Nonchemotherapy Treatment of Immunoglobulin Light Chain Amyloidosis

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Keywords
Immunoglobulin light chain amyloidosis · Monoclonal antibody · Daratumumab · Venetoclax · CAEL-101 · NEOD001

Abstract
Immunoglobulin light chain amyloidosis (AL amyloidosis) is a rare, life-threatening disease characterized by the deposition of misfolded proteins in vital organs such as the heart, the lungs, the kidneys, the peripheral nervous system, and the gastrointestinal tract. This causes a direct toxic effect, eventually leading to organ failure. The underlying B-cell lymphoproliferative disorder is almost always a clonal plasma cell disorder, most often a small plasma cell clone of <10%. Current therapy is directed toward elimination of the plasma cell clone with the goal of preventing further organ damage and reversal of the existing organ damage. The standard of care for the treatment of AL amyloidosis is autologous stem cell transplantation, which has been shown to be a very effective treatment in patients with AL amyloidosis, although it cannot be widely applied as patients are often frail at presentation, making them ineligible for transplantation. Treatment with cyclophosphamide, bortezomib, and dexamethasone has emerged as the standard of care for the treatment of AL amyloidosis. Novel anti-plasma cell therapies, such as second generation proteasome inhibitors, immunomodulators, monoclonal antibodies targeting a surface protein on the plasma cell (daratumumab, elotuzumab), and the small molecular inhibitor venetoclax, have continued to emerge and are being evaluated in combination with the standard of care. However, there is still a need for therapies that directly target the amyloid fibrils and reverse organ damage. In this review, we will discuss current and emerging nonchemotherapy treatments of AL amyloidosis, including antifibril directed therapies under current investigation.

Introduction

Immunoglobulin light chain amyloidosis (AL amyloidosis) is a lymphoproliferative B-cell disorder, almost always a plasma cell clone. It is characterized by the abnormal production and extracellular deposition of toxic misfolded β-sheet autologous proteins [1]. This results in fibril deposition of amyloid in tissue and direct toxicity. The most commonly affected organs include the heart, the kidneys, peripheral nerves, and the gastrointestinal tract, leading to significant organ damage [2]. Although over 36 proteins have been described to cause amyloidosis, the most common form is AL amyloidosis due to light chain amyloid formation [3]. It is a rare disease, with approximately 10 cases per million persons per year [4]. Unlike patients with multiple myeloma (MM), the
plasma cell clone and abnormal light chain levels are relatively low in patients with AL amyloidosis [2]. The manifestations of organ dysfunction result as a direct toxic effect of amyloid deposition rather than as a result of CRAB (hypercalcemia, renal failure, anemia, and bone disease) symptoms as seen in patients with MM [2]. The extent of cardiac involvement is the major determinant of overall mortality [5]. N-terminal pro-peptide (NT-proBNP) and cardiac troponin (cTnT), both markers of cardiac injury, correlate with therapeutic response and are predictors of survival [6, 7].

The goal of therapy is to maintain and improve organ function. At present, the available treatments for AL amyloidosis target elimination of the plasma cell clone. Current plasma cell-directed therapies can achieve hematologic control and suppress the production of pathologic light chain precursor proteins. The degree of organ response to plasma cell-directed therapies remains low [8]. Alkylators, proteasome inhibitors (PI), immunomodulatory imides (IMID), daratumumab, and elotuzumab for the treatment of AL amyloidosis have been extrapolated from their use in MM [9]. However, there are differences in the disease biology of MM and AL amyloidosis, making the adaptation of MM regimens a challenge. At present, there are no FDA-approved drugs for the treatment of AL amyloidosis. Imperative to the reversal of organ damage are agents to facilitate the removal of pathological fibril deposits.

