Viewpoint

Advances in the Diagnosis and Treatment of Cardiac Amyloidosis

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Introduction

In recent decades, significant advances have led to a complete reformulation of clinical and epidemiological concepts about cardiac transthyretin (ATTR) amyloidosis, summarized in Figure 1.

Advances in the diagnosis of cardiac amyloidosis

The greatest advance in ATTR diagnosis has been the discovery of anomalous uptake of bisphosphonate bone radiotracers in myocardial amyloid deposits, thus allowing non-invasive identification through scintigraphy. Non-invasive ATTR diagnosis does not require an endomyocardial biopsy in the vast majority of cases, provided that monoclonal light chains are safely ruled out.[1,2]

It is important to mention that having a single clear diagnostic flowchart for diagnosing ATTR is a substantial advance of great impact in clinical practice[3] (Figure 2).

Advances in the treatment of ATTR

Historically, liver transplantation has been the only recommended treatment for interrupting the production of variant and unstable TTR, thus slowing the progression of the disease. However, late follow-up of patients who received transplants due to familial amyloid polyneuropathy showed late progression of the disease.

A considerable advance has been the development of tafamidis, a drug that stabilizes the TTR tetramer, interrupting the amyloidogenic cascade and reducing amyloid fibril tissue deposition. Its clinical benefit was initially demonstrated in patients with familial amyloid polyneuropathy.

In 2018, the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial showed that tafamidis was superior to placebo for treating wild or inherited ATTR, with a 30% reduction in all-cause mortality (hazard ratio 0.7; $p < 0.001$) and 32% reduction in hospitalizations for cardiovascular causes.

Keywords

Amyloidosis; Cardiomyopathies; Prealbumin; Heart Failure

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Manuscript received April 13, 2023, revised manuscript April 14, 2023, accepted April 14, 2023

DOI: https://doi.org/10.36660/abchf.20230024

These results were confirmed in a long-term extension study (ATTR-ACT LTE).[4,5] Based on this evidence, the Brazilian regulatory agency (ANVISA) approved of the use of tafamidis 80 mg/day for ATTR treatment.

New therapies have been developed and tested in the clinical scenario of ATTR to silence gene expression through RNA interference technology (patisiran and vutrisiran) and antisense oligonucleotide (inotersen). Both therapeutic platforms have already demonstrated good clinical and safety outcomes in patients with familial amyloid polyneuropathy in randomized multicenter studies.[6]

In September 2022, the preliminary results of the APOLLO-B study, which tested patisiran vs placebo in patients with wild type or variant ATTR, showed the benefits of patisiran, with significant improvement at 12 months, greater distance covered in the test 6-minute walk, improved quality of life, and lower NT-ProBNP levels.[7]

Eplontersen, an antisense oligonucleotide, is being tested in a multicenter phase 3 study in patients with TTR-mediated amyloid cardiomyopathy (variant and wild-type) in the CARDIO-TTRansform study (NCT04136171).[8]

The first study to use CRISPR-Cas9 *in vivo* gene editing reported results in 6 patients: a lasting reduction in TTR production with few side effects.[9] This revolutionary therapy would allow, in theory, permanent silencing of variant TTR protein expression with a single application. A phase 2 and 3 multicenter trial is being scheduled for 2023.

Advances in light chain amyloidosis treatment

Light chain (AL) amyloidosis is a systemic and heterogeneous disease that most commonly affects the heart (82% of cases). It is the main factor associated with unfavorable clinical outcomes, and its prognosis is directly related to the extent of cardiac involvement.[10] The clonal plasma cell population, responsible for the production of amyloidogenic light chains, leads to organ dysfunction through 2 main mechanisms: direct proteotoxicity through the action of unstable circulating oligomers, and distortion of the tissue architecture through the deposition of insoluble amyloid fibrils.

Thus, there are different therapeutic targets in AL amyloidosis: the plasmacytic clone, to reduce immunoglobulin production and amyloid formulation and deposition; and the amyloid fibril, to remove deposited amyloid tissue and recover organ function (Figure 3).[11,12]

Given the rarity of the disease, AL amyloidosis therapy was, for a long time, based on retrospective studies and experience with more common neoplasms, such as multiple myeloma. Thus, anti-plasmacytic therapies were

