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ADVANCES IN TARGETED THERAPIES FOR THE TREATMENT OF LIGHT CHAIN AMYLOIDOSIS

AVANÇOS NAS TERAPIAS DIRECIONADAS PARA O TRATAMENTO DA AMILOIDOSE DE CADEIA LEVE

AVANCES EN LAS TERAPIAS DIRIGIDAS PARA EL TRATAMIENTO DE LA AMILOIDOSIS DE CADENAS LIGERAS

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ABSTRACT

Light chain amyloidosis (AL) is a complex disorder resulting from the deposition of misfolded proteins in vital organs, requiring rapid interventions to prevent irreversible damage, especially in the cardiac and renal systems. This study aims to analyze recent scientific evidence on advances in targeted therapies for the disease, using a narrative literature review based on PubMed data from the past five years. The results indicate that the introduction of the monoclonal antibody daratumumab into the standard regimen (Dara-CyBorD) has revolutionized first-line treatment, increasing complete hematologic response rates to over 50%. For cases of relapse or refractory disease, promising options have emerged, such as elranatamab and venetoclax, the latter specifically targeting patients with the t(11;14) translocation. In addition, new research directions focus on therapies that remove existing amyloid deposits, aiming at direct recovery of affected organs. It is concluded that the management of AL amyloidosis is moving toward increasingly personalized precision medicine, where early diagnosis and the achievement of deep hematologic responses are key to transforming the prognosis into a chronic and controllable condition.

Keywords: AL Amyloidosis. Daratumumab. Immunotherapy. Precision Medicine. Hematologic Response.

RESUMO

A amiloidose de cadeia leve (AL) é uma patologia complexa decorrente da deposição de proteínas mal dobradas em órgãos vitais, exigindo intervenções rápidas para evitar danos irreversíveis, especialmente nos sistemas cardíaco e renal. Este estudo objetiva analisar as evidências científicas recentes sobre os avanços nas terapias direcionadas para a doença, utilizando uma revisão bibliográfica narrativa pautada em dados do PubMed dos últimos cinco anos. Os resultados apontam que a introdução do anticorpo

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monoclonal daratumumab ao regime padrão (Dara-CyBorD) revolucionou o tratamento de primeira linha, elevando as taxas de resposta hematológica completa para mais de 50%. Para casos de recidiva ou refratariedade, surgem opções promissoras como o elranatamab e o venetoclax, este último voltado especificamente para pacientes com a translocação t(11;14). Além disso, novas frentes de investigação focam em terapias que removem depósitos amiloides já existentes, visando a recuperação direta dos órgãos afetados. Conclui-se que o manejo da amiloidose AL caminha para uma medicina de precisão cada vez mais personalizada, onde o diagnóstico precoce e a obtenção de respostas hematológicas profundas são determinantes para transformar o prognóstico da doença em uma condição crônica e controlável.

Palavras-chave: Amiloidose AL. Daratumumab. Imunoterapia. Medicina de Precisão. Resposta Hematológica.

RESUMEN

La amiloidosis de cadenas ligeras (AL) es una patología compleja derivada de la deposición de proteínas mal plegadas en órganos vitales, lo que exige intervenciones rápidas para evitar daños irreversibles, especialmente en los sistemas cardíaco y renal. Este estudio tiene como objetivo analizar la evidencia científica reciente sobre los avances en terapias dirigidas para la enfermedad, utilizando una revisión bibliográfica narrativa basada en datos de PubMed de los últimos cinco años. Los resultados indican que la introducción del anticuerpo monoclonal daratumumab en el régimen estándar (Dara-CyBorD) ha revolucionado el tratamiento de primera línea, elevando las tasas de respuesta hematológica completa a más del 50%. Para los casos de recaída o refractariedad, han surgido opciones prometedoras como el elranatamab y el venetoclax, este último dirigido específicamente a pacientes con la translocación t(11;14). Además, nuevas líneas de investigación se centran en terapias que eliminan los depósitos amiloides ya existentes, con el objetivo de lograr la recuperación directa de los órganos afectados. Se concluye que el manejo de la amiloidosis AL avanza hacia una medicina de precisión cada vez más personalizada, donde el diagnóstico precoz y la obtención de respuestas hematológicas profundas son determinantes para transformar el pronóstico de la enfermedad en una condición crónica y controlable.

Palabras clave: Amiloidosis AL. Daratumumab. Inmunoterapia. Medicina de Precisión. Respuesta Hematológica.

