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Monoclonal antibodies and amyloid removal as a therapeutic strategy for cardiac amyloidosis

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Cardiac amyloidosis (CA) is an infiltrative disease caused by progressive deposition of amyloid fibres in the heart. The most common forms include immunoglobulin light-chain and transthyretin amyloidosis. Current therapies for CA either stabilize or block the production of amyloidogenic precursors, preventing further amyloid deposition. This approach, while reducing cell damage and disease progression, does not target pre-existing amyloid deposits. Conversely, amyloid removal might stimulate functional recovery of the affected organ, thus improving quality of life and survival. A therapeutic strategy based on monoclonal antibodies capable of selectively binding amyloid deposits and inducing their removal has recently been tested in various clinical trial, with promising results, and could represent a key treatment for CA in the near future.

Introduction

Cardiac amyloidosis (CA) is a progressive infiltrative disease resulting from the deposition of amyloid fibrils in the heart. The most common forms include immunoglobulin light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR), caused by the deposition of unstable immunoglobulin free light chains and transthyretin (TTR), a tetrameric transport protein produced by the liver. Two forms of ATTR amyloidosis are recognized: wild-type (ATTRwt), due to aggregation of native TTR, showing a prevalent cardiac involvement; and hereditary (ATTRv), caused by mutations in the *TTR* gene leading to familial polyneuropathy (ATTR-FAP) and cardiomyopathy or a combinations based on the specific mutation.[1,2]

Cardiac amyloidosis has long been considered a rare disease, with few available therapies and limited life expectancy. The major determinant of outcome in amyloidosis is the extent of cardiac involvement, suggesting that its removal may increase quality of life and survival.[3] However, currently available therapeutic approaches aim to halt or stabilize the production of amyloidogenic precursors, thus impairing further amyloid deposition. To date, the standard of care includes: (i) chemotherapy and autologous stem cell transplantation for AL amyloidosis and (ii) stabilizer agents and gene silencers for ATTR amyloidosis.[1,2] Even after deposition is stopped, amyloid progressively continues to impair tissue function. Therefore, therapies that directly address the clearance of toxic amyloid are needed to restore organ physiology. One possible approach consists of targeting amyloid deposits with specific monoclonal antibodies (mAbs), thus stimulating their removal through phagocytic cells.[4]

This review summarizes the current evidence regarding the use of mAbs in the treatment of CA.

Disease-modifying therapies currently available for cardiac amyloidosis

Light-chain amyloidosis

The aim of treatment for AL amyloidosis is to eradicate plasma cell clones that produce amyloidogenic light chains. Most therapeutic strategies are adapted from those used for multiple myeloma.

Chemotherapy associated with autologous stem cell transplantation (ASCT) provides the best long-term outcome. The standard approach involves high-dose melphalan (an alkylating agent) combined with ASCT. However, only 20% of the patients are eligible for ASCT, which is

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reserved for patients with good functional status and no severe renal and cardiac involvement.[1] For transplant-ineligible patients, the initial treatment is oral melphalan with dexamethasone. The two other common regimens are cyclophosphamide–bortezomib–dexamethasone (CyBorD) and bortezomib–melphalan–dexamethasone. Indeed, an improvement in AL amyloidosis therapy has been represented by the introduction of proteasome inhibitors such as bortezomib, which either as a single agent or in combination with alkylating agents and/or dexamethasone, reduces the production of amyloidogenic light chains from plasma cells.[1] Second-generation proteasome inhibitors, carfilzomib and ixazomib, have been associated with a haematological response in more than half of patients with refractory AL amyloidosis, further improving their survival. Furthermore, immunomodulating agents such as thalidomide, lenalidomide, and pomalidomide, which act by inhibiting IL-6 expression and activating pro-apoptotic pathways, constitute important strategies for chronic therapy, maintaining a long-term haematological response.[1]

Transthyretin amyloidosis amyloidosis

For a long time, the only therapy available for ATTR amyloidosis was liver transplantation or combined liver–heart transplantation. However, accumulation of ATTR in pre-existing amyloid deposits can progress even after liver transplantation. Recently, new pharmacological therapies directed towards different points of the amylogenic cascade have entered clinical practice.

