What is New in Amyloidosis Treatment? Part 1: Ligh chains*

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ABSTRACT

AL amyloidosis is a disease caused by the deposit in different organs and tissues of protein fibrils formed by light chains synthetized by pathological clonal plasma cells. Its treatment is currently aimed at eradicating this plasma cell clone and it has been historically extrapolated from available and validated treatments for other blood dyscrasias.

In 2020, the Amyloidosis Study Group prepared different clinical practice guidelines for the treatment of AL amyloidosis.

Since then, clinical trials have been published that confirm and strengthen the knowledge available up to now, and new lines of research are being developed that stimulate study in the area. In this review, an update of the existing guidelines regarding the treatment of AL amyloidosis is made.

As relevant evidence, in the last year, results of clinical trials have been made available that support the use of regimens based on Daratumumab (an anti-CD38+ monoclonal antibody) for patients with newly diagnosed AL amyloidosis as first line therapy. In addition, for the treatment of refractory or relapsed AL amyloidosis, where the availability of supporting literature is scant and extrapolated from the treatment of multiple myeloma, there is currently quality evidence to recommend the use of ixazomib, an oral reversible proteasome inhibitor, only available in Argentina since 2020.

Finally, some research lines exploring the efficacy of other monoclonal antibodies and therapeutic experiments based on the use of CAR-T cells are mentioned.

Key words: amyloidosis, light chains, treatment, guidelines.

¿Qué hay de nuevo en el tratamiento de amiloidosis? Parte 1: Cadenas livianas*

RESUMEN

La amiloidosis AL es una enfermedad debida al depósito, en órganos y tejidos, de fibrillas formadas por cadenas livianas producidas de forma patológica por plasmocitos clonales. Su tratamiento actualmente

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está orientado a erradicar el clon de células plasmáticas; este históricamente se extrapoló de tratamientos disponibles y estudiados para otras discrasias sanguíneas.
En el año 2020, el Grupo de Estudio de Amiloidosis (GEA) confeccionó distintas guías de práctica clínica para el tratamiento de la amiloidosis AL.
Desde entonces se han publicado ensayos clínicos que arrojan contundencia al conocimiento disponible hasta el momento, y están en desarrollo nuevas líneas de investigación que robustecen y estimulan el estudio en el área. En esta revisión se realiza una actualización de las guías existentes en lo que respecta al tratamiento de la amiloidosis por cadenas livianas.
Como evidencia de relevancia, en el último año estuvieron disponibles resultados de ensayos clínicos que respaldan el uso de esquemas basados en daratumumab (un anticuerpo monoclonal anti-CD38+) para pacientes con diagnóstico reciente de amiloidosis AL como primera línea. Además, para el tratamiento de la amiloidosis AL refractaria o recaída, la disponibilidad de bibliografía respaldatoria es escasa y extrapolada del tratamiento del mieloma múltiple; sin embargo, actualmente existe evidencia de calidad para recomendar el uso de ixazomib, un inhibidor de proteosoma reversible por vía oral disponible en la Argentina desde 2020.
Por último, se mencionan algunas líneas de investigación con otros anticuerpos monoclonales y terapéuticas basadas en el uso de CAR-T *cells*.

Palabras clave: amiloidosis, cadenas livianas, tratamiento, actualización, guías de práctica clínica.

Amyloidosis is considered a rare disease and, as such, has always represented a diagnostic and therapeutic challenge. However, in recent years, significant advances have been made in diagnosing and treating the different types of amyloidosis. At the Hospital Italiano de Buenos Aires, since 2010, there has been a transdisciplinary group of specialists, formed by professionals from different specialties and of national reference, focused on assistance, teaching, and research, who have been working together to optimize the care of people with amyloidosis. In 2020, this group –called the Amyloidosis Study Group (ASG)– prepared several clinical practice guidelines for the treatment of light chain amyloidosis in order to provide the medical community with fundamental guidelines based on the best available evidence and taking into account the applicability of the different recommendations.

Since its creation until the present date, multiple high-quality clinical trials have emerged shedding light on the effectiveness of new treatments, and new lines of research have experienced exponential development. This narrative review aims to explore the state of the art in topics related to the treatment of AL amyloidosis. To this end, the available information is expanded based on the recommendations previously published by GEA[1,2].

• Review of Recommendations for AL Amyloidosis Treatment

Recommendation 1

For selected patients with AL amyloidosis, autologous hematopoietic stem cell transplantation is recommended following induction with bortezomib-based regimens, with doses adjusted based on patient characteristics, as it is likely to deepen hematologic and organ response, enhance their durability, and improve overall survival[1,2].

