Review

Future Developments in the Treatment of AL Amyloidosis

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Abstract: The treatment of AL amyloidosis has evolved, and outcomes have improved, but primarily for patients with low or intermediate-risk disease. Recent advances have been limited to improvements in anti-clonal therapies, which, alone, cannot change the poor prognosis of patients with high-risk disease. Thus, new strategies are needed that combine different approaches to the treatment of the disease. Targeted therapies against plasma/B-cell clones that avoid chemotherapy or potentially cardiotoxic drugs may improve the depth of hematologic responses and reduce complications. Amyloid fibril and light-chain oligomer targeting may reduce direct toxicity and enhance tissue clearance. Future combinations should be tailored to clone characteristics and specific amyloid properties, but early identification of those at high risk to develop AL amyloidosis will also be integrated into management algorithms.

Keywords: amyloidosis; non-transplant chemoimmunotherapy in AL amyloidosis; amyloid-fibril targeting therapy in AL amyloidosis

1. Introduction

AL amyloidosis is a multisystemic hematological disorder which is characterized by the presence of a usually small, more often plasma cell and less lymphoplasma/lymphocytic clone. Immunoglobulin-free light chains (FLCs) are produced from clonal plasma cells, which have unique physicochemical characteristics that cause them to misfold and eventually form amyloid cross β-fibrils. The amyloid fibrils deposit in target organ tissues and cause progressive organ failure [1].

The rationale behind the current approach to the management of the disease has been to target and eliminate the light-chain producing plasma cell clone, adopting and adapting the anti-clonal agents originally developed for multiple myeloma (MM) (Figure 1). As the therapeutic field in MM has developed exponentially over the past years, the use of anti-clonal agents, in a risk-adapted manner has led to outcome improvements in AL patients. In a recent single-center review, two-year survival increased to 60% over the 2010–2014 period compared with 42% over 2000–2004 [2]. Despite the increased efficacy and safety of novel anti-clonal therapies, the benefits have fallen short for patients at the highest risk [3]. Managing patients with high-risk disease features, with the major determinant being the presence of advanced cardiac disease at diagnosis, remains a challenge. Achieving a hematological response via the elimination of the plasma cell clone is necessary but not enough. Organ function improvement is required to alter the disease course and improve outcomes across all risk categories. Agents that target and effectively clear the amyloid deposits allowing organ dysfunction reversal are therefore necessary. In addition, we need new anti-clonal agents that can overcome resistance and can act synergistically. The review will provide an overview of anti-clonal and anti-amyloid agents in clinical development and will lay out a potential future version of the treatment landscape in AL amyloidosis.
Figure 1. Actionable cellular molecules and signaling pathways to target plasma cells in AL amyloidosis. Created with BioRender.com (accessed on 3 January 2022).

2. Therapies Targeting the Plasma Cell Clone

2.1. Current Treatment Algorithm

The combination of Daratumumab, Cyclophosphamide, Bortezomib, Dexamethasone (Dara-VCd) is currently the novel and preferred standard of care for newly diagnosed patients with AL amyloidosis and the only Food and Drug Administration (FDA) and EMA-approved treatment for this disease. This approval was based on the results of the recent phase III randomized control trial ANDROMEDA [4] which compared VCd to Dara-VCd and demonstrated substantial improvement in complete hematologic response rates without new safety concerns. After a median follow-up of 20.3 months, the hematologic CR rate was 59% in the daratumumab group vs. 19% in the control group, and at least VGPR was seen in 79% vs. 50%, respectively [5]. At six-month landmark analysis, the CR rate was 49.7% in the Dara-VCd vs. 14% in the VCd group, the cardiac response rate was 41.5% vs. 22.2% and the renal response rate was 53% vs. 23.9%, respectively. At the 12-month landmark, organ responses improved further (57% vs. 28% and 57% vs. 27%, respectively), which is most likely attributed to the depth and rapidity of hematologic response. Adverse events were consistent with the daratumumab and VCd safety profiles and the most common grade 3–4 AEs were lymphopenia, pneumonia, cardiac failure, diarrhea, syncope, and peripheral edema [4]. Due to the exclusion of patients with stage 3B disease from Andromeda, Dara-VCd has not been approved for patients with such high-risk disease. However, if daratumumab is not available or accessible, alternative options include VCd [3], Bortezomib-Melphalan-dexamethasone (BMdex) [6], or bortezomib plus dexamethasone [7]. BMDex has been shown to also improve overall survival over Mdex.
in a randomized study, however, stage 3B patients were also excluded from this study. Mdex alone [8] or IMiD-based therapy (lenalidomide-based mostly) may be an option for special patients.