1 INTRODUCTION

Light chain (AL) amyloidosis is a plasma cell disorder characterized by the production and subsequent extracellular deposition of misfolded immunoglobulin light chain fragments in various organs and tissues (Sidiqi and Gertz, 2021; Gertz, 2024). Unlike transthyretin amyloidosis (ATTR), which originates from proteins synthesized by the liver, AL amyloidosis results from a malignant clone in the bone marrow, requiring rapid cytotoxic interventions to stop the production of the amyloidogenic precursor (Gertz, 2022; Ruberg and Maurer, 2024). Clinical severity is determined primarily by cardiac and renal involvement, often manifesting as preserved ejection fraction heart failure and nephrotic syndrome (Gertz, 2024; Bou Zerdan et al., 2023).

The therapeutic landscape of AL amyloidosis has undergone a profound revolution in recent years, migrating from protocols based on conventional chemotherapy to the use of targeted therapies and monoclonal antibodies (Gertz, 2024). The introduction of daratumumab as a first-line therapy has set a new standard of care, allowing for the achievement of deep and rapid hematological responses, which are essential for the reversibility of organ dysfunctions and improved prognosis (Bou Zerdan et al., 2023; Vianna et al., 2025). Given the complexity of relapses and the need for precision medicine approaches, understanding new molecular targets and emerging immunotherapies is critical for the modern clinical management of these patients (Vianna et al., 2025; Sidiqi and Gertz, 2021).

2 METHODOLOGY

The present study is characterized as a narrative literature review, developed with the objective of synthesizing and analyzing the most recent scientific evidence related to advances in therapies aimed at the treatment of light chain amyloidosis. The search was carried out in the PubMed database, using the descriptors "Immunoglobulin Light-chain Amyloidosis" and "Therapeutics", combined using the Boolean operators AND and OR, according to the terminology of Medical Subject Headings (MeSH). Articles published in the last five years, fully available and written in Portuguese or English, that directly addressed the topic were included. Studies that did not have a direct relationship with the central theme, duplicate publications, narrative reviews with low methodological rigor, and articles not indexed in the database used were excluded. The selection of studies was conducted in two stages: screening of titles and abstracts, followed by the evaluation of

full texts to confirm relevance. The information extracted was organized in a descriptive way.

3 RESULTS

Contemporary literature highlights that incorporation of the anti-CD38 monoclonal antibody, daratumumab, into the standard regimen of cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD) dramatically altered the initial management. Based on the ANDROMEDA study, this protocol has raised complete hematologic response rates to more than 50%, making it the therapy of choice on a global scale (Gertz, 2022; Gertz, 2024; Bou Zerdan et al., 2023). For eligible patients, autologous stem cell transplantation (TACT) remains as a consolidated option for response consolidation, although the efficacy of Dara-CyBorD is reducing the need for immediate transplantation in specific subgroups (Sidiqi and Gertz, 2021; Bou Zerdan et al., 2023).

In the field of patients with relapse or refractoriness (RRAL), significant advances have been documented with the use of new immunotherapies. Elranatamab, a bispecific antibody that recruits T cells to the BCMA (B-cell maturation antigen) target, has demonstrated remarkable clinical efficacy, achieving responses in strongly pretreated patients (Vianna et al., 2025). Similarly, belantamab mafodotin, an anti-BCMA drug-antibody conjugate, and the use of CAR-T cells are pointed out as promising tools for therapeutic rescue (Bou Zerdan et al., 2023; Sidiqi and Gertz, 2021). Additionally, precision medicine has advanced with the application of venetoclax for patients with the t-translocation(11; 14), offering a highly effective oral therapy targeted to this specific genetic signature (Gertz, 2024; Bou Zerdan et al., 2023).

4 DISCUSSION

Academic discussion emphasizes that success in the treatment of AL amyloidosis depends on the depth of the hematologic response. Reducing the gap between involved and uninvolved light chains (dFLC) to less than 10 mg/L is the new milestone for preventing progressive tissue damage (Gertz, 2022; Gertz, 2024). An emerging point of debate is the development of therapies focused on removing amyloid deposits already installed in organs, such as CAEL-101 and birtamimab antibodies (NEOD001). Unlike chemotherapies that target only the plasmacytic clone, these drugs seek to accelerate

organ recovery, and are currently being tested in combination with anti-plasma cell regimens (Bou Zerdan et al., 2023; Gertz, 2024).

