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Multiple sclerosis and its treatment with anti-CD20+ therapy: a brief review

Usos e benefícios da terapia anti-CD20+ na esclerose múltipla: uma mini revisão

Guilherme Nobre Nogueira[1], Leonardo Elias Araujo dos Santos[2], Leonardo José Rodrigues de Araújo Melo[2], Bruno Henrique Alcantara Lopes de Sousa[2], Fabrício da Silva Freitas[2], Rafaela Fernandes Gonçalves[3], Maroan Soraia Santos Navas Ribeiro[4], Gustavo Rassier Isolan[5]

ABSTRACT

Introduction: Multiple sclerosis is an autoimmune disease that affects the central nervous system. In this condition, the immune system attacks myelin, a substance that coats nerve fibers, causing damage to communication between the brain and the body. This can result in a wide range of symptoms, including muscle weakness, coordination difficulties, fatigue, visual disturbances, and even cognitive problems.

Objective: This article aims to gather recent advances in the treatment of multiple sclerosis with anti-CD20+ monoclonal antibodies, considering the emerging understanding of the involvement of B lymphocytes in the pathogenesis of the disease.

Method: Integrative review using PubMed and ScienceDirect as databases, utilizing the terms "Antigens CD20," "Multiple Sclerosis," and "Monoclonal Antibodies." Inclusion criteria for articles were a publication period of up to 5 years, English language, and freely available text.

Result: The discovery of the involvement of B lymphocytes in various stages of multiple sclerosis has enabled the use of pharmacological treatment with the use of anti-CD20+ monoclonal antibodies. This therapy has proven effective in treating early stages, reducing the rate of progression of debilitating symptoms in patients.

Conclusion: Due to their depletion of immune system cells, adverse effects such as type II hypersensitivity reactions and the emergence of opportunistic infections have been often observed.

KEYWORDS: Monoclonal antibody. Treatment. Immune cells.

Central Message

The efficacy and importance of the use of anti-CD20 monoclonal antibodies in the treatment of relapsing-remitting multiple sclerosis (MS), especially with the introduction of drugs such as ocrelizumab, has been highlighted. The text highlights the role of B cells in the pathophysiology of MS and the evolution of therapies targeting these cells, underlining the relevance of early treatment for better clinical and radiological outcomes.

Perspective

The use of anti-CD20 antibodies represents a significant advance in the management of MS, offering a more promising option in terms of controlling disease progression and reducing relapses. However, it also points to the need for careful monitoring due to the risk of adverse events and complications, emphasizing that therapy should be individualized and adjusted according to the stage of the disease.

RESUMO

Introdução: EM é doença autoimune que afeta o sistema nervoso central. Nessa condição, o sistema imunológico ataca a mielina, substância que reveste as fibras nervosas, causando danos à comunicação entre o cérebro e o corpo. Isso pode resultar em ampla gama de sintomas, incluindo fraqueza muscular, dificuldades de coordenação, fadiga, distúrbios visuais, e até mesmo problemas cognitivos.

Objetivo: Descrever os avanços no tratamento de EM com anticorpos monoclonais anti-CD20+.

Método: Revisão integrativa utilizando como banco de dados Pubmed e ScienceDirect, utilizando os termos "Antigens CD20", "Multiple Sclerosis" e "Antibodies Monoclonal". Os critérios de inclusão dos artigos foram período de publicação de até 5 anos, idioma em inglês e texto disponibilizado gratuitamente.

Resultado: Com a descoberta da participação de linfócitos B em diversos estágios de EM, possibilitou-se o uso de tratamento farmacológico com a utilização de anticorpos monoclonais anti-CD20+. Por agirem de forma a depletar célula do sistema imune, efeitos adversos se mostraram frequentes, como reações de hipersensibilidade tipo II e aparecimento de infecções oportunistas.

Conclusão: Esta terapêutica se mostrou eficiente no tratamento de estágios iniciais, com redução da velocidade de progressão de sintomas incapacitantes nos pacientes.