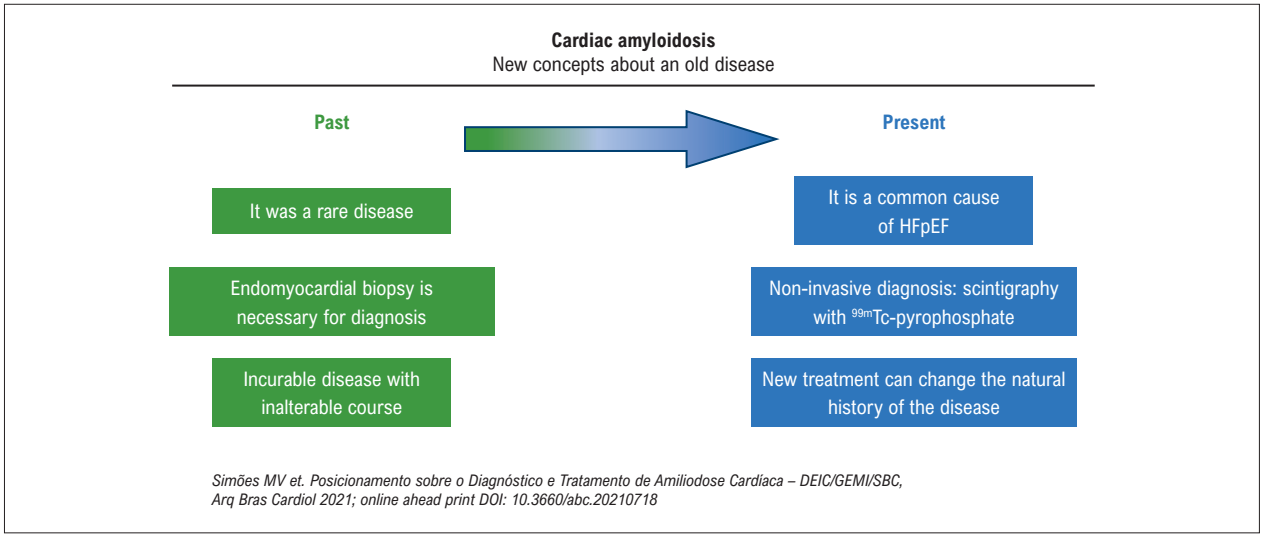

Figure 1 – *Summary of the reformulation of concepts on cardiac amyloidosis. HFpEF: heart failure with preserved ejection fraction.*