Anti-Plasma Cell Therapies

Proteasome Inhibitors

Treatment paradigms for plasma cell disorders have dramatically changed in the last decade, starting with the approval of the first PI, i.e., bortezomib, in 2003 for MM. Bortezomib, carfilzomib, and ixazomib have all been evaluated in patients with AL amyloidosis. In the late 20th century, melphalan-based therapies dominated the treatment landscape of AL amyloidosis, followed by autologous stem cell transplantation when the patient was eligible. After its success in MM, the combination of cyclophosphamide, bortezomib, and dexamethasone (CyBoRd) was investigated in patients with AL amyloidosis. With bortezomib as the backbone to a chemotherapy combination, significantly high rates of response were seen in patients with newly diagnosed and relapsed/refractory AL amyloidosis [10–12]. Therefore, CyBoRd has become the standard of care for patients with newly diagnosed AL amyloidosis. The second-generation PI carfilzomib has been shown to be a safe and effective alternative in patients with peripheral or autonomic neuropathy where bortezomib may not be the ideal choice [13]. In a phase I/II trial of 28 patients with relapsed/refractory AL amyloidosis, a quarter of whom had neuropathy, the overall response rate (ORR) was 63%. The maximal tolerated dose was 36 mg/m² biweekly, which was associated with cardiac, pulmonary, and renal toxicity [14]. Although a hematologic response is seen with both PI, there is concern regarding the use of bortezomib centers around worsening peripheral neuropathy, and carfilzomib worsening cardiac function, resulting in a high discontinuation rate.

Ixazomib is the first orally available second-generation PI. Ixazomib is attractive given the frequency of neuropathy and cardiomyopathy seen in patients with AL amyloidosis. A phase I/II study of ixazomib ± dexamethasone in previously treated patients showed a hematologic ORR of 53, a 45% cardiac response, and a 45% renal response [15]. The phase III TOURMALINE-AL1 (NCT01659658) study was an international, randomized, controlled, open-label, multicenter trial assessing ixazomib in combination with dexamethasone versus physicians’ choice of chemotherapy regimen for patients with relapsed/refractory AL amyloidosis. Patients were randomly selected to receive ixazomib plus dexamethasone, or physicians’ choice of dexamethasone plus melphalan, dexamethasone plus cyclophosphamide, dexamethasone plus thalidomide, dexamethasone plus lenalidomide, or dexamethasone alone. The study did not meet its 2 primary end points of overall improvement of the hematologic response and 2-year vital organ (heart or kidney) deterioration and mortality rates, and the trial was discontinued [16]. However, ixazomib appeared to be most effective in patients not previously exposed to bortezomib. Currently, there are 2 ongoing studies evaluating ixazomib, cyclophosphamide, and dexamethasone in newly diagnosed AL amyloidosis patients (NCT03236792) and ixazomib, daratumumab, and dexamethasone in previously treated AL amyloidosis patients (NCT03283917).

Immunomodulators (IMID)

IMID target the CUL4-RBX1-DDB1-CRBN (CRL4CRBN) E3 ligase and induce the ubiquitination and proteasome degradation of Ikaros family zinc finger proteins, i.e., Ikaros (IKZF1) and Aiolos (IKZF3), which are critical transcription factors for myeloma cell survival [17]. IMIDs also costimulate CD4⁺ and CD8⁺ T cells, suppress regulatory T cells, and enhance NK cell antibody-dependent cytotoxicity [18]. The IMID thalidomide, pomalid-
Treatment of AL Amyloidosis

Elotuzumab

Elotuzumab is an IgG1k immunostimulatory monoclonal antibody targeting the signaling lymphocytic activation molecule F7 (SLAMF7). It received FDA approval in 2015 for patients with relapsed/refractory MM in combination with lenalidomide and dexamethasone. Its mechanism of action is mainly via NK-cell-mediated ADCC. Elotuzumab standard dosing is administered intravenously at 10 mg/kg every week in the first two 28-day cycles and every 2 weeks subsequently [29]. Its efficacy is now being assessed in AL amyloidosis. In a single case report, elotuzumab in combination with lenalidomide and dexamethasone showed activity in a patient with heavily pretreated MM and AL amyloidosis [30]. The patient achieved both hematologic and organ responses. An ongoing phase II trial using lenalidomide, dexamethasone, and elotuzumab ± cyclophosphamide in patients with relapsed AL amyloidosis is underway, with the primary outcome of major hematologic response (NCT03252600).