PALAVRAS-CHAVE: Anticorpo monoclonal. Células imune. Tratamento.

[1]Advanced Center of Neurology and Neurosurgery, Porto Alegre, Rio Grande do Sul, Brazil, UniveRio Grande do Sulidade Federal do Ceará, Fortaleza, Ceará, Brazil
[2]Federal University of Ceará, Fortaleza, Ceará, Brazil
[3]Advanced Center of Neurology and Neurosurgery, Porto Alegre, Rio Grande do Sul, Brazil
[4]Advanced Center of Neurology and Neurosurgery, Porto Alegre, Rio Grande do Sul, Brazil; Cilla Tech Park, Guarapuava, Paraná, Brazil

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INTRODUCTION

Multiple sclerosis (MS) is a neurological disease of an autoimmune nature that is manifested both through mild symptoms such as fatigue, tingling of the limbs, high sensitivity to touch and balance problems, as well as by more serious symptoms such as muscle spasms, chronic pain, cognitive problems, difficulty in daily activities such as speaking, eating and walking, and may even have cases of loss of vision and voice. The disease has a demyelinating and neurodegenerative character in the central nervous system, being the main cause of non-traumatic neurological disability in young adults.[1]

The pathological feature of MS is the formation of demyelinating lesions in the brain and spinal cord, which may be associated with neuroaxonal damage. The chronic inflammatory character of the central nervous system is caused by aberrant immune activation, resulting in damage to the myelin sheaths in the brain, spinal cord, and axonal loss.[2] Focal lesions are thought to be caused by infiltration of immune cells, including T cells, B cells, and myeloid cells, into the central nervous system parenchyma, with associated injury.[3]

The disease is predominant in women, aged between 18 and 55 years, and in Brazil its prevalence rate is close to 15 cases per 100,000 inhabitants.[4] The rate of hospitalizations increases from the age of 15 in both sexes and intensifies in the age groups of 20-29 years (22.2%), 30-39 years (28.6%), 40-49 years (21.8%), and 50-59 years (13.2%). Thus, 85.9% (24,986) of the total hospitalizations (29,088) occur between 20-59 years of age.[5]

Approximately 85% of newly diagnosed patients have the relapsing-remitting MS phenotype (RRMS or RRMS). After an average time of approximately 20 years, the vast majority evolve to the so-called "secondary progressive MS" phase (SPMS or SPMS).[6]

The treatment is diverse and has evolved over the years since its discovery. As it is a chronic disease, treatment is continuous and has the main objective of controlling acute attacks, controlling progressive worsening and remedying uncomfortable or disabling symptoms.[7] The pharmacological set used is diverse and consists of groups that focus on reducing symptoms. Immediately after diagnosis, 2 drug conducts follow: the first aims to reduce the time of the acute phase, and the second consists of trying to increase the interval between one outbreak and another.

For the first case, the reduction of the time of the acute phase, the management is done as in other autoimmune diseases: with the use of corticosteroids. In the second measure, which increases the interval between outbreaks, the use of immunosuppressants and immunomodulators help to expand the episodes of recurrence and the negative impact they cause in the lives of MS patients.

Although steroids do not affect the course of the disease, over time they have been shown to reduce symptoms, improve motor function, and shorten recovery time from acute attacks. Corticosteroids can be administered orally or parenterally, and it is assumed that their effect on the immune system depends on dose and duration.[8] Although long-term use of low-dose corticosteroids has been shown to be effective and relatively safe, shorter courses of high-dose corticosteroids are generally preferred to treat acute exacerbations of inflammatory disorders.[8]

However, the drug group responsible for the increase in the time of recurrence of clinical manifestations is more specific to the pathophysiology of the disease, especially in the action of the damage associated with inflammation caused by the perivenular infiltrate composed of T and B lymphocytes, macrophages, antibodies, and complement. DMT's (disease-modifying therapy) during the RRMS phase (Relapsing-remitting multiple sclerosis) has consistently demonstrated a significant impact on the annual relapse rate (ARR) and disability progression in the short term.[5-7]