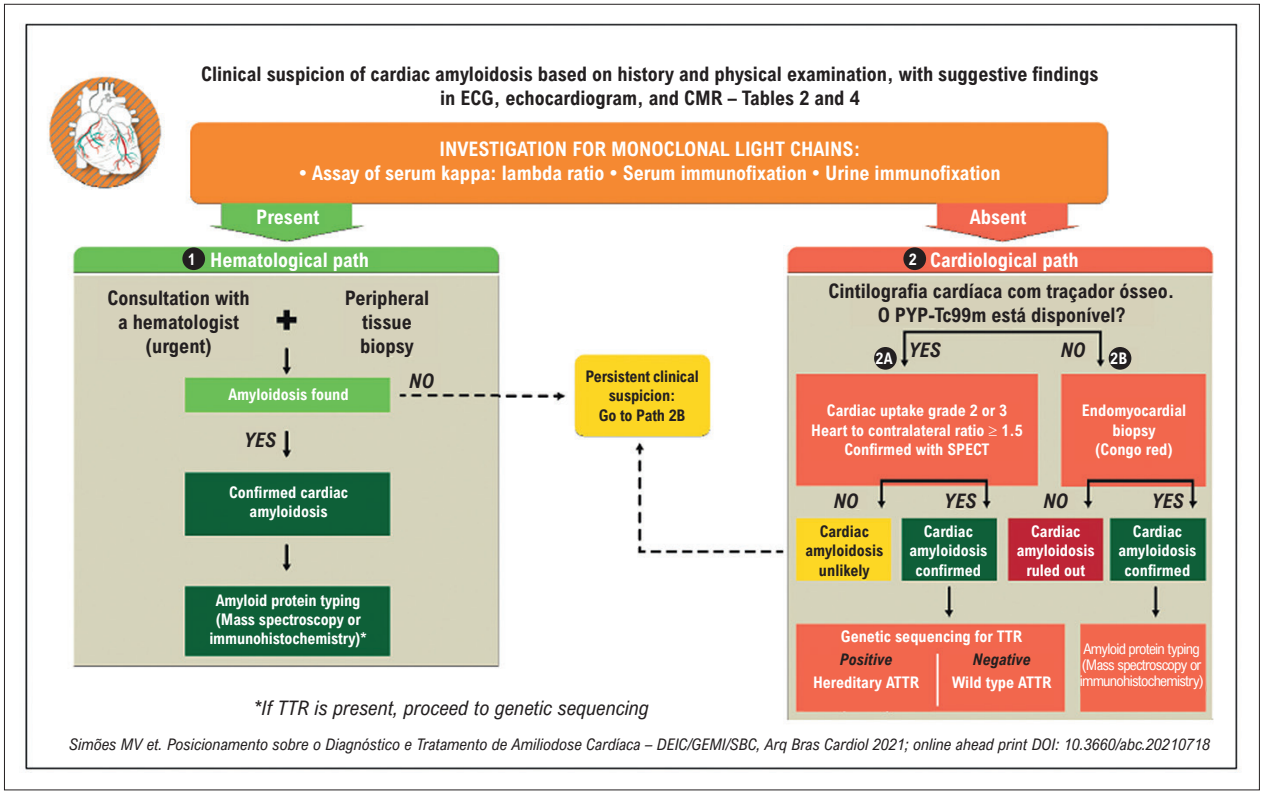

Figure 2 – *Diagnostic flowchart. ATTR: cardiac transthyretin amyloidosis; CMR: cardiovascular magnetic resonance; ECG: electrocardiogram.*

a pillar, represented mainly by autologous bone marrow transplantation and proteasome inhibitors (bortezomib). However, there has been a recent shift towards evidence-based therapy by consolidating the use of bortezomib and incorporating immunotherapy in the therapeutic strategy through anti-CD-38 monoclonal antibodies (daratumumab).[13,14]

Associating daratumumab with standard anti-plasma cell therapy has achieved rapid, profound, and sustained elimination of clonal plasma cells, which has led to a paradigm shift in AL amyloidosis treatment. The ANDROMEDA study demonstrated that effectively reducing amyloidogenic light chain production (hematological response) leads to improved

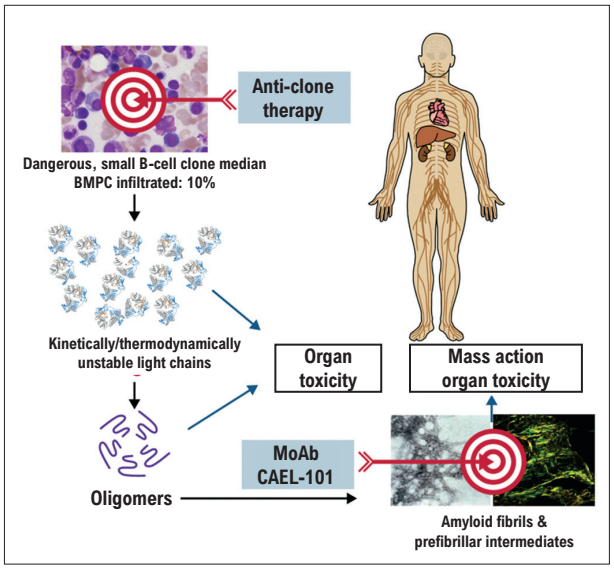

Figure 3 – *Illustrating the main therapeutic targets of light chain–associated amyloidosis: anticlone therapy and therapy aimed at removing deposited tissue. BMPC: bone marrow precursor cell; mAb: monoclonal antibody.*

organ function (organic response). With 25.8 months of follow-up, the rate of complete hematological response in patients receiving daratumumab + bortezomib [Velcade], cyclophosphamide, and dexamethasone was 3 times higher than a control group that received this combination without daratumumab (59.5% vs 19.2%, respectively; odds ratio 6.0; $p < 0.0001$).[15] Cardiac response, assessed as decreased NTproBNP levels or improved New York Heart Association functional class, was 2 times higher in the intervention group than the control group at 18 months of follow-up (53% x 24%, respectively; odds ratio 3.7; p< 0. 0001). This occurred in all subgroups, regardless of the initial cardiac involvement, showing that the daratumumab combination is effective and safe.[15,16]

Even with increased therapeutic efficacy due to the introduction of daratumumab, there are still unmet needs in AL amyloidosis treatment, including earlier organic response and improved outcomes in patients with advanced heart disease. Nevertheless, perspectives are positive due to developing evidence, including the testing of anti-amyloid drugs (CAEL-101 and birtamimab) that bind to cryptic epitopes in kappa and lambda light chains when they form non-native structures (amyloid tissue).[12] Two phase 3 multicenter studies are currently recruiting patients to evaluate the efficacy and safety of CAEL-101 (NCT04512235 and NCT04504825).[17]

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Critical revision of the manuscript for important intellectual content: Simões MV, Ávila DX, Garibaldi PMM; Writing of the manuscript: Simões MV, Ávila DX, Garibaldi PMM.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

There were no external funding sources for this study.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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