be effective in all patients with this disease.[19]

In the case of *rheumatoid arthritis*, the monoclonal antibody **Infliximab** is capable of binding to the tumor necrosis factor and to the TNF membrane receptors of the target cells, which will cause cell lysis. Studies have proven an improvement in the quality of life of patients treated with this monoclonal antibody.[20] The use of the **Rituximab** antibody has also been approved (as in the case of myasthenia gravis), this monoclonal antibody binds specifically to the CD20 receptor of B lymphocytes and to a region of the IgG-type antibody.[21]

Limitations of the treatment with monoclonal antibodies

The use of the monoclonal antibody **belimumab** for the treatment of SLE has been analyzed, and it has been shown to be a great alternative in the treatment for patients suffering from this disease, no abnormalities have been observed. It has been observed that it is capable of inhibiting the survival of B cells and their differentiation into immunoglobulins, producing plasma cells. The most commonly observed side effect is an infection in the respiratory tract; however, no type of immunogenicity has been demonstrated in patients using this treatment.[22]

The **anifrolumab** was tested in mice to assess its tolerability, this model showed a great response to this treatment. Similarly, it was well tolerated and in the results we can see that it is capable of reducing the consequences of this disease.[18]

As for the monoclonal antibody known as **eculizumab** to treat *myasthenia gravis*, its safety has been demonstrated in terms of its use. This medication has been shown to be well tolerated by people and there have been no reports of

infections due to the use of this medication. Events such as headache, diarrhea, nasopharyngitis were observed in studies, however, this was observed in patients who were administered placebo, so this drug has proven to be effective for the long-term treatment of myasthenia gravis.[23]

Rituximab is a monoclonal antibody that when bound will show circulating B cells. Studies have been carried out where it has been seen that it is effective in 50-70 % of patients with this disease. This drug has been shown to be highly effective and safe for use by people with this disease, including being shown to be more successful in anti-MuSK than in other subtypes.[24]

The monoclonal antibody **efgartigimod** has been shown to lower the levels of IgG and anti-AChR antibodies and in a phase II study it was observed that 75 % of patients showed an improvement in the levels of the aforementioned antibodies. This medication has been shown to be not only effective, but also safe and tolerable by patients, leading it to enter phase III studies.[25]

Regarding rheumatoid arthritis, the **infliximab** antibody has been shown to reduce the symptoms and signs of this disease, and it has also proven to improve the quality of life of patients who use this type of treatment. This has been demonstrated by X-rays of the joints, showing their reduced damage thanks to this treatment.[26]

Rituximab can also be used to treat this disease in patients that usually have no response to antirheumatic drugs. Multiple studies have shown the efficacy of this monoclonal antibody to treat rheumatoid arthritis, however, it may be more effective in certain patients. This medicine has begun to show that it may be able to reactivate the infection, immunization may fail or there may be reactions.[27]

Conclusion

Monoclonal antibodies are an important therapeutic alternative in the treatment of systemic and organ-specific autoimmune diseases. The progress of science and technology over the years has allowed the constant improvement and adaptation of this technique to different alternatives in the treatment of specific pathologies.

Drug creation technology is a fundamental pillar in the development and evolution of monoclonal antibodies. Being a trending topic with high potential, the development of new lines of research allows for a broad spectrum of application for this technique in different diseases that affect humans around the world.

Autoimmune diseases are a topic of great importance worldwide, the constant increase in cases and their unknown etiology has led to them being a topic of main interest in the field of research. Application of MABs in the treatment of these diseases has made it possible to improve the quality of life in patients with this type of pathologies, allowing them to be controlled and even completely cured. The application of biotechnology in the health sciences has allowed the evolution of the way we live, treat and overcome many of the diseases that are known today.

Financiación

No existió financiamiento para la realización del proyecto.

Conflicto de intereses

Los autores declaran que no existen conflictos de intereses.

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