A significant proportion of patients will not achieve a sufficiently deep hematologic response with first-line treatment, or the disease will relapse. There is no consensus currently regarding the optimal time point and circumstances under which salvage therapy should be initiated [9,10]. The patient should be carefully evaluated and previous exposure and refractoriness to daratumumab and bortezomib are critical for the choice of salvage therapy; prior high dose therapy with ASCT or current eligibility for ASCT are also important considerations. If patients had not had previous exposure to daratumumab, a daratumumab-based combination should be opted for. Response rates, including CR, were high (63–100%) in heavily pretreated patients who received daratumumab monotherapy [11] and organ responses were relatively high [12]. Daratumumab can be administered in combination with bortezomib but also immunomodulatory (IMiDs) agents which have significant anti-clonal plasma cell activity. IMiDs are considered currently mostly as rescue therapy as they can overcome resistance to alkylating agents and PIs. In a pooled analysis of IMiDs-based trials, 39% of relapsed patients with AL achieved VGPR or better, and the responders had prolonged OS and PFS [13]. Lenalidomide induces hematologic responses in 41–67% of relapsed patients, with CR and VGPR in up to 29% and 20%, respectively [14–18]. Pomalidomide is active in patients refractory to lenalidomide, and several studies have demonstrated rapid and durable hematological responses in 48–68% of patients [19–21]. Patients previously exposed to bortezomib can still have clinical benefits with ixazomib, an oral PI, as salvage therapy [22]. In a retrospective series, the combination of ixazomib with lenalidomide and dexamethasone also appears to induce deep responses in 47% of relapsed AL patients [23].

Treatment of patients who are failing to achieve a deep hematologic response or who relapse after first-line therapy remains challenging. The use of daratumumab as part of primary therapy also generates new challenges for the management of clonal disease in the relapsed or refractory setting.

2.2. IgM-Amyloidosis

AL amyloidosis is caused by an underlying B-cell lymphoproliferative/lymphoplasmacytic clone (usually Waldenstrom Macroglobulinemia [WM]) that secrete an intact IgM in 5–7% of cases [24]. Treatment combinations designed for non-IgM AL amyloidosis have been tested with unsatisfactory results. ASCT and Rituximab-based combinations with bortezomib or other chemotherapeutic agents have elicited ORR of 43–73% with low rates of deep responses and unsatisfactory organ responses up to 15% in some series [25]. Among IgM-related AL amyloidosis patients about 71% harbor the somatic mutation L265P in the MYD88 gene [26]. The introduction of Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor has correlated with impressive results in WM patients. However, our experience in IgM-related AL amyloidosis has been disappointing. In the first report, eight patients received ibrutinib, two patients achieved hematologic response (1 VGPR, 1 PR) and one patient achieved an organ response. Ibrutinib was ill-tolerated with edema and neuropathy being the most common AEs, while two patients developed atrial fibrillation and one patient experienced a transient ischemic attack [27]. In this population that is at risk for cardiac complications, ibrutinib should be considered for meticulously selected patients. Future management of IgM-related AL amyloidosis could also include a number of anti-CD20 and anti-CD19 CAR T-cells and BiTEs that are currently under evaluation for other low-grade lymphomas. The rarity of this distinct clinical entity makes the management challenging and the design of prospective clinical trials difficult.

2.3. Clonal Characteristics of Plasma Cells and BCL2 Inhibition

A significant proportion of patients with AL amyloidosis harbors cytogenic abnormalities and future therapies are expected to be adapted to the clonal characteristics of
the amyloidogenic plasma cells. Translocation t(11;14) is the most common, seen in about 40–60%, followed by hyperdiploidy [28]. Alternative therapeutic strategies are warranted for patients that harbor t(11;14) as they display inferior responses to bortezomib and immunomodulatory-based regimens [29]. Hyperdiploidy has also been confirmed as a poor prognostic factor. One-fourth of patients will have gain/amplification of 1q21 and with worse outcomes when treated with melphalan [30] and probably show inferior outcomes to daratumumab-based therapy [28]. Translocation t(11;14) is associated with increased dependence to B-cell lymphoma 2 (BCL-2) family of proteins which regulate apoptosis. The development of novel small-molecule inhibitors of the major pro-survival proteins from the apoptosis-regulating bcl-2 family, called “BH3 mimetics” has created a great therapeutic opportunity. Patients who harbor t(11;14) are more likely to respond to BCL-2 inhibitors such as venetoclax [31,32]. Venetoclax is an oral selective BCL-2 inhibitor that induces cellular apoptosis and is effective in patients with myeloma, particularly those with t(11;14). Siddiqui et al. reported a retrospective series of 12 patients [11/12 had t(11;14)] with relapsed AL treated with venetoclax-based regimens. The dose of venetoclax was 400–800 mg/d, and seven (58%) patients received it alone or in combination with dexamethasone. The hematologic response was evaluable in eight patients (67%) with an overall HR rate of 88%; four patients achieved CR, one patient was MRD negative, and three patients had VGPR. The median time-to-response was 3.4 months. One in four patients with cardiac involvement achieved a cardiac response at three months, and two of six patients with renal involvement achieved a renal response at 10 and 16 months, respectively [33]. Another retrospective study with 43 patients with relapsed/refractory AL showed that patients with t(11;14) had a higher overall hematologic response rate (81% vs. 40%), higher CR/VGPR rate (78% vs. 30%), high rate of organ responses (83% vs. 17%) and reduced risk for progression or death (HR: 0.292 95% CI: 0.046–1.855, $p = 0.192$) [34]. Toxicity was minimal in both studies, with the most common grade 3 or higher adverse events being infections and thrombocytopenia, but to a lesser extent than observed in MM studies.