Some therapies inhibit *TTR* gene expression through siRNA or antisense oligonucleotides. Patisiran is an siRNA which targets hepatocytes and mediates cleavage of TTR-mRNA to prevent its expression, and it has been approved for clinical use in patients with ATTR-FAP.[5] Moreover, patisiran and vutisiran (another anti-TTR siRNA) are currently undergoing Phase III clinical trial for patients with ATTR-related cardiomyopathy in APPOLLO B (NCT03997383) and HELIOS B (NCT04153149) studies, respectively. Inotersen is an antisense oligonucleotide that binds to TTR-mRNA, thereby promoting its degradation. Inotersen is approved for the treatment of patients with ATTR-FAP.[5] A promising perspective is represented by the CRISPR (clustered regularly interspaced short palindromic repeats)–Cas9 gene editing system, which has been proven to efficiently delete the *TTR* gene *in vivo*, reducing its production in the liver. This method is currently being investigated in a Phase I trial (NCT04601051).

Transthyretin stabilizers include tafamidis, acoramidis (AG-10), and diflunisal. These drugs interact with the tiroxine-binding site of TTR, thus inhibiting tetramer dissociation, which is the rate-limiting step in amyloidogenesis. Tafamidis was the first disease-modifying drugs to be approved for the treatment of patients with ATTR-related cardiomyopathy, after showing a reduction in all-cause mortality and in cardiovascular hospitalizations in the Phase III trial ATTR-ACT.[2] AG-10 is being evaluated in a Phase III trial on patients with ATTR-related cardiomyopathy (ATTRibute-CM, NCT03860935).

Other potential approaches for the treatment of ATTR amyloidosis are the inhibition of oligomer aggregation by epigallocatechin-3-gallate and the use of doxycycline and tauroursodeoxycholic acid, which promote amyloid fibrils disaggregation and might be a cheaper and feasible option, currently under evaluation in a Phase III trial (NCT03481972).[2]

Monoclonal antibodies in the treatment of amyloidosis

In 1975, Kohler and Milstein demonstrated the possibility of producing mAbs with predetermined specificity and low toxicity. Recently, mAbs have gained increasing interest in the treatment of several pathologies, such as cancer, autoimmune, and infectious diseases.

In CA, mAbs may potentially be used to target misfolded amyloidogenic precursors, plasma cell clones, or amyloid fibrils, thus inducing amyloid removal through different mechanisms depending on the specific target. Among them, antibody-dependent cellular toxicity (ADCC), opsonization, and neutralization of the amyloid burden have been found. Studies suggest that mAbs against cardiac amyloid mainly activate immune response with subsequent clearance by phagocytic cells.[4]

Monoclonal antibodies in the treatment of light-chain amyloidosis

Monoclonal antibodies targeting plasma cell clone

Daratumumab is a human anti-CD38 IgG1κ mAb (*Table 1*). CD38 is a surface antigen expressed on plasma cells. Daratumumab induces direct apoptosis of plasma cells through ADCC and is the first therapeutic anti-CD38 mAb approved for the management of multiple myeloma.[4] Daratumumab has shown promising efficacy both as monotherapy and as combination therapy in the treatment of AL amyloidosis. In the Phase III ANDROMEDA trial, designed to assess the tolerability of daratumumab in addition to CyBorD, the safety run-in cohort of 28 patients showed an overall response rate of 96% and a complete response of 36% during the 1-year follow-up. Cardiac response was observed in 53% of the 17 evaluable patients.[6] An extension of this study confirmed these results, showing a higher haematologic response (92 vs. 77%) and significant higher rates of cardiac responses (42 vs. 22%) compared with the control group (CyBorD without daratumumab).[7] Based on this results, in 2021 FDA granted accelerated approval to daratumumab in combination with CyBorD for the treatment of AL amyloidosis.[8]

Isatuximab is a chimeric IgG1κ mAb that binds to CD38. A Phase II study on isatuximab for patients with relapsing AL amyloidosis or refractory to conventional therapies reported haematologic complete response, very good partial response, and partial response in 3, 54, and 20% of the treated patients, respectively.[9]