The preferred induction regimen, if possible, should include daratumumab + bortezomib (a proteasome inhibitor). The suggested regimen is daratumumab + bortezomib + cyclophosphamide (an alkylating agent) + dexamethasone, abbreviated as "Dara+VCd" or "Dara+CyBorD."

The ANDRÓMEDA study compared endpoints (time to hematologic response and organ response) between patients undergoing hematopoietic stem cell transplantation after induction with the VCd regimen (bortezomib + cyclophosphamide + dexamethasone) vs. daratumumab + VCd. In the Dara+VCd treatment group (13 patients), the hematologic response was earlier and more profound, and the organ response was better than in

the VCd-only treatment group (20 patients), with similar safety standards for both groups[3].

Recommendation 2

For selected patients with AL amyloidosis in specialized centers, autologous hematopoietic stem cell transplantation with melaphan conditioning is recommended, as it may deepen hematologic and organ response, improve their durability, and enhance overall survival, although the evidence is uncertain.

Implementation considerations: Melphalan conditioning varies in dosage and should be adjusted based on the patient's baseline characteristics. The dosage range is from 140 mg/m² to 200 mg/m², intravenously[1,2].

Conditioning is described with doses of 200 mg/m² of melphalan (full intensity) or reduced doses (100-140 mg/m²) (the latter being a strategy for more comorbid patients who may not tolerate higher doses). In specialized centers with availability for all treatments, knowing that lower doses of melphalan correspond to lower rates of complete remission and subsequent overall survival, when the patient is not eligible for full-intensity melphalan, new alternative therapies to autologous transplantation are chosen, which have shown good responses currently (Dara+VCd)[4].

In a report[5] of 629 transplanted patients at Boston University, complete hematologic response was higher in patients receiving full-intensity melphalan than in those receiving reduced doses (200 mg/m² vs. 100-140 mg/m², 45% vs. 34%, respectively; P = 0.0091). The median overall survival was higher in the high-dose group vs. the low-dose group (10.5 vs. 5.2, respectively; P = 0.0001).

Recommendation 5

For patients with AL amyloidosis, first-line treatment with daratumumab-based regimens (Dara+CyborD) is suggested whenever ready for use as it may achieve hematologic and organ response and improve overall survival, but the evidence is uncertain. Quality of evidence: Low. Strength: Weak in favor[1,2].

Regarding this recommendation, there is currently high-quality evidence supporting the use of daratumumab-based regimens for patients with a recent diagnosis of AL amyloidosis as a first-line treatment.

In the ANDRÓMEDA study[3], a phase 3, open-label, randomized, controlled trial concluded in 2019, we measured complete hematologic response in patients with newly diagnosed AL amyloidosis assigned to two groups–one receiving chemotherapy with bortezomib + cyclophosphamide + dexamethasone, and the other with the addition of daratumumab, followed by maintenance with this monoclonal antibody as a single agent.

During the follow-up (median of 11.4 months), 104 patients had a complete hematologic response, 53.3% in the daratumumab group and 18.1% in the control group (significant difference, RRR 2.9; 95% CI: 2.1 to 4.1; OR: 5.1; 95% CI: 3.2 to 8.2; P < 0.001 for both comparisons). Hematologic responses were also more profound and occurred earlier in the daratumumab treatment group. Organ deterioration-free survival (renal or cardiac) and hematologic progression-free survival were longer in the daratumumab group vs. the control group (Hazard ratio for organ dysfunction, hematologic progression, or death 0.58; 95% CI: 0.36 to 0.93; P = 0.02).

• New recommendations in the treatment of AL amyloidosis. New recommendation for refractory or relapsed AL.

Ixazomib

The TOURMALINE[6], a phase 3 study published in 2021 comparing ixazomib+dexamethasone vs. "physician's choice" treatments (dexamethasone+thalidomide/dexamethasone+lenalidomide/dexamethasone+melflufen/dexamethasone+cyclophosphamide), demonstrated that for refractory or relapsed AL, treatment with ixazomib+dexamethasone produces profound and lasting hematologic responses within a safety margin.

In those refractory or relapsed patients, naive to proteasome inhibitor treatment, who received ixazomib+dexamethasone, progression-free hematologic survival was considerably longer than in those with previous exposure to proteasome inhibitors (25.8 months vs. 10.7 months), implying a clinically relevant benefit in this selected group of patients. Additionally, in those with ixazomib+dexamethasone (whether naive or not to previous proteasome inhibitor treatment) vs. other treatments, time-dependent endpoints were always more prolonged, although with a statistically non-significant difference (organ damage-free progression time, hematologic progression time, treatment failure time, time to initiation of new therapy).