Combining venetoclax with proteasome inhibitors [35] and monoclonal antibodies (daratumumab) [36] has demonstrated improved responses in MM patients but at the expense of toxicity. The alarming safety signals require further follow-up before similar studies in patients with AL amyloidosis are designed. Several novel selective BCL-2 inhibitors are currently under evaluation in preclinical and early phase I studies (BGB-11417, S65487, S55746, APG-2575 and FCN-338) [37]. In patients with relapsed or refractory chronic lymphocytic leukemia (CLL) and other hematologic malignancies, including MM and WM, APG-2575 (lisftoclax) was well tolerated, with no laboratory or clinical evidence of tumor lysis syndrome (TLS), and it showed ORR of 85.7% [38]. A phase Ib/II clinical trial that combines lisftoclax with pomalidomide and/or daratumumab in MM and AL amyloidosis has initiated recruitment in 2021 (NCT04942067). Another dose-escalation and cohort-expansion study is evaluating the safety and efficacy of BGB-11417 in combination with carfilzomib and dexamethasone in RRMM patients (NCT04973605). In patients with relapsed/refractory AL amyloidosis a study with a novel selective BCL-2 inhibitor, ZN-d5 (NCT04500587), is also anticipated to start in 2022.

Two other pro-apoptotic proteins in the BCL2 family, BCLXL and MCL1, have been reported to be expressed in MM [39–41]. Increased BCLX1 and MCL1 expression have been associated with worse outcomes and disease progression. Clonal plasma cells seem to be MCL1 dependent and MCL1 inhibitors are likely to be effective in a broader range of patients with clonal plasma cell disease [not only those with t(11;14)] [42]. The importance of MCL1 in myeloma cell survival was first established with the use of antisense oligonucleotides to knockdown MCL1 which results in myeloma cell death [43]. There are currently five MCL1 inhibitors in early clinical trials, S64315 (MIK665), AZD5991, AMG176, AMG397, and ABBV467. MM is amongst the most sensitive cell types to these MCL1 inhibitors both in vitro and in vivo with responses seen beyond t(11;14) myeloma [44–46]. However, there is a risk of cardiac toxicity associated with AMG397, as confirmed in a phase I trial, leading
to a temporary hold of AMG397 and AMG176. BCLXL inhibition is associated with significant thrombocytopenia due to platelet dependence of BCLXL. BCLXL inhibitors continue to be developed but none has entered clinical development yet. A dual BCL2/BCLXL inhibitor, AZD4320, is however being studied in MM (NCT04214093) [47].

What is necessary for all these drugs is an understanding of the biology that drives the heterogeneity in BCL2 dependence of the clonal plasma cell. This is likely influenced by both intrinsic factors (tumor-specific genetics and metabolism) and extrinsic parameters such as the microenvironment.

Multiple myeloma and AL amyloidosis are related plasma cell disorders but the extent of apoptotic dependencies in AL amyloidosis is likely to differ to a considerable extent and needs further exploring. In addition, the toxicity profile of BCL2 inhibitors in the AL amyloidosis population is also likely to be different. Unfortunately, the clinical development of BCL2 inhibitors, including venetoclax, in AL amyloidosis has been slow, despite the very encouraging clinical observations, due to concerns for infectious complications that were recorded on the clinical trials in MM patients. Despite these delays, this drug class may become a major option for patients with AL amyloidosis in the near future.

2.4. Antibody Drug Conjugates

Antibody–drug conjugates consist of a tumor-specific monoclonal antibody connected to a small cytotoxic molecule with a chemical linker [48]. Following the binding of the antibody–drug conjugate to the tumor antigen, it is internalized leading to the release of the small cytotoxic molecule, tumor cytotoxicity, and cell death.

Belantamab Mafodotin

B-cell maturation antigen (BCMA) is a transmembrane glycoprotein, non-tyrosine kinase receptor expressed on the surface of late memory B-cells and plasma cells. Belantamab mafodotin (GSK2857916) is a first-in-class, anti-BCMA immunoconjugate with humanized IgG1 anti-BCMA monoclonal antibody conjugated by a protease-resistant linker to auristatin F (MMAF), a microtubule disrupting agent. It has shown very promising activity in heavily pretreated MM patients. In a phase I trial, patients with RRMM achieved an ORR of 60% and median PFS of 12 months with a median duration of response of 14.3 months and in phase II trial of 196 patients with MM who were refractory to an IMiD, a PI and had prior exposure to an anti-CD38 antibody, the ORR was 33% [49]. The most common grade 3 or 4 adverse events in the MM population are keratopathy, thrombocytopenia, and anemia [49].

Clonal amyloidogenic plasma cells seem to have a different profile in terms of BCMA expression. In one study, clonal plasma cells of patients with AL amyloidosis were found to express high BCMA levels (median BCMA expression at diagnosis 80% and at time of relapse 75%) [50]. Another study showed that median membrane-bound BCMA on CD138+ cells was 39%. Serum BCMA levels seem to correlate with bone marrow plasma cell percentage and involved free light-chain levels, suggesting that it may serve as a dynamic marker of the disease [51]. C-secretase, a protease, sheds mBCMA into plasma. LY-411575 is a c-secretase inhibitor. In vitro, when AL plasma cell lines are exposed to LY-411575, mBCMA expression increases significantly pointing to the therapeutic potential of c-secretase inhibition in order to enhance anti-BCMA immunotherapies [52].