While ATTR amyloidosis benefits from protein stabilizers (tafamidis) and gene silencers (vutrisiran), the challenge in AL lies in the fragility of patients, especially those with advanced heart disease (Mayo Stage IV), who have high early mortality and low tolerance to intensive regimens (Ruberg and Maurer, 2024; Gertz, 2022). Close monitoring of complications, such as cytokine release syndrome (CRS) in bispecific immunotherapies, is vital (Vianna et al., 2025). In sum, the evolution of targeted therapies, from proteasome inhibitors to bi-specific and mutation-agnostic therapies, signals a future where AL amyloidosis can be managed as a chronic and controlled condition, prioritizing the preservation of end-organ function (Bou Zerdan et al., 2023; Vianna et al., 2025).

In addition, prognostic stratification in AL amyloidosis has evolved significantly with the incorporation of cardiac and hematological biomarkers, allowing a more accurate assessment of risk and survival. Systems such as Mayo staging use NT-proBNP levels, troponins, and the difference between involved and uninvolved free light chains (dFLC), the latter being an important marker of tumor burden. Studies have shown that high levels of these markers are directly associated with worse prognosis and higher early mortality, especially in patients with advanced cardiac involvement (GERTZ, 2024; BOU ZERDAN et al., 2023). Thus, early identification and correct staging are essential to direct therapeutic intensity and improve clinical outcomes.

Another relevant aspect refers to the diagnostic challenges of the disease, often related to its nonspecific clinical presentation and similarity with other more prevalent conditions. Diagnostic confirmation requires tissue biopsy with Congo red staining and typing of amyloid material, preferably by mass spectrometry, considered the gold standard. The literature shows that diagnostic delays are common, which can exceed months or years, which contributes to irreversible progression of organ dysfunction and worse prognosis (GERTZ, 2022; GERTZ, 2024). In this context, high clinical suspicion in patients with unexplained heart failure, nephrotic syndrome, or neuropathies associated with monoclonal gammopathies is essential for early diagnosis.

In the therapeutic field, it is observed that the approach to AL amyloidosis must be individualized, taking into account factors such as frailty, extent of organic involvement, and eligibility for transplantation. Although autologous stem cell transplantation remains an effective strategy in selected patients, most are not eligible due to advanced age and

comorbidities. Thus, bortezomib-based regimens associated with monoclonal antibodies, such as daratumumab, have become the current standard of care, providing deep and rapid hematological responses, which are determinant for the reversal of organ damage (BOU ZERDAN et al., 2023; GERTZ, 2024). Continuity of treatment until complete response is achieved is recommended to maximize clinical benefits.

Finally, future perspectives in the management of AL amyloidosis include the development of innovative therapies that act not only on the suppression of the plasmacyte clone, but also on the removal of already established amyloid deposits. In this scenario, antibodies targeting amyloid fibrils and immunotherapies as bispecific agents and cell therapies have shown promising results in recent studies, especially in patients with relapsed or refractory disease (VIANNA et al., 2025; BOU ZERDAN et al., 2023). Such advances reinforce the trend towards increasingly personalized medicine, with the potential to significantly modify the natural course of the disease in the coming years.

5 CONCLUSION

The management of light chain (AL) amyloidosis has witnessed a revolution in recent years, driven by the relentless search for deep and rapid hematological responses, which are essential to prevent irreversible organ damage. The introduction of daratumumab in the first-line regimen (Dara-CyBorD) has set a new standard of care, raising complete hematologic response rates to more than 50%. In the setting of relapse or refractoriness, the emergence of new immunotherapies — such as the bispecific antibody elranatamab and the targeted application of venetoclax to patients with the t-translocation(11; 14) — solidifies the transition to increasingly personalized precision medicine.

However, therapeutic success remains intrinsically linked to early diagnosis, which is often delayed due to the nonspecific clinical presentation of the disease. Prognostic stratification, enhanced by the incorporation of cardiac and hematological biomarkers (such as NT-proBNP and dFLC), is vital to guide treatment intensity, especially in frail patients with advanced heart disease.

The future perspectives reinforce a dual therapeutic approach, focused not only on the suppression of the plasmacyte clone, but also on the development of innovative therapies (such as fibril-targeted antibodies, such as CAEL-101 and birtamimab) that aim

to remove already established amyloid deposits to accelerate the recovery of target organs. In summary, the continuity of these advances signals a promising future, in which AL amyloidosis has the potential to be managed as a chronic and controlled condition, significantly modifying the prognosis and natural course of the disease.

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