• New Therapies in AL Amyloidosis

Venetoclax

Up to 50% of patients with AL amyloidosis exhibit the t(11;14) translocation, leading to clonal plasma cells that depend on activation through cyclin D1. Inhibiting BCL-2, as offered by agents like the venetoclax, implies suppression of the anti-apoptotic mechanisms in these cells. Patients carrying this translocation are coincidentally those with the worst response to proteasome inhibitors. According to the 20227 ISA guidelines, the available experience is with venetoclax as a single agent or in combination with bortezomib and daratumumab in multiple myeloma patients. Additionally, there is retrospective information on refractory/relapsed amyloidosis treated with venetoclax, documenting deep and lasting responses. There are no prospective data on dosage.

The recommendation according to the 2022 ISA guidelines for the use of venetoclax in patients with

AL amyloidosis and this specific cytogenetics is Grade B, Level III as monotherapy and Grade B, Level III in combination therapy with bortezomib + dexamethasone[7].

Isatuximab

Isatuximab is an anti-CD38, similar to daratumumab. It has been used in refractory myeloma in combination with other drugs with good results. The dose is intravenous, 10 mg/kg weekly for four weeks, then biweekly. Preliminary results from a phase 2 study for relapsed AL amyloidosis patients have reported an overall hematologic response of 77%, with a complete response of only 3%, but a very positive overall response of 54% and a partial response of 20% (n: 35 patients)9.

• Other Strategies Under Investigation in the Treatment of AL Amyloidosis

The B-cell maturation antigen (BCMA) is a molecule expressed in plasma cells and their progenitors. Experience with targeted therapies for this marker is limited in AL amyloidosis. Belantamab, an anti-BCMA antibody-drug conjugate, has shown promising responses in advanced refractory myeloma. It is currently under investigation for refractory AL amyloidosis, with the possibility of managing lower doses than in myeloma patients (thus reducing some dose-dependent severe adverse effects). The current recommendation in the 2022 ISA guidelines for belantamab monotherapy in relapsed AL is Grade B, Level III.

In line with this, BCMA is also a target for CAR-T cells and BiTE therapy (chimeric antigen receptor T-cells and bispecific T-cell engagers, respectively). However, at the moment, their use is not recommended outside of clinical trials7. As for treatments to eliminate amyloid deposits from tissues to improve organ function, monoclonal antibodies such as CAEL-101 or birtamimab (NFOD001) are currently under investigation.

Birtamimab

A monoclonal antibody that can bind to soluble amyloid, preventing its deposition and promoting the clearance of already deposited fibrillar amyloid. In 2018, the VITAL study (Phase 3) assessed the efficacy of birtamimab in reducing all-cause mortality and time to hospitalization for cardiac causes. Although the study was terminated early for futility, the final hazard ratio (HR) favored birtamimab + standard of care over placebo + standard of care (0.835; 95% CI: 0.5799-1.2011; p = 0.330), and a post-hoc analysis of mortality after nine months revealed a survival benefit (HR = 0.413; 95% CI: 0.191-0.895; p = 0.025). In a subgroup of patients at high risk of early mortality (Mayo stage IV), it demonstrated clinical and quality of life benefits. Recruitment is now underway for the AFFIRM-AL study, a Phase 3 and double, placebo-controlled trial to assess overall survival and all-cause mortality at nine months in Mayo stage IV patients. They will receive 24 mg/kg of intravenous birtamimab every 28 days or a placebo (always with standard of care and bortezomib-based chemotherapy; NCT04973137)[10].

CAEL-101

A monoclonal antibody that binds to a neoepitope conformational site within the first 18 amino acids of misfolded light chains of immunoglobulins. It promotes phagocytosis, destruction, and subsequent removal of amyloid deposits. In December 2021, the results of an open-label Phase 1a and 1b study were published, involving 27 AL amyloidosis patients who received the drug intravenously weekly for four weeks. The patients showed deep hematologic responses but persistent organ disease. Of the 24 patients with cardiac, renal, hepatic, gastrointestinal, or soft tissue involvement, 15 (63%) had a therapeutic response to the CAEL-101 monoclonal antibody, as evidenced by a decrease in serum biomarkers or objective imaging modalities with a median time to response of 3 weeks. CAEL-101 mAb infusions were well-tolerated and, for the majority, improved organ function, especially for those with heart failure (NCT02245867)11.

Finally, at the 18th International Symposium on Amyloidosis (ISA), which took place from September 4th to 8th, 2022, in Heidelberg, Germany, intriguing preclinical data were presented by the University of Tennessee College of Medicine regarding their study on novel human chimeric antigen receptor macrophages (CAR-M) as a potential therapeutic approach for amyloid elimination.

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