Elotuzumab is a humanized IgG1κ mAb that targets the cell-surface glycoprotein CD2 subset 1 expressed on plasma cells. Similar to daratumumab, elotuzumab appears to predominantly act through ADCC. However, elotuzumab has a maximal effect when combined with other agents such as lenalidomide or bortezomib.[8,10] A Phase II trial (NCT03252600) is currently evaluating the maintenance of treatment with elotuzumab, lenalidomide, and dexamethasone with or without cyclophosphamide, in first-relapsed AL amyloidosis.

Monoclonal antibodies targeting amyloid deposits

Birtamimab (NEOD001) is a humanized IgG1 mAb that binds to an epitope derived from a cleavage site of serum amyloid protein A (an apolipoprotein and one of the main acute phase proteins synthesized by the liver) and a cryptic epitope on AL amyloid fibrils exposed during

Table 1 Main clinical trials using monoclonal antibodies for the treatment of light-chain amyloidosis

Clinical trials identifier	Antibody and dose	Study design	Enrolled patients Main inclusion criteria	Main efficacy endpoints	Main safety outcomes
NCT03283917 (recruiting)	Daratumumab Daratumumab + Ixazomib + Dexamethasone	Phase I, open label, single group assignment	20 participants Newly diagnosed or refractory and/or relapsed AL amyloidosis	*Secondary outcomes*: • Overall haematologic response rate • Progression-free survival and OS	*Primary outcomes*: • Dose-limiting toxicity rate • Recommended Phase II dose
NCT02841033 (completed)	Daratumumab Daratumumab, 16 mg/kg for subsequent doses, starting from once weekly for 2 months	Phase I/II, open label, single group assignment	22 participants with systemic AL amyloidosis; relapsed or refractory to at least 1 prior treatment	• Haematologic response (CR, VGPR, PR) 90% • Organ response 73% (Cardiac response 50%)	• No patient experienced a grade 3/4 IRR
ANDROMEDA NCT03201965 (active, not recruiting)	Daratumumab CyBorD ± Daratumumab (1800 mg subcutaneously)	Phase III, open label, randomized, parallel assignment	Safety run-in cohort of 28 participants 418 participants (2022) with systemic AL amyloidosis; no previous therapies; no NT-proBNP >8500 ng/L or NYHA IIIb or IV	• Haematologic response: 92% vs. 77% (daratumumab vs. control group) ($P < 0.001$) - CR 53% vs. 18% - VGPR 78% vs. 49% • Cardiac response 42% vs. 22%	• SAEs in 43% vs. 36%; most common: pneumonia
NCT03499808 (active, not recruiting)	Isatuximab	Phase II, open label, single group assignment	43 patients (February 2020) with refractory/relapsed AL amyloidosis; ≥1 prior line of therapy	• Overall haematologic response rate 77% • CR 3% • VGPR 54% • PR 20%	
NCT04754945 (recruiting)	Isatuximab Isatuximab + dexamethasone 4 mg p.o./i.v. days weekly; if tolerated, increasing treatment	Phase I, open label, single group assignment	25 participants; high-risk AL amyloidosis (NT-proBNP > 8500 ng/L or cTnT ≥ 50 ng/L; Mayo Stage IV) No >1 prior line of therapy	*Secondary outcomes*: • Complete haematologic response proportion (up to 19 months)	*Primary outcomes*: • Event-free proportion (at 3 months)
NCT03252600 (active, not recruiting)	Elotuzumab EloRD ± cyclophosphamide followed by EloRD maintenance as second-line therapy for patients with relapsed AL amyloidosis	Phase II, open label, randomized, parallel assignment	53 participants; AL amyloidosis after 1 prior line of therapy; dFLC ≥ 50 mg/L	*Primary outcomes* • Major haematologic response (≥VGPR) *Secondary outcomes* • Anti-drug parameters • CR rate; OR rate; OS • Organ response	-
NCT01707264 (completed)	Birtamimab (NEOD001) Dose escalation of intravenously NEOD001, starting from 0.5 mg/kg	Phase I/II, open label, sequential assignment	69 participants with AL amyloidosis after >1 prior therapy	*Secondary outcomes* • Cardiac response 57%	• No SAE • No anti-drug antibodies reported
PRONTO	Birtamimab (NEOD001)	Phase IIb, quadruple-blinded,	129 participants with pre-treated AL amyloidosis	*Primary outcomes* • No significant cardiac response (NT-proBNP) 39%	

