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EMERGING THERAPEUTIC OPTIONS FOR PATIENTS WITH CARDIAC AMYLOIDOSIS, EVALUATING THEIR CLINICAL CHARACTERISTICS AND DISCUSSING THE IMPACT OF THESE INTERVENTIONS IN REDUCING THE PROGRESS OF THE DISEASE AND IMPROVING THE QUALITY OF LIFE

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Abstract: OBJECTIVE: The aim of this study was to identify emerging therapeutic options and the most effective treatments for patients with cardiac amyloidosis, assessing their clinical characteristics and discussing the impact of these interventions on reducing disease progression and improving quality of life. METHODS: A literature review was carried out using the Scielo and PubMed databases. A total of 297 articles were found, from which 18 studies that met the inclusion criteria were selected. RESULTS: Treatment of senile cardiac amyloidosis mainly involves measures to prevent and stop amyloid deposition, taking into account the patient's comorbidities. The importance of early diagnosis and administration of therapy before the condition evolves to significant cardiac dysfunction and other systemic manifestations is highlighted, since treatment is more effective in the early stages of the disease. Treatment is modulated according to risk stratification, aiming to offer greater comfort and survival to the patient, and requires the involvement of a multidisciplinary and competent team. CONCLUSION: The diagnosis of senile cardiac amyloidosis is challenging due to its nonspecific clinical manifestations, which often results in delayed treatment. The main therapeutic approaches have been chemotherapy with melphalan and prednisone, autologous stem cell transplantation (ASCT) and anti-plasma cell therapy in more advanced stages of the disease. With the advancement of therapies, a good prognosis and clinical improvement of patients has been observed.
Keywords: Amyloidosis; Cardiac; Therapy; Quality of life.

INTRODUCTION

Senile cardiac amyloidosis is a specific form of cardiac amyloidosis that predominantly occurs in the elderly. In this condition,

amyloid proteins accumulate in cardiac tissue, leading to structural and functional changes in the heart. Senile cardiac amyloidosis is often associated with transthyretin-like amyloid protein (ATTR) deposition resulting from genetic mutations or aging-related processes. Amyloid protein deposition in the heart can cause ventricular stiffness, diastolic dysfunction, heart rhythm disturbances, and congestive heart failure. Accurate diagnosis of senile cardiac amyloidosis is essential for proper patient management, involving clinical evaluation, cardiac imaging, biopsy, and molecular analysis. The understanding of the underlying mechanisms and the development of specific therapeutic approaches are essential to improve the prognosis and quality of life of individuals affected by this form of cardiac amyloidosis (RUBERG & BERK, 2012).

Recent advances in understanding this condition have clarified its pathophysiology and therapeutic strategies. In a comprehensive review of progress and challenges in the treatment of cardiac amyloidosis, providing an overview of current literature. They emphasize the importance of early diagnosis and multimodal therapeutic approaches to improving patient outcomes and demonstrate ongoing efforts to improve our understanding and management of cardiac amyloidosis, with a view to improving patient outcomes and quality of life. 2021).

Although cardiac amyloidosis is considered a very rare disease, 13% of heart failure patients with preserved ejection fraction and 16-26% of elderly patients with severe aortic stenosis develop transthyretin cardiac amyloidosis. Autopsy results show that the incidence of amyloid deposition is 32% in subjects over 75 years of age and 8% in subjects under 75 years of age. It was also found that amyloid deposition is closely associated with age, but the relationship between amyloid deposition and sex remains unclear, despite a male trend being reported, with more amyloid accumulation in men (ÇAVUŞOĞLU et al., 2019).

The diagnostic approach to cardiac amyloidosis presents significant difficulties. These are expressed through the need for clinical manifestations and associated secondary pathologies, such as limitation in the left ventricular ejection fraction, and medical suspicion through a set of symptoms, so that, the absence of a better characterization of cardiomyopathy delays the correct diagnosis and increases the morbidity of patients (MESQUITA et al., 2017). Due to this factor, the treatment, although effective, is postponed, presenting the need for deepening in different points. For example, in the case of the pharmacological medication tafamidis, its use has therapeutic benefits, however, its effectiveness in conjunction with other drugs and for the treatment of secondary complications, such as atrial fibrillation, is still uncertain (VAN DEN BERG et al., 2019).

In recent years, there has been an increasing number of studies and articles published on senile cardiac amyloidosis, exploring the characteristics of the disease and the evolution of its therapy, which has allowed for greater discussion among researchers and cardiologists about aspects involving this pathology. This discussion becomes increasingly necessary in the scientific field, given that the life expectancy of the world's population increases, for the most part, bringing with it new challenges for cardiac functioning and systemic complications to the body of senile individuals (MESQUITA et al, 2017). Thus, in view of the emerging scenario, it is essential to address the treatment options available for senile cardiac amyloidosis and the impact on quality of life, since, as it is a progressive cardiomyopathy, the delay in diagnosis directly affects the prognosis and conditions of patients' lives (ÇAVUŞOĞLU et

al., 2019).