Given that AL is caused by a relatively indolent clone and that anti-BCMA therapy is not targeting organs that are involved in AL amyloidosis, belantamab mafodotin could be a new treatment option for relapse setting. A phase II study is currently recruiting patients with RR AL amyloidosis who receive therapy with belantamab at 2.5 mg/kg every six weeks for a maximum of eight cycles (NCT04617925).

Other ADC currently in the early stages of clinical development in patients with MM are lorvotuzumab mertansine [IMGN901] against CD56, milatuzumab doxorubicin (hLL1-DOX) against CD74 and indatuximab ravtansine [BT062] [53]. They are being investigated as monotherapy or combination treatments with other anti-myeloma agents. It is
still early to assess whether these agents could be evaluated for the treatment of patients with AL amyloidosis.

2.5. Bispecifics Active in MM also Relevant in AL Amyloidosis

Immunotherapy with bispecific antibodies and chimeric antigen receptor T (CAR-T) cells has yielded promising results in MM and are currently being evaluated in AL amyloidosis. Bispecific antibodies have two distinct antigen-recognition domains in one molecule and can inhibit simultaneously multiple signaling pathways or redirect immune cells to the tumor via the expression of T-cell or natural killer (NK) cell-activating receptors. BiTEs (bispecific T-cell engagers) target an epitope on MM-cells and a T-cell antigen (usually CD3). They activate and stabilize the immunologic synapse leading to myeloma cell lysis and death. Most BiTEs developed for use in MM target BCMA and CD3 but others that target CD38 and CD3 or BCMA and the NK-cell antigen CD16a are also in clinical development [54–57].

BI836909 (AMG420) is a BCMA/CD3 BiTE. In phase 1, the first in human, dose-escalation study, AMG420 was administered in a six-week cycle consisting of four weeks of continuous IV infusion followed by two weeks off treatment. Serious AEs included mostly infections and CRS. At the maximum tolerated dose (MTD) (10 patients who received this dose), ORR was 70% and MRD-negative rate was 50% with a median duration of response of nine months [58]. PF-3135 is another humanized IgG bispecific monoclonal antibody targeting both BCMA and CD3 which has been assessed in a phase I dose-escalation study [59]. CC-93269 is an asymmetric humanized two-arm IgG T-cell engager (TCE) that binds monovalently to CD3 and bivalently to BCMA of myeloma cells (BCMA 2 + 1 TCE). Nineteen patients with MM were included in the dose-escalation study, ORR was 83.3% and 89.5% experienced CRS which were mostly grade 1 or 2 [60].

G-protein-coupled receptor family C group 5 member D (GPRC5D) is highly expressed in myeloma cells. Talquetamab is a first-in-class dual-targeting antibody which targets GPRC5D and CD3. A phase I study in heavily pretreated patients recommended the dose of 405 µg/kg SC every two weeks. In 157 patients with RRMM, ORR was 78% for the IV dosing and 67% for SC dosing [61]. The most common grade 3–4 AEs were anemia, neutropenia, lymphopenia. Cytokine release syndrome (CRS) was seen in 47% of patients but only 8% were grade 3–4. Treatment-related neurotoxicity was reported in 5% of patients.

Cevostamab is a dual-targeting antibody targeting Fc receptor homolog 5 (FCRH5) and CD3. FCRH5 is expressed on B-cells, plasma cells, and almost 100% of myeloma cells. Data from the single step-up dosing cohort of the phase I study in heavily pretreated MM patients [62] were presented in ASH 2020. At the time of data cut-off, 46 patients were evaluable for efficacy; responses were observed in 51.9%. The most common AE was also CRS which was Gr 1–2 in 72.5% of patients and Gr3 in 2%. Other AEs reported were neutropenia, lymphopenia, thrombocytopenia, and an increase in aspartate aminotransferase.

Dual-targeting antibody/bispecific antibodies that have been developed show very high anti-clonal plasma cell activity. However, their introduction in the treatment of AL amyloidosis may be more difficult than in myeloma, since patients with AL amyloidosis may be vulnerable to complications such as CRS and neuropathy. Another approach could include bispecific antibodies that target amyloid fibril antigens and macrophages at the same time, inducing enhanced cell-mediated phagocytosis of the amyloid fibrils. Such antibodies are in preclinical development.