Continued

Table 1 Continued

Clinical trials identifier	Antibody and dose	Study design	Enrolled patients Main inclusion criteria	Main efficacy endpoints	Main safety outcomes
NCT02632786 (completed)	NEOD001 IV every 28 days at 24 mg/kg vs. placebo	randomized, parallel assignment	and cardiac involvement (650 < NT-proBNP < 5000)	(NEOD001 group) vs. 48% (placebo) ($P = 0.319$) *Secondary outcomes* • 6MWT Distance	
VITAL	Birtamimab (NEOD001)	Phase III, quadruple-blind, randomized, parallel assignment	260 participants with newly diagnosed AL amyloidosis; cardiac involvement		*Primary outcomes* • Time to composite of all-cause mortality or CH
NCT02312206 (terminated, due to futility analysis)	NEOD001 IV every 28 days at 24 mg/kg vs. placebo				
AFFIRM-AL	Birtamimab (NEOD001)	Phase III, quadruple-blind, randomized, parallel assignment	150 participants, newly diagnosed and AL amyloidosis treatment-naïve with cardiac involvement (Mayo Stage IV)	*Secondary outcomes* • PCS score of SF-36v2 • 6MWT distance	*Primary outcomes* • Time to all-cause mortality
NCT04973137 (recruiting)	Birtamimab plus SoC Chemotherapy (CyBorD): 24 mg/kg vs. placebo				
NCT02245867 (completed)	Chimeric Fibril-reactive mAb 11-F4 Ch mAb 11-1F4 dose escalation from 0.5 mg/m^2	Phase Ia/b, open label, non-randomized, single group assignment	31 participants, with previously treated refractory or relapsed AL amyloidosis	*Secondary outcomes* • Amyloid-related organ responses in 67%	*Primary outcomes* • No DLT up to 500 mg/m^2 • No drug-related AEs • No dose-limiting toxicity at 1000 mg/m^2
NCT04304144 (active, not recruiting)	Anselamimab (CAEL-101) CAEL-101 with SoC CyBorD (Part A) and Daratumumab (Part B)	Phase II, open label, non-randomized, sequential assignment	25 participants, AL amyloidosis Mayo Stage I, II, or IIIa	*Primary outcomes* • Dose toxicity	
NCT04512235 (recruiting)	Anselamimab (CAEL-101) CAEL-101 combined with SoC plasma cell dyscrasia vs. placebo	Phase III, double-blind, randomized, parallel assignment	267 estimated participants with AL amyloidosis Mayo Stage IIIa	*Secondary outcomes* • KCCQ-OS; GLS%; 6MWT	*Primary outcomes* • Time from the date of randomization to date of death or end of study • AEs
NCT04504825 (recruiting)	Anselamimab (CAEL-101)	Phase III, double-blind, randomized, parallel assignment	124 estimated participants AL amyloidosis Mayo Stage IIIb	*Secondary outcomes*: • KCCQ-OS; GLS%; 6MWT	*Primary outcomes:* • Time from the date of randomization to date of death or end of study • AEs

ADA, anti-drug antibodies; AEs, adverse events; AL, immunoglobulin light-chain amyloidosis; ATTR, transthyretin amyloidosis; Ch, chimeric; CyBorD, cyclophosphamide/bortezomib/dexamethasone; CH, cardiac hospitalization; CR, complete response; dFLC, different of free light chains; DLT, dose-limiting toxicity; EloRD, elotuzumab with lenalidomide and dexamethasone; GLS%, global longitudinal strain improvement; IRR, infusion-related reaction; i.v., intravenously; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Score; 6MWT, 6 min walk test; NT-proBNP, N-terminal prohormone B natriuretic peptide; NYHA, New York Heart Association; OR, overall response; OS, overall survival; PCS, Physical Component Summary; PR, partial response; SAE, serious adverse event; SF-36v2, Short Form-36, version 2; SoC, standard of care; VGPR, very good partial response.