From the immunological point of view, the existence of immune cell infiltrates in the central nervous system as a reason for the existence of the disease directs attention to its management and the search for new, more effective treatments. B lymphocytes are classified into regulatory and pro-inflammatory B cells, the latter with a role in regulating the polarization of T cells and, consequently, their inflammatory response. B cells are identified by markers expressed in all their stages of maturation, such as the CD20 transmembrane protein, which plays a role in cell differentiation and independent responses of T cells. The CD20 antigen is mostly associated with B cells; however, it is possible to find it in some T cell lines.[8]

In the inflammatory reaction, after the autoantigen is presented to the T lymphocytes, they induce the differentiation of B cells into plasmoblasts, which secrete antibodies, and can differentiate into plasma cells and maintain the emission of antibodies for long periods of time in the bloodstream. After differentiation into plasmoblasts, CD20 expression is reduced by downregulation but remains present in immunological memory B lymphocytes.[9]

In view of the importance of B cells in the pathophysiology of MS and, consequently, of the CD20 antigen, the various clinical trials aimed at the use of monoclonal antibodies specific to this protein are explained.[9] Monoclonal antibodies act to induce B cell depletion by means such as apoptosis, and may reach CD20-expressing T cells, which would contribute to greater efficacy in the treatment of MS, due to the involvement of both cells.[10]

Initially, MS was thought to be a T-cell-mediated demyelinating disease of the central nervous system. Disease-modifying therapies targeting T cells have, in fact, demonstrated remarkable efficacy in patients with relapsing-remitting MS (RRMS). However, these therapies also target B cells, and a CD20 B-cell-depleting monoclonal antibody, for example, ocrelizumab, which was recently approved for MS therapy and is effective not only in relapsing forms, but also in some patients with a primary progressive form.[10]

In view of the above, this study aimed to describe the advances reported in the literature on the treatment of MS with anti-CD20+ monoclonal antibodies.

METHOD

The present study is a narrative review of the literature, which used the DeCS/MeSH descriptors "Antigens CD20", "Multiple Sclerosis" and "Antibodies Monoclonal", intersected with the Boolean operator "AND", to search the PubMed and ScienceDirect databases. The selected period was from 2020 to 2023. Thus, 172 articles were found, according to the inclusion criteria (English language, period of publication, text available in full at the IP of the institution where the research was carried out and being inserted according to the guiding question of the research). A total of 98 review articles were excluded. In the end, 27 articles were analyzed, by title and abstract, of which 6 were selected to compose the present review, as they were in agreement with the guiding question and addressed the theme expressed by the review.

DISCUSSION

Although MS has traditionally been considered a T-cell-mediated autoimmune disease, in recent years, evidence about the participation of B cells in its pathophysiology has accumulated both in the early stage and with the progression of the disease. B cells have therefore emerged as an important target for several established MS therapies, including the use of interferon-β (IFN-β), fingolimod hydrochloride, and cladribine. However, more selective depletion of B cells can be obtained with the use of anti-CD20 monoclonal antibodies (mAbs), being a more promising and efficient therapy for the treatment of the disease.[11]

Of the antibodies approved until 2021, ocrelizumab, a humanized antibody applied intravenously, is considered the best and, therefore, the most indicated for use in patients with relapsed forms of the disease, showing excellent anti-inflammatory activity via inhibition of regulatory B cells and the ability to slow the progression of MS, which has been demonstrated in randomized phase III clinical trials.[12,13]

This antibody was approved in 2017 by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for patients with RRMS and PPMS. It can be used in a dose of 600 mg, administered fractionally into 2 doses of 300 mg, at an interval of 2 weeks between the first infusion and the second. After this period, a single dose of 600 mg every 24 weeks is indicated to maintain the therapeutic effects of the drug. In addition, ocrelizumab has shown promising results in individuals who have other autoimmune diseases, especially rheumatoid arthritis.[14]