**Daratumumab**

Daratumumab is a humanized monoclonal antibody targeting an epitope on CD38. Its action in elimination of the plasma cell clone is via antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity [31]. Its activity in AL amyloidosis was demonstrated in a retrospective single-institution study of 25 patients with relapsed/refractory AL, with a hematologic ORR of 76%, with minimal toxicities [9]. The efficacy of daratumumab in relapsed/refractory AL was assessed further in 2 phase II studies. The first study showed an ORR rate of 63% and a decrease in dFLC of more than 30% after a single dose in responding patients [32]. In the subsequent trial, a hematologic response rate of 86% was seen, with a median of 3 months to the best hematologic response. Renal and cardiac responses occurred in 67 and 50% of the patients [33]. In one of the largest retrospective studies using daratumumab in AL amyloidosis, 72 patients with previously treated AL amyloidosis received daratumumab + dexamethasone. The 2-year overall survival was 86.9% (median OS not reached) and the 2-year time to next treatment or death (TTNT)- free survival was 62% (the median TTNT was not reached). Forty of 52 (77%) evaluable patients achieved a hematologic response, with >60% achieving a VGPR or better. The median time to hematologic response was 1 month. Of the 57 patients (79%) with cardiac involvement, 55% of evaluable patients achieved a cardiac response. This was associated with an improvement in OS. Of the 47 patients (65%) who had renal involvement, 52% of the evaluable patients achieved a renal response [34]. This study highlights the efficacy of daratumumab in achieving hematologic and organ responses.

Adverse events of note included neutropenia, which was noted in 73% of the patients. The most common nonhematologic adverse event was fluid overload, cardiac arrhythmia, renal dysfunction, and anemia, occurred in 35% of the patients [28]. Because of the significant dose-limiting cardiac and renal toxicities, IMiDS are not recommended in the upfront setting and should only be used in select cases without cardiac involvement.

The combination of ixazomib, lenalidomide, and dexamethasone was studied in 40 patients with newly diagnosed AL amyloidosis. The majority of the patients had cardiac involvement. The hematologic ORR was 88% and the organ ORR was 35% (likely underestimated) [26], showing the combination of an IMiD and PI to be effective. In the phase II study investigating lenalidomide and dexamethasone in AL amyloidosis, 34 patients, newly diagnosed and pretreated, received lenalidomide at 25 mg for 21 days of a 28-day cycle. There was an amendment to the protocol due to several patients requiring a dose reduction following the first 2 cycles. Subsequent patients received lenalidomide at 15 mg for 21 days of a 28-day cycle [21]. An interim analysis of this study showed treatment with lenalidomide to be associated with worsening renal function, specifically in those with advanced age, greater urinary protein excretion, and underlying renal amyloidosis at baseline. There was no relationship between baseline eGFR and development of renal dysfunction after initiation of lenalidomide [27]. In the same study, there was also a notable increase in BNP of >30% in most of the enrolled patients. In other studies, a worsening cardiac function was noted to be the most common nonhematologic adverse event when using a lenalidomide chemotherapy combination [22, 23]. The combination of ixazomib, lenalidomide, and dexamethasone was evaluated in 40 patients with relapsed AL amyloidosis. Best hematologic responses occurred in 5.6 and 13.3% of the cases, cardiac and renal responses occurred in 17.9% and 13.3% of the cases, respectively. Serious adverse events, including infection, fluid overload, cardiac arrhythmia, renal dysfunction, and anemia, occurred in 35% of the patients [28]. Because of the significant dose-limiting cardiac and renal toxicities, IMiDS are not recommended in the upfront setting and should only be used in select cases without cardiac involvement.

**Elotuzumab**

Elotuzumab is an IgG1k immunostimulatory monoclonal antibody targeting the signaling lymphocytic acti-
The safety and efficacy data of the run-in period of the phase III ANDROMEDA study, examining the combination of subcutaneous daratumumab + CyBorD versus CyBorD in newly diagnosed AL amyloidosis (NCT03201965), was presented at the 24th Congress of the European Hematology Association [35]. Twenty-eight patients received 1,800 mg of DARA subcutaneously weekly for cycles 1 and 2, every 2 weeks for cycles 3–6, and every 4 weeks thereafter for ≤2 years in combination with CyBorD. Fifty-four and 61% of the enrolled patients had cardiac and renal involvement, with 21% being Mayo cardiac stage IIIA at screening. The overall hematologic response rate was 96%, with 83% achieving a VGPR or better. Ten patients (36%) achieved a CR, and an additional 5 patients (18%) achieved a CR based on negative serum and urine immunofixation. At the time of data cutoff, all patients achieving a CR continued to respond and the median duration of CR was not reached. The median time to the first response was 23 days. Enrollment of the randomized portion of the study is completed and data are expected soon.