This literature review aims to identify emerging therapeutic options and the most effective treatments for patients with cardiac amyloidosis, evaluate treatment based on clinical features, and discuss the impact of these interventions on reducing disease progression and improving quality of life.

METHODOLOGY

Bibliographic review study developed according to the criteria of the PVO strategy, which represents: population or research problem, variables and outcome. The research was guided by the following question: "What are the emerging therapeutic options and treatments that are most effective in reducing the progression of cardiac amyloidosis and improving the quality of life of patients?". In this sense, according to the criteria mentioned above, the population or problem of this research refers to patients with cardiac amyloidosis, and the objective was to identify emerging therapeutic options and for more effective treatments to reduce the progression of the disease and improve the quality of care. patients' lives. Searches were performed in the PubMed database, using the descriptors "Amyloidosis, Cardiac, Aged, Therapeutics, Quality of Life" in combination with the Boolean term "AND". Eighteen relevant articles were found, which were subsequently submitted to the selection criteria. Inclusion criteria were: articles published in English, Portuguese and Spanish; published in the period from 2017 to 2022; that addressed the themes proposed for this research; review studies and cohort studies available in full. The exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria. After associating the descriptors used in the searched databases, a total of 297 articles were found. Of which, 266 articles belonged to the PubMed database and 31 articles to Scielo. After applying the inclusion and exclusion criteria, 12 articles were selected from the PubMed database and 5 articles from Scielo, using a total of 17 studies to compose the collection.

RESULTS

EMERGING THERAPEUTIC OPTIONS

The treatment of cardiac amyloidosis focuses on the prevention of complications and the interruption of amyloid deposition through specific therapies. Patient support encompasses the management of heart failure, arrhythmias, conduction disorders, thromboembolism and severe aortic stenosis. Specific treatment seeks to modify the amyloid deposition process, interfering with the production of the precursor protein or the formation of fibrils (GARCIA-PAIVA et al., 2021).

In the case of light-chain cardiac amyloidosis, misfolded proteins infiltrate the heart muscle, leading to organ failure. The severity of AL disease is related to the deposition of light chain fibrils and their toxicity (STERN & PATEL, 2022). Patients with light-chain amyloidosis have a hematologic malignancy and are susceptible to treatment toxicity due to multiorgan involvement. The goal of treatment is to eradicate the clone of plasma cells responsible for excess light chains, using appropriate chemotherapy regimens to improve organ function and survival (MACEDO et al., 2020). There is a specific and adequate stratification, being classified as low, medium or high risk based on factors such as the level of cardiac injury, blood pressure, age, creatinine clearance, among other important data that contribute to the choice of adequate treatment (SIMÕES et al. al., 2021).

Patients classified as low-risk for light-chain amyloidosis are eligible for high-dose chemotherapy therapy followed by hematopoietic stem cell transplantation. High-risk patients, such as the elderly or patients with significant cardiomyopathy, undergo treatment with chemotherapy in adjusted doses, since they constitute a group with an unfavorable prognosis and may not tolerate cytotoxic treatment. Patients who are ineligible for hematopoietic stem cell transplantation/ conventional chemotherapy, due to advanced heart disease, kidney failure, involvement of more than two organs, or advanced age, are assigned anti-plasma cell therapy, which combines drugs such as cyclophosphamide, bortezomib and dexamethasone (SIMÕES et al., 2021).

Initial treatment of light chain amyloidosis with melphalan and prednisone chemotherapy to normalize free light chain concentration. Autologous stem cell transplantation (ASCT) is also used to rapidly eradicate amyloidogenic light chains produced by plasma cells (MACEDO, et al., 2020). The treatment strategy varies according to the risk assessment, and the cardiac response is related to the hematological response (STERN & PATEL, 2022). In cases of high tumor burden or when ASCT is not a viable option, chemotherapy regimens with proteasome inhibitors have shown favorable results (MACEDO, et al., 2020).

In the case of ATTR cardiac amyloidosis, there are several steps that culminate in the formation and deposition of amyloid fibrils in cardiac tissue. Therapeutic strategies aim to interrupt these steps, including liver transplantation, transthyretin tetramer stabilizers, inhibitors of hepatic TTR synthesis and degradation and reabsorption of deposited amyloid fibrils (SIMÕES et al., 2021).

Several therapeutic approaches are under study for the treatment of ATTR cardiac amyloidosis. The use of siRNA as a therapy based on RNA interference has shown promising results in preclinical and animal studies. In addition, TTR tetramer stabilizers such as diflunisal and tafamidis have been shown to be effective in stabilizing TTR tetramers in clinical studies. Therapies are also being explored that aim at the degradation and reabsorption of deposited amyloid fibrils through the use of monoclonal antibodies or synthetic peptides (SIMÕES et al., 2021).