2.6. Chimeric Antigen Receptor (CAR) T-Cells

CAR-T cells are genetically engineered T-cells with a recombinant T-cell receptor derived from the antigen recognition portion of a monoclonal antibody combined with T-cell receptor domains and co-stimulatory domains. These engineered T-cells recognize tumor antigens and subsequently activate the cytotoxic machinery of the T-cell, causing tumor cell death [63]. They have emerged as potent treatment strategies against B-cell neoplasms with impressive outcomes but challenging safety profiles [64–66]. Two CD19-targeting
CAR T-cell products gained FDA approval in 2017 for acute lymphoblastic leukemia and certain subtypes of large B-cell lymphomas [64,66]. The majority of CAR-T cells in clinical development for patients with MM act against BCMA. Several clinical trials with diverse BCMA-CAR T-cell constructs in RRMM patients are currently underway and results are promising [59,67]. The CAR-T product idecapsengene cicleucel (ide-cel) has been evaluated in a phase 1 and a phase 2 study with high rates of deep response (ORR was 73–85% with 33–45% CR, and most MRD negative) [68]. Ciltacabtagene autoleucel (cilta-cel), is based on bi-epitopic BCMA targeting [69] and in a phase 1b/2 study in myeloma patients with three or more prior lines or refractory to a PI and an IMiD and anti-CD38 (n = 97, median 6 prior lines) overall response rate was 97% with 67% sCRs [59]. Other studies evaluate alternative CAR-T cell constructs and different strategies, different manufacturing approaches [70–72], dual targeting [73], and allogeneic CAR-T cells [74].

In one prospective study, clonal plasma cells of patients with AL amyloidosis were found to express low levels of BCMA but high levels of SLAMF7 [75]. A SLAMF7 CAR-T cell has shown anti-tumor activity in an AL amyloidosis model in one preclinical study; SLAMF7 CAR-T cells were injected into xenograft models of AL amyloidosis [75]. SLAM7 CAR-T cells are being assessed in two phase I clinical trials in MM patients and in combination with lenalidomide and daratumumab. Clinical trials in AL amyloidosis patients are also being planned. Dual SLAMF7/BCMA CAR T-cells are also in preclinical development. Other CAR-T cells are being developed to target CD38, CD138, immunoglobulin light chain, CD56, and CD19 in MM. Some of these are expected to be tested in patients with AL amyloidosis in the future.

There might be a place for CAR-T cells in particular for a subgroup of AL amyloidosis patients. IgM AL amyloidosis is caused by an underlying B-cell lymphoproliferative/lymphoplasmacytic clone that secretes an intact IgM in 5–7% of cases [24]. Patients with IgM-related AL amyloidosis have poor results with current anti-CD20 targeting therapies. Treatment combinations designed for non-IgM AL amyloidosis have been tested with unsatisfactory results. CD19 CAR T-cells have gained FDA and EMA approval for patients with relapsed/refractory large B-cell lymphomas and B-cell precursor acute lymphoblastic leukemia (see Table 1). Ongoing clinical trials have expanded the disease spectrum to include more indolent lymphomas. Other anti-CD20 and bispecific CD20/CD19 CAR T-cells are currently in clinical development for patients with Non-Hodgkin Lymphoma and Chronic lymphocytic leukemia and their efficacy offers some hope for evaluation also in patients with IgM AL amyloidosis.

2.7. Pathway Directed Therapy

2.7.1. BRAF Inhibitors and MEK Inhibitors

The RAS/RAF/MEK/ERK pathway of intracellular kinases is involved in proliferation, growth, adhesion, and apoptosis. Mutations of the MAPK-pathway are found in 43–53% of MM patients and are more frequent at the time of relapse [76–79]. The focus in the development of MAPK-pathway inhibitors has been on downstream targets of RAS, such as BRAF and MEK. BRAF V600E/K mutation inhibitors, such as vemurafenib, encorafenib, and dabrafenib, are highly effective in tumors that carry the mutant BRAF (including MM, being present in 2–4% of NDMM and 8% of RR patients) [76] but resistance develops quickly as the gain of activation mutations leads to alternative signaling and bypassing of BRAF. To overcome the issue of resistance dual BRAF and MEK inhibition has been explored. Preliminary results of the GMMG-BIRMA study that evaluated the combination of encorafenib and binimetinib showed an ORR (≥PR) of 82% with variable duration of response (>1 year for some patients) [80]. There is another ongoing study of dabrafenib and/or trametinib (NCT03091257) in BRAF mutated patients but also in patients who only have RAS mutations.

Cobimetinib (MEK inhibitor) in combination with other agents has achieved an ORR (≥PR) of 27% and 29% [81] and is evaluated along with venetoclax and/or avelozolizumab in RRMM patients (NCT03312530). Another phase I trial assessed the safety and efficacy
of the pan-RAF-inhibitor CH5126766 in patients with solid tumors and MM patients with RAS/RAF/MEK pathway mutations [82]. An umbrella trial that uses molecular stratification (MyDRUG-trial, NCT03732703) and other basket trials that include MM patients are ongoing, but no results have been published yet. (TAPUR NCT02693535 and CAPTUR, NCT03297606).

Pathway inhibition is feasible, at least for some MM-patients, and perhaps will offer a treatment option for some, few, patients. However, the frequency of targetable mutation in patients with AL amyloidosis is unknown and is expected to be very low.