**Venetoclax**

Venetoclax (VCL) is a selective oral small-molecule BCL-2 inhibitor approved by the FDA for use in chronic lymphocytic leukemia and acute myeloid leukemia. It has been shown to have activity as monotherapy and in combination with bortezomib and dexamethasone for the treatment of MM, particularly in disease harboring t(11;14) [36,37]. Approximately 60% of patients with AL amyloidosis harbor this translocation [38], making BCL-2 a target worthy of examination in this population. Preliminary evidence of efficacy of VCL in relapsed/refractory AL amyloidosis has been shown in case reports [39,40]. In 1 case report, a 73-year-old patient with AL amyloidosis initially achieved a VGPR with bortezomib, melphalan, and dexamethasone before experiencing disease progression. Over the next 7 years the patient achieved transient responses to bendamustine, ixazomib, CAEL-101 (chimeric fibril-reactive monoclonal antibody 11-1F4), carfilzomib, lenalidomide, pomalidomide, and daratumumab but experienced disease progression. Repeat bone marrow biopsy showed t(11;14) in 28% of plasma cells. The patient was initiated on VCL at 400 mg daily, bortezomib at 1.3 mg/m², and dexamethasone at 10 mg weekly and achieved a CR after 2 cycles. Eleven months later, the patient remained in CR after receiving only 2 cycles of treatment. The second patient not harboring t(11;14) with heavily pretreated AL amyloidosis with cardiac and skin involvement achieved a CR after 17 days of treatment [37]. One monocentric retrospective analysis of 8 patients with relapsed/refractory AL amyloidosis with cardiac involvement showed the use of VCL alone or in combination to be promising in patients with t(11;14) [41]. In a systematic retrospective multicenter analysis of relapsed/refractory AL amyloidosis in 24 patients, VCL-containing regimens were shown to be highly efficacious, with manageable toxicities. The ORR for all patients was 75%. For those harboring t(11;14), the ORR was 86.7% and non-t(11;14) patients had an ORR of 55.6% [42]. A phase I trial (NCT03000660) examining VCL and dexamethasone in relapsed AL amyloidosis has been suspended due to interim data from the BELLINI trial (NCT02755597), i.e., VCL-bortezomib-dexamethasone in relapsed and refractory MM patients resulted in an increased risk of death in the VCL arm (21.1%) compared to the control arm (11.3%).

**Anti-Amyloid Fibril Therapies**

**NEOD001**

NEOD001 is no longer in development for the treatment of patients with AL amyloidosis, but deserves mention. It is a humanized IgG1k monoclonal antibody directed against an epitope on amyloid fibrils that binds with a high affinity in a conformation dependent manner to misfolded light chains. It was originally developed for the treatment of AA amyloidosis. During the deposition of AA amyloid, the sAA precursor protein undergoes proteolytic cleavage, exposing the C terminal amino acid sequence Ala-Glu-Asp-Ser. The antibody binds with a high specificity to this site on the amyloid protein [43]. The AL amyloid protein has a similar C-terminal amino acid sequence, and the murine antibody 2A4 has been shown to bind AL κ and λ amyloid tissue samples [44]. The proposed mechanism by which NEOD001 decreases the amyloid burden is neutralization of soluble light chain aggregates and clearance of the aggregates and insoluble fibrils via macrophage signaling and phagocytosis [45].