misfolding. A Phase I/II study confirmed that birtamimab is safe and well tolerated in patients with AL amyloidosis. A Phase IIb study (PRONTO) evaluated birtamimab in patients with cardiac dysfunction and previously treated AL amyloidosis. However, the study did not meet the primary endpoint (cardiac response) after 12 months of follow-up. Therefore, the planned Phase III trial (VITAL) was halted. In the PRONTO trial, only Mayo Stage IV patients showed a significant survival benefit after birtamimab treatment. Thereby, a Phase III study on this category of patients (AFFIRM-AL; NCT04973137) was started in August 2021 and is estimated to be completed by June 2024.[4]

The monoclonal IgG1 antibody anselamimab (CAEL-101) is the chimeric form of murine mAb 11-1F4, which binds to a conformational neo-epitope of misfolded light chains, thus triggering the activation of macrophages.[4] A Phase Ia/b study which enrolled patients with relapsed or refractory AL amyloidosis found early and sustained organ response in 67% of evaluable patients which was associated with a significant improvement in global longitudinal strain, while the remaining patients showed stable heart disease.[11] A Phase II trial (NCT04304144) is currently evaluating safety of the combination of CAEL-101 with CyBorD and the recommended dose of CAEL-101. Two Phase III studies have started enrolling patients with AL amyloidosis and advanced cardiac involvement (NCT04512235 and NCT04504825).

Monoclonal antibodies in the treatment of transthyretin amyloidosis amyloidosis

PRX004 is a humanized mAb specific to ATTRv amyloidosis (*Table 2*). A phase I study (NCT03336580) was designed to evaluate the safety of PRX004; however, it was terminated early due to the COVID-19 pandemic. Among the seven patients with available cardiac involvement, the authors reported an improved global longitudinal strain. Furthermore, no treatment-related serious adverse events were observed.[4,12]

NI301A is a human mAb that binds to the linear epitope WEPFA, which is only accessible on misfolded TTR and ATTR deposits, triggering phagocytosis of ATTR aggregates by human macrophages, thus accelerating fibril removal.[12] NI301A is currently undergoing a Phase I clinical trial (NCT04360434) in patients with ATTR-related cardiomyopathy.[4,12]

Ab-A is a human IgG1 mAb that targets aggregated TTR, with beneficial effects in a murine model of ATTRwt. Ab-A, which binds with high affinity to ATTR fibrils, was able to induce significant removal of ATTR aggregates by antibody-dependent phagocytosis. The ability to bind ATTR fibrils has also been demonstrated in human heart tissue samples with ATTRwt amyloidosis.[13]

Pan-amyloid antibodies?

A novel perspective derives from the development of pan-amyloid removal (PAR) therapeutics based on molecules capable of selectively binding amyloid deposits in all types of amyloidosis and at all stages of the disease.

Monoclonal antibodies targeting serum amyloid P

The first attempts to develop therapies against all amyloid deposits have focused on serum amyloid P (SAP), a protein

Table 2 Main clinical trials using monoclonal antibodies for the treatment of transthyretin amyloidosis

Clinical trials	Antibody and dose	Study design	Enrolled patients Main inclusion criteria	Main efficacy outcomes	Main safety outcomes
NCT03336580 (terminated, due to the pandemic of COVID-19)	PRX004 Dose escalation in up to 6 dose levels: (0.1, 0.3, 1, 3, 10, and 30 mg/kg) i.v. every 28 days Expansion of previously studied cohort(s) from dose escalation extended dosing at RP2D	Phase I, open label, single group assignment 3 phases: dose escalation phase, expansion phase, long-term extension phase	DE: 21 participants with ATTRv Long-term extension phase: 17 patients	*Primary outcomes* • GLS improvement • *Secondary outcomes* • PK parameters • Immunogenicity indicators	*Primary outcomes* • No drug-related serious AEs
NCT04360434 (recruiting)	NI301A NI301A vs. placebo	Phase I, double-blind, randomized, parallel assignment	42 estimated participants with confirmed diagnosis of ATTRwt/v-CM	*Secondary outcomes* • PK profile	*Primary outcomes* • Treatment emergent AEs and SAEs at 4, 12, additional up to 10 months