Table 1. Future treatments for AL amyloidosis.

| Name                              | Mechanism of Action | Study Phase     | Results in Patients with AL Amyloidosis                                                                 | Comments                          |
|-----------------------------------|---------------------|-----------------|---------------------------------------------------------------------------------------------------------|-----------------------------------|
| Venetoclax                        | BCL-2 inhibitor     | Phase III (in MM) | Yes in retrospective studies ORR: 81%, CR/VGPR: 78%, Organ response rate: 83%                           | Only in patients with (t11;14)     |
| Liftasoclax                       | BCL-2 inhibitor     | Phase I/II (in MM and AL) | No, only in patients with myeloma                                                                         | Only in patients with (t11;14) |
| Belantamab mafodotin              | Anti-BCMA ADC       | Phase II (in AL)  | Study is recruiting                                                                                      | Ocular toxicity of concern        |
| Milatuzumab doxorubicin           | Anti-CD56           | Phase I (in MM)  | No, only in patients with myeloma                                                                           |                                   |
| Indatuximab ravtansine           | Anti-CD138          | Phase I/IIa (in MM) | No, only in patients with myeloma                                                                          |                                   |
| Talquetamab                       | BiTEs (GP3C5D/ CD3 on T cells) | Phase I       | No, only in patients with myeloma                                                                          |                                   |
| Cevostamab                        | BiTEs (FcRH5/CD3)   | Phase I         | No, only in patients with myeloma                                                                          |                                   |
| Idecaptagine cicleucel            | BCMA targeting CAR-T cells | Phase II      | No, only in patients with myeloma                                                                         | Toxicity is a concern–selected patients only |
| Ciltacabtagene autoleucel         | BCMA targeting CAR-T cells | Phase I/IIa    | No, only in patients with myeloma                                                                         | Toxicity is a concern–selected patients only |
| Tisagenlecleucel                  | CD19 CAR T-cell     |                 | Approved for RR B-cell precursor acute Lympoblastic leukemia and large B-cell lymphoma                     | Ongoing phase II studies in B-cell lymphomas to include also indolent diseases |
| Axicabtagene ciloleucel           | CD19 CAR-T-cell     |                 | Approved for RR large B-cell lymphoma                                                                       | Future option for IgM amyloidosis |
| Brexucabtagene autoleucel         | CD19-CAR-T-cell     |                 | Approved for RR mantle cell Lymphoma and B-cell precursor acute lymphoblastic leukemia                      |                                   |
| Lisocabtagene maraleucel          | CD19 CAR-T cell     |                 | Approved for RR Large B-cell Lymphomas                                                                      |                                   |
Table 1. Cont.

| Name                          | Mechanism of Action                  | Study Phase | Results in Patients with AL Amyloidosis | Comments |
|-------------------------------|--------------------------------------|-------------|----------------------------------------|----------|
| Iberdomide (CC-220)           | IMiDs                                 | Phase II    | No, only in patients with myeloma      |          |
| CC-92480                      | IMiDs                                 | Phase I/II  | No, only in patients with myeloma      |          |
| Encorafenib and binimetinib   | Dual BRAF and MEK inhibitor           | Phase II    | No, only in patients with myeloma      | In patients with BRAF V600E mutation |
| TLX66                         | Bone marrow conditioning agent        | Phase I/II (in AL) | Yes, hemResponse in 7/9 patients       | Potential as a conditioning regimen for patients otherwise ineligible for high dose therapy |
| Cael-101                      | Amyloid targeting                     | Phase 3     | Yes, cardiac response: 67%, renal response: 50% | Phases 2 data available, ongoing phase 3 study in newly diagnosed patients with stage 3 disease |
| Birtamimab                    | Amyloid targeting                     | Phase 3     | Yes, 50% relative risk reduction for all-cause mortality for Mayo stage IV patients | Initial phase 2 data positive, not confirmed in randomized phase 2 and phase 3. Under evaluation in stage IV (Mayo 2012) based on positive results in post hoc analysis |

2.7.2. PI3K/AKT Pathway Directed Therapies

AKT (protein kinase B) is a key component of the PI3K/AKT/mTOR pathway which is involved in signaling pathways linked to cell proliferation, cell survival, plasma cell development, and angiogenesis. The rationale behind AKT inhibition is based on the high levels of activation seen in MM cells compared to cells from patients with MGUS or smoldering MM. However, AKT-pathway mutations are uncommon in MM patients, indicating that there is an alternate mechanism for the activation of the pathway such as the MAPK pathway, IL-6 signaling, or the NFkB network [83].

A few clinical trials have assessed the efficacy of perifosine, an AKT-inhibitor, as monotherapy or in combination regimens with mixed results [84,85], while a phase III trial that evaluated the combination of perifosine with bortezomib and dexamethasone was stopped at the interim analysis due to lack of efficacy in terms of ORR and PFS in the perifosine arm compared to the placebo arm [86].

Afuresertib is a novel, more specific AKT-inhibitor; as a single-agent it has an RR of 8.8% with a long median duration of responses of 319 days [87]. It is being assessed in a phase I/II trial in combination with bortezomib and preliminary data showed a RR (≥PR) of 41% in RRMM patients [88].