Studies have investigated the use of daratumumab, an anti-CD38 monoclonal antibody, as therapy for refractory or relapsed light chain amyloidosis. This therapy has demonstrated high hematological response rates (76-78%) and mean time to first response of less than three months (MACEDO, et al., 2020; STERN & PATEL, 2022). Furthermore, epigallocatechin-3-gallate (EGCG), found in green tea, has been studied as an adjunctive therapy to stabilize misfolded amyloid fibrils and prevent the formation of insoluble fibrils (STERN & PATEL, 2022). Doxycycline, an antibiotic that also acts as an inhibitor of matrix metalloproteinases, has been associated with improvements in survival and cardiac response when used in combination with chemotherapy (MACEDO, et al., 2020). However, some studies have not shown clear benefit with doxycycline in combination with certain chemotherapy regimens (STERN & PATEL, 2022).

The use of second-generation therapies based on RNAi (RNA interference), which aim to improve the stability, specificity and efficacy of the treatment. These therapies aim to further reduce the production of mutant TTR and the formation of amyloid fibrils in cardiac tissue, delaying disease progression (GRIFFIN et al., 2021).

Another therapeutic approach being studied is the use of TTR tetramer stabilizers.

Compounds such as diflunisal, tafamidis and AG10 aim to prevent TTR destabilization and aggregation, preventing the formation of amyloid fibrils. Clinical studies have demonstrated efficacy in stabilizing TTR tetramers. Liver transplantation is not the first choice therapy for ATTR cardiac amyloidosis, due to low organ availability and possible immunosuppressive complications. However, when available, liver transplantation associated with double heart transplantation can increase survival by up to 20 years. Therefore, liver transplantation is considered an additional therapy to inhibit transthyretin synthesis (SIMÕES et al., 2021).

In summary, the therapeutic approach varies according to the type of cardiac amyloidosis, either light chains or ATTR. Strategies such as chemotherapy, hematopoietic stem cell transplantation, anti-plasma cell therapy, TTR tetramer stabilizers and second-generation RNAi-based therapies are being explored. New therapies are also under study to promote the degradation and reabsorption of deposited amyloid fibrils. The continued development of these therapies has the potential to improve the prognosis and quality of life of patients with cardiac amyloidosis (GRIFFIN et al., 2021; MACEDO et al., 2020; STERN & PATEL, 2022).

EVALUATION OF THE IMPACT OF THERAPEUTIC INTERVENTIONS

The treatment of amyloidosis is complex and aims to improve cardiac function and reduce amyloid deposition in the heart. Among the therapeutic options available, the use of drugs such as tafamidis, patisirán and inotersen stands out. Tafamidis has been used in the hereditary form of the disease, proving to be effective in preventing the progression of the disease and improving the functional capacity and quality of life of patients. On the other hand, patisirán and inotersen have been used in the treatment of ATTR cardiac amyloidosis, providing stabilization of echocardiographic parameters and symptomatic improvement in different stages of the disease (COSTABEL et al., 2020; ADAM et al., 2021).

In addition to drugs, other therapeutic approaches have been investigated. Autologous stem cell transplantation and the use of chemotherapy have been considered as options for AL cardiac amyloidosis. These interventions can lead to improved survival and disease remission. However, not all patients qualify for these treatments, especially due to multi-organ involvement. In addition, the use of immunomodulators such as thalidomide and lenalidomide has been shown to increase survival, although with significant cardiac and hematological toxicity (STERN et al., 2022).

Although senile cardiac amyloidosis presents significant therapeutic challenges, interventions such as tafamidis, patisirán and inotersen have shown benefits in reducing disease progression and improving patients' quality of life. Early diagnosis and adequate choice of treatment are essential to obtain better results. Furthermore, other therapeutic options, such as autologous stem cell transplantation and chemotherapy, have shown benefits for AL cardiac amyloidosis, albeit with limitations related to patient eligibility and drug toxicity (TAHIR et al., 2019; COSTABEL et al., 2020; ADAM et al., 2021; STERN et al., 2022).

CONCLUSION

In patients with cardiac amyloidosis, therapeutic options and treatments that are more effective in reducing the progression of the disease and improving quality of life are committed. The diagnosis is difficult to perform because it is a pathology with nonspecific clinical manifestations, which infers in the delay of treatment. This focuses

on the prevention of complications and the interruption of amyloid deposition, through melphalan and prednisone chemotherapy, and autologous stem cell transplantation (ASCT), initially, or with anti-plasma cell therapy, in more severe cases. Daratumumab can also be used in refractory or recurrent cases, in AL disease. In ATTR, therapies with inotersen or siRNA are used as the first line, but there are also TTR tetramer stabilizers, liver transplantation, which is not effective in isolation, and the degradation and reabsorption of amyloid fibrils deposited by means of monoclonal antibodies or synthetic peptides. In clinical practice, cardiac amyloidosis is a pathology associated with age and of paramount importance to be discussed due to the increase in life expectancy of the population, which directly increases the incidence of the disease, but which presents a better prognosis after significant advances in therapeutic methods.

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