Patients with previously treated AL amyloidosis and a partial hematologic response or better but with persistent organ dysfunction were enrolled into a phase I/II clinical trial using the humanized 2A4 antibody NEOD001 as a single agent [46]. The best cardiac and renal response rates in evaluable patients were 53 and 63%, respectively [47]. The conclusion was that NEOD001 is safe, well tolerated, and shows promising cardiac and renal responses in patients with AL amyloidosis. Based on this data, 2 phase Ib studies in previously treated patients with a hematologic response with persistent cardiac (PRONTO NCT02632786) and renal (RAIN NCT03168906) dys-
function were designed. The phase III VITAL study compared NEOD001 with placebo in newly diagnosed patients receiving a PI (NCT02312206). The PRONTO study failed to meet its primary and secondary endpoints. Based on this, an interim futility analysis was done on the VITAL study, and it was terminated. Development of NEOD001 and all studies were discontinued [48]. The reason for the lack of a difference between NEOD001 and placebo in these trials is not completely clear. Perhaps it is the fact that NEOD001 was originally developed for the treatment of AA amyloidosis and its C terminal bears imperfect homology to light chain amyloid [43]. Furthermore, the antibody was brought into clinical testing based on limited mice data showing cross-reactivity of the antibody to AL amyloidosis [45]. Lastly, imaging studies showing in vivo binding of NEOD001 to amyloid deposits was not performed [59].

A recent post hoc analysis of the VITAL study showed a significant benefit in patients with stage IV cardiac involvement, those at the highest risk for early mortality, and those treated with NEOD001 compared with placebo [50]. More recently, the anti-plasma cell antibody, i.e., daratumumab, in combination with NEOD001 showed more rapid hematologic and organ responses compared to treatment with daratumumab alone [51].

Monoclonal Antibody 11–1F (CAEL-101)

CAEL-101, formerly known as 11-1F4, is an IgG1k monoclonal antibody that binds directly to the conformational epitope present on human light chain amyloid fibrils, regardless of the κ or λ isotype [52]. CAEL-101 has been shown to lead to neutrophil chemotaxis and activation, causing Fcy receptor-mediated opsonization and proteolysis of deposited amyloid fibrils, leading to reversal of AL amyloidomas in mice models [53]. Confirmation of its specificity for amyloid was demonstrated when I-124-labeled 11-1F4 was visualized in amyloid-laden organs on PET/CT imaging in human subjects [52]. CAEL-101 was evaluated in a phase Ia/b trial in patients with relapsed/refractory AL amyloidosis [54]. In phase 1a, 63% of the evaluable patients demonstrated an organ response after the first infusion, and 61% of the evaluable patients showed an organ response in phase 1b. The median time to response was 2 weeks after the initiation of treatment, with faster responses seen at higher doses. There were no grade 4 or 5 drug-related events or dose-limiting toxicities. The organ response was independent of the light chain type. Cardiac function, as evaluated by global longitudinal strain (GLS) and NT-proBNP, showed that, of the 10 patients who received CAEL-101, nine had improvement in GLS (Fig. 1a). Patients without cardiac involvement had an unaffected GLS (Fig. 1b). Improvement in GLS correlated with improvement of NT-proBNP in the phase 1b study [55].

A phase II multicenter, open label, sequential cohort, dose escalation study of CAEL-101 in combination with CyBorD in patients with newly diagnosed AL amyloidosis with Mayo stage I-IIIA is anticipated (NCT04304144). The primary objective is the safety and tolerability of CAEL-101. The study will employ a 3 + 3 dose escalation design (cohort 1, dose of 500 mg/m²; cohort 2, dose of 750 mg/m²; and cohort 3, dose of 1,000 mg/m²). CAEL-101

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**Fig. 1.** The mean GLS at screening was $-15.58 \pm 4.14\%$ in patients with cardiac amyloidosis vs. $-22.77 \pm 3.12\%$ in patients without cardiac amyloidosis. **a** The mean GLS improved significantly in 9 out of 10 patients with cardiac involvement, i.e., from $-15.58 \pm 4.14\%$ at screening to $-17.37 \pm 3.53\%$ at week 12 ($p = 0.004$). **b** There were no changes in GLS in patients without cardiac involvement (mean GLS: $-22.77 \pm 3.12\%$ at screening and $-22.36 \pm 3.02\%$ at the end of treatment).

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![Graph showing GLS improvement](image-url)
will be administered weekly for the first 4 weeks, and then every other week until the end of the study in combination with the standard of care, i.e., CyBorD.