2.7.3. Transcription Factor Directed Therapies

One of the most common high-risk genetic abnormalities in MM involves deletion of the p53 locus on chromosome 17p. It is present in 8% of NDMM patients which increases up to 45% in the RR setting. Nutlin-3 increases the activity of p53 by inhibiting its association with MDM2, an E3-ubiquitin-protein ligase, preventing its degradation [89]. In vitro, nutlin-3 has potent anti-myeloma activity and acts in a synergistic manner with melphalan and bortezomib but this mechanism is dependent on the presence of wildtype p53 [90]. Early phase studies evaluate MDM2 inhibitors (idasanutlin, AMG232) in combination with PIs
or ImiDS (NCT02633059, NCT03031730). RITA is another inhibitor of the p53/MDM2 interaction which triggers synergistic cell killing when combined with nutlin. PRIMA-1 is a molecule designed to restore the activity of mutant p53. Both have shown significant antmyeloma activity in vitro [91,92]. HDP-101 is an antibody-drug conjugate that couples a BCMA-antibody with a synthetic version of amanitin which targets POLR2A, (RNA polymerase subunit II) which is located in close proximity to the p53 locus on chromosome 17p and has been proposed as a collateral vulnerability target. A phase I/II study with this agent in patients with RRMM will be initiated in 2021 (NCT04879043).

Given the shared characteristics of the plasma cell clone between patients with MM and AL amyloidosis and the presence of 17p deletion in a small proportion at diagnosis and relapse, there is a potential future role for these agents in very few, selected patients with AL amyloidosis as well.

2.8. New Immunomodulatory Agents (IMiDs)

Cereblon (CRBN) targeting immunomodulatory agents, lenalidomide and pomalidomide, are currently major options for rescue therapy in AL amyloidosis as they can overcome resistance to alkylating agents and PIs (and potentially daratumumab). Currently, more potent next-generation cereblon E3 ligase modulators (CELMoDs®)-iberdomide (IBER) and CC-92480 are in clinical development for patients with MM. If their safety and efficacy are established in the MM setting, clinical trials in AL amyloidosis patients are expected to follow.

Compared to IMiDs, CELMoD structures contain additional phenyl and morpholino moieties which enable enhanced interactions with cereblon or substrates. They bind with enhanced activity, induce more potent degradation of Ikaros and Aiolos and that possibly explains the superior cell-autonomous activity of these compounds [93,94]. Phase I studies of IBER and CC-92480 have included mostly MM patients refractory to IMiDs (NCT02773030, NCT03374085). The results point to a broader clinical activity for these agents compared to ImiDs. Ongoing clinical trials aim to inform rational combinations (Pis, CD38 antibodies, etc.) for these agents in view of cell-autonomous, immunomodulatory, and adverse effects of these agents. The safety profile of CELMoD structures remains to be determined based on the results of ongoing clinical trials. So far, grade 3/4 neutropenia has been reported with IBER-dexamethasone in 30% of patients and grade 3/4 thrombocytopenia in 12% [95]. IMiDs are not very well tolerated in patients with AL amyloidosis; whether CELMoDs will be better tolerated remains to be seen, since the toxicity will be crucial (along with clinical activity) for evaluation and adoption in the treatment of AL amyloidosis.

2.9. TLX66

TLX66 (90Y-besilesomab) is the therapeutic analogue of 99mTc-labeled murine anti-granulocyte mAb BW250/183 and has been granted orphan drug designation status in Europe for bone marrow conditioning for autologous stem cell transplantation (HSCT) [96,97]. It targets CD66, a receptor expressed on granulocytes but also bone marrow plasma cells. TRALA (Targeted Radiotherapy for AL Amyloidosis) is a phase I/II trial which aims to evaluate the safety and toxicity of TLX66 as the sole bone marrow conditioning agent prior to HSCT in patients with AL amyloidosis. (EudraCT Number: 2015-002231-18). Nine patients with AL amyloidosis were enrolled and all (100%) were successfully engrafted following bone marrow conditioning with TLX66 and autologous HSCT without any chemotherapy. Hematologic response was seen in seven out of nine patients (two CRs and five PRs) within 100 days post-transplant. At a median follow-up of 31 months (14–57 months) all patients remain alive.

3. Special Considerations; Toxicity Associated with Anti-Clonal Therapies

Novel anti-clonal agents have improved hematologic responses in AL amyloidosis but safety remains a major concern for these patients as regardless of age, they are frail and have multiorgan dysfunction. Patients with advanced cardiac disease, in particular, make up
a distinct subcategory which requires a unique therapeutic approach. Immunosuppression and neurotoxicity, secondary to anti-clonal therapy, can shift easily the very fine balance associated with multiorgan dysfunction and increase morbidity and mortality.

Daratumumab is overall well tolerated with no signal of cardiac or renal toxicity [98]. For patients with advanced cardiac involvement, the concern of volume overload is relevant with the use of intravenous daratumumab. Thus, the approval of subcutaneous administration based on the results of the ANDROMEDA study is of particular importance for this population. Infusion-related reactions and infections are the most significant adverse events. Lymphopenia and hypogammaglobulinemia may be related to the increased risk of infections [99].

Bortezomib is generally safe and well-tolerated. The main safety issue associated with bortezomib, and other PIs to a lesser extent, is neurotoxicity. It is not a first-line option in patients with peripheral neuropathy and it can cause a deterioration of autonomic neuropathy when present. VCD has been associated with a 40% treatment mortality in patients with advanced cardiac disease (Mayo Stage III) and concern of low-grade cardiac toxicity remains, especially for patients with stage 3B disease.