Rituximab is a second-generation chimeric anti-CD20 (junction of human and mouse IGg1) that was approved in 1997 for B-cell lymphoma, but is being used off-label in several neurological diseases, including neuromyelitis optica (NMOSD), myasthenia gravis, and MS. There are several different rituximab dosing protocols; however, MS patients are most commonly being treated with 500 mg or 1000 mg intravenously every 6-12 months, in some cases after 2 initial injections 2 weeks apart.[15]

As for obinutuzumab, it has certain benefits in patients with membranous nephropathy associated with phospholipase A2 receptors. Ofatumumab, a fully humanized antibody, is applied subcutaneously and was initially developed for the treatment of chronic lymphatic leukemia.[16] It later received approval for the treatment of people with RRMS, a process in which it binds to a small extracellular loop of the CD20 membrane protein and acts by stimulating the c1q protein of the complement system, leading to cell lysis of regulatory B cells.[9,10]

Finally, ublituximab has also been approved for use in RRMS, as well as for the treatment of neuromyelitis optica spectrum disorder. It is a novel anti-CD20 monoclonal antibody that is glycoengineered to enhance the targeting of the response to B cells through cytotoxicity. Its development aims to allow the reduction of doses and the shortening of drug infusion times.[3,14]

The importance of an early start for anti-CD20+ therapies was also established. Treatment in the early stages, in all articles, was related to considerable improvement in both clinical and radiological outcomes of MS patients. This includes reduction in relapses (promoted by outbreaks of demyelination) as well as slower progression of the patient's disabling symptoms.

However, the presence of serious and varied adverse events, with some frequency, in patients who use these monoclonal antibodies, shows that the use of these drugs still requires adequate long-term monitoring and risk management. For ocrelizumab, in particular, the most common adverse effects were Infusion Related Reactions (IRR), possibly formed by type II hypersensitivity reactions. In addition, other problems arise from opportunistic infections of the upper respiratory tract (predominantly nasopharyngitis) and urinary tract. Serious infections also occurred in 1.3% of patients treated with ocrelizumab. Approximately 30% of patients also had hypogammaglobulinemia, which also significantly increases the risk of infection.[13-16]

CONCLUSION

The therapeutic approaches achieved throughout history, especially regarding MS, were of great scientific importance in the modern world. The pathophysiology, which for a long time was enigmatic, today has a better understanding and thus favored the evolution of more specific treatments. The use of the anti-CD20 monoclonal antibody in a disease with autoimmune and neurological characteristics evidences this achievement in the therapeutic evolution. The most recent articles have addressed the evolution of patients, and some cases not only in the RRMS phase, but also in PPMS. In addition, the use of anti-CD20 and its follow-up favor new perspectives of the pathophysiology of the disease, which still has some inconsistencies, after all, it is still a chronic disease. However, it is also important to point out that despite all the advances in anti-CD20 therapy, there are still some factors that must be evaluated, as it is a medication that is not exempt from causing complications and side effects. For these reasons, regular and long-term follow-up should be carried out. The application of medications in this pharmacological group should also be evaluated in the issue of the phase of the disease, as promising results may not be maintained depending on whether it is, for

example, the case of an SPMS, emphasizing in most cases early use.

Authors' contributions

Guilherme Nobre Nogueira: Validation, Writing – review & editing
Leonardo Elias Araujo dos Santos: Formal analysis, Methodology
Leonardo José Rodrigues de Araújo Melo: Validation, Writing – review & editing
Bruno Henrique Alcantara Lopes de Sousa: Data curation, Writing – original draft
Fabrício da Silva Freitas: Validation, Writing – review & editing
Rafaela Fernandes Gonçalves: Project administration
Maroan Soraia Santos Navas Ribeiro: administration
Gustavo Rassier Isolan: Project administration

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