**Anti-Serum Amyloid Protein Antibody**

Serum amyloid protein (SAP) is a nonfibrillary glycoprotein that circulates in the human serum, and it is also bound to the amyloid protein, protecting it from proteolysis [56]. Imaging of patients with amyloidosis using radioactive iodine-labeled SAP shows a high sensitivity and specificity for the detection of AL and AA amyloidosis [57]. Miridesap (previously CPHPC) is a small molecule that binds with a high affinity to human SAP and leads to significant clearance of SAP from the serum [58]. Its ability to remove SAP-bound amyloid from tissue is limited. Dezamizumab is a fully humanized monoclonal IgG1 Ab that binds to SAP-bound amyloid and has been shown to lead to resorption of amyloid in tissues [59]. In a phase I clinical trial using the combination of miridesap and dezamizumab for systemic AL amyloidosis, organ response was seen as evidenced by a decrease in liver stiffness, extracellular volume, and SAP scintigraphy in patients who received more than 200 mg of dezamizumab [60]. Based on these results, a phase II trial in patients with cardiac amyloidosis was initiated (NCT03044353); however, it was prematurely terminated due to an apparent change in the risk-benefit profile of the therapy.

**Doxycycline**

The antibiotic doxycycline has been shown to interfere with amyloid fibril formation [61]. The theory is overproduction of members of the matrix metalloproteinases can result in AL renal and cardiac damage [62], and tetracyclines possess the ability to inhibit members of the matrix metalloproteinases endopeptidases. A retrospective analysis compared 30 patients with cardiac AL amyloidosis who received doxycycline in addition to standard chemotherapy with age- and disease-matched controls who received only chemotherapy. Responses were superior in the doxycycline group (hematologic response rate, 93 vs. 59%; cardiac response rate, 60 vs. 18%; and survival rate at 12 months, 82 vs. 53%) [63]. In an open-label, single-center, phase II pilot trial (DUAL NCT02207556), patients with newly diagnosed AL amyloidosis were treated with doxycycline at 100 mg orally twice daily in conjunction with chemotherapy at the physicians’ discretion. Among the 25 patients with systemic AL amyloidosis, the hematologic ORR was 100% in patients surviving at 1 year; the rate of early mortality was 20%, and 60% of the patients went on to receive melphalan-based autologous stem cell transplantation [64]. There was also improvement in QoL in the physical and mental domains.

Another prospective study looking at doxycycline in AL amyloidosis is comparing doxycycline to standard supportive therapy in newly diagnosed cardiac AL amyloidosis patients being treated with bortezomib-based therapy (NCT03474458).

**Conclusion**

The outcomes in AL amyloidosis remain poor due to a delay in diagnosis, poor organ function, and a poor performance status. With the available myeloma therapies to suppress the plasma cell clone, hematologic response rates have improved, but with a lag in organ response. There remains an unmet need for novel anti-amyloid therapies that can reverse organ impairment. Ongoing research will hopefully bring therapies that can accelerate the removal of amyloid fibrils from tissues. Although the premature termination of NEOD001 was disappointing, the post hoc analysis of the phase 3 VITAL study showed a benefit in all-cause mortality in patients with stage IV cardiac amyloidosis. This suggests that patients at the highest risk of early mortality may benefit from NEOD001, especially in combination with daratumumab. The development of the anti-SAP Ab dezamizumab was prematurely terminated due to an apparent change in the risk-benefit profile of the therapy. Further details were not provided by the developer. At present, the most promising anti-amyloid Ab, i.e., CAEL-101, is currently being tested in a phase III clinical trial. More robust data from phase III clinical trials are needed to determine the role of doxycycline as an anti-amyloid treatment.

**Author Contributions**

Layla Van Doren and Suzanne Lentzsch contributed equally to the design, acquisition and interpretation of data, and writing of this paper.

**Disclosure Statement**

Suzanne Lentzsch reports leadership in Caelum Biosciences; stock and other ownership interests in Caelum Biosciences; a consulting or advisory role in Janssen, Caelum Biosciences, Sanofi, and Amgen; a speakers’ bureau role in PeerView; patents, royalties, other intellectual property (patent 11-1F4 mAb for use in AL amyloidosis); and membership of the Data Safety Monitoring Board for Sorrento and Celularity.
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