AEs, adverse events; ATTRwt/v-CM, wild-type/variant ATTR cardiomyopathy; GLS, global longitudinal strain; PK, pharmacokinetic; RP2D, recommended Phase 2 dose; SAEs, serious adverse events; TEAEs, treatment emergent adverse events.

belonging to the pentraxine family present in all human amyloid deposits, as it binds with high affinity but reversibly to amyloid fibres, inhibiting proteolytic degradation.[14] Miridesap is a small molecule capable of promoting hepatic clearance of circulating SAP, but is unable to induce the removal of amyloid fibrils from tissues. Therefore, the possibility of combining miridesap with anti-SAP mAbs was tested to specifically target the remaining SAP in the deposits, with the aim of destabilizing amyloid fibrils and causing their removal. Dezamizumab is a fully humanized monoclonal IgG1 anti-SAP antibody, capable of binding amyloid deposits and inducing a response from giant multinucleate cells.[15] In a Phase I trial in patients with systemic amyloidosis, the combination miridesap/dezamizumab was well tolerated and was able to improve liver function and reduce the amyloid load evaluated on imaging (SAP scintigraphy and cardiac magnetic resonance) in patients who had received a sufficient dose of antibodies in relation to their initial amyloid load.[15] Patients with cardiac involvement were excluded; however, in an extension of the same study, miridesap therapy was evaluated in six patients with CA, in the absence of evidence of a reduction in cardiac amyloid load.[16] The combination miridesap/dezamizumab was subsequently tested in patients with CA in a Phase II study (NCT03044353), which was terminated prematurely due to an excess of adverse events (mainly skin rashes). Since then, the development of this therapeutic approach has been discontinued.

New therapies of pan-amyloid removal

AT-02 was derived from the fusion of the PAR p5R peptide with an IgG1 antibody. The peptide binds to all amyloid types and has been shown to release the antibody at the site of interest by promoting a phagocytic response to amyloid deposits both *in vitro* and *in vivo* in an AL amyloidosis mouse model.

AT-02 will soon be tested in a Phase I clinical trial (NCT05521022).

AT-03 was obtained by fusion of the SAP protein with a single chain of the Fc portion of an igG1 antibody, which can interact with macrophages by inducing fibril phagocytosis. AT-03 ability to bind AL and ATTR human amyloid deposits has been tested *in vitro* and in murine CA models [data presented at the 13th Congress of the International Society of Amyloidosis (ISA), 2022].

AT-04 is a protein formed by fusion of a PAR peptide to the Fc component of an Ab igG1. It has been shown that this molecule binds with high affinity to AL, ATTR, and cerebral amyloid, inducing a phagocytic response (data presented at the 13th ISA Congress, 2022).

Conclusion

Early treatment of CA, both AL and ATTR, can significantly improve prognosis. However, current therapies can only block the deposition of additional amyloid without removing pre-existing deposits. Monoclonal antibodies offer an alternative mechanism of action compared to standard pharmacological treatments, with the advantage of high selectivity towards amyloid. Monoclonal antibodies directed against plasma cell clones are promising; therefore, daratumumab has already been approved for use in clinical practice. Similarly, Phase II and III trials are currently evaluating the safety and effectiveness of mAbs directed against AL or ATTR amyloid deposits. The production of anti-SAP antibodies, which initially showed promising results, was later stopped because of the suboptimal safety profile. However, a similar approach has been used to develop novel pan-amyloid therapies that could potentially be applied to all types of amyloidosis. Generally, anti-amyloid mAbs are intended as a complementary and synergistic approach to the current therapies for CA. Future studies evaluating combination therapies with drugs that reduce circulating levels of the amylogenic precursor and others that accelerate the amyloid removal from tissues are highly warranted.

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