IMiDs have a less favorable safety profile. The combination of lenalidomide, bortezomib, dexamethasone in newly diagnosed patients, required dose reductions in 37.5% and 27% discontinued lenalidomide due to toxicity which was mostly non-hematologic in advanced disease patients [100]. The most common grade 3 or 4 toxicities include fatigue, myelosuppression, rashes, infections, arrhythmias, thrombotic events, neuropathy, and kidney dysfunction in patients with proteinuria. The combination of Pomalidomide with bortezomib and dexamethasone as primary therapy was also associated with toxicity and early mortality [101]. A paradox with all IMiDs is a usually transient increase in NT-proBNP, which interferes with cardiac response assessment.

With therapies such as CAR-T cells and bispecifics, a major concern is whether patients with cardiac or multiorgan involvement will be able to tolerate the toxicities such as cytokine release syndrome (CRS) [102]. Cardiovascular manifestations of CRS include tachycardia, hypotension, troponin elevation, reduced left ventricular ejection fraction, pulmonary oedema, and cardiogenic shock [102]. Patients with amyloid-induced cardiac dysfunction may not have enough cardiac reserve to tolerate CRS. ICANS and neurotoxicity are also major concerns since many patients with AL amyloidosis also present with peripheral and autonomic neuropathy.

4. Treatment Strategies Targeting Immunoglobulin mRNA

In many patients with AL amyloidosis, the production of the precursor protein cannot be sufficiently eradicated by anti-clonal therapies. Furthermore, in ultra-high-risk patients with advanced cardiac disease even complete eradication of amyloid clones cannot improve survival or organ function and additional combined therapies that target different aspects of amyloidogenesis are needed. Beyond regimens that target the B-cell clone, molecules that control gene expression could also lead to suppression of AL amyloidosis precursor protein. Small interference RNA (siRNA) or antisense oligonucleotide (ASO) are non-coding RNA that bind to messenger RNA (mRNA) through complementary base pairing and halt translation by mRNA degradation. Gene silencing drugs, delivered through lipid nanoparticles into the target cells, have been tested in different types of amyloidosis. Patisiran (siRNA) and intoersen (ASO), which have been approved by FDA and EMA for the treatment of hereditary transthyretin amyloidosis (hATTR) with polyneuropathy, reduce hepatic production of transthyretin resulting in significant improvement of symptoms and quality of life without major toxicities [103,104]. Knockdown of amyloid precursor protein has been explored in mice with AA amyloidosis and findings reveal lower SAA levels in serum and less amyloid deposits in organs [105]. In neurodegenerative diseases that are associated with the aggregation of misfolded proteins (amyloid-beta protein, alpha-sunuclein, tau protein, prion, huntingtin), gene interference has been evaluated, as well.
At the present time, RNA silencers for AL amyloidosis have been investigated only at the preclinical level, in vitro, and in vivo [106–110]. It has been established that the variable region of immunoglobulins plays a critical role in the formation of misfolded fibrils. The administration of ASO that recognizes the variable region of λLC (Vλ) was the first attempt to silence the FLC gene using myeloma plasma cell lines [106]. Although a decrease in light chain serum concentration was observed, there are no updated data in amyloid plasma cell lines, while ASO which is a single-stranded RNA, tends to be less stable than other RNA-targeted therapies [111].

More focus has been given on siRNA in AL amyloidosis that targets either the variable region or the constant region of both the κ and λ light chain [112]. siRNA modifies the expression of LC genes and reduces LC intracellular production and circulating levels in vitro and in vivo. Pharmacokinetic studies show that siRNA activity in vitro could last for almost a week, rendering weekly administration plausible [108]. Most recently, a group of investigators identified an anti-κLC CR siRNA that is safe and efficient in vitro with a reduction of circulating κ-LC for 8–12 days after administration, but more research is warranted [113].

A significant advantage of this anti-light chain approach is the high specificity of siRNA therapeutics that allows us to design sequence-specific and patient-specific strategies by targeting the variable region of LC. At the same time, siRNAs that target the constant region of LCs results in excess of intracellular unpaired heavy chain that enhance apoptotic signaling by triggering UPR and caspase 3/7 activity. Moreover, RNA silencers, especially those that target the VR, do not show toxicities related to conventional chemotherapy, such as myelosuppression or immunodeficiency, or other systemic side effects [108]. This is extremely relevant for frail patients with multiorgan involvement and advanced cardiac disease that are ill-tolerated to chemotherapy AEs.

A major challenge of siRNAs is the need to discover a delivery method that will allow us to target plasma cells in the bone marrow. Lipidoid nanoparticles have been used while monoclonal antibodies that bind to a specific antigen in the surface of plasma cells could also be an option.

Another issue regarding siRNAs is that the targeted sequence of the LC gene needs to be isolated and determined separately for every patient in order to be effective. It is worth mentioning that λ-LC AL amyloidosis which is the most common subtype has more genetic diversity, rendering the process of siRNA synthesis more demanding. Furthermore, reducing amyloidogenic LC levels by interfering with LC gene expression means that siRNA treatment ought to be lifelong unless combined with anti-clonal therapies.

5. Anti-Amyloid Targeting Treatment Options

Targeting the amyloid fibrils and their precursors to reduce oxidative stress and facilitate amyloid clearance from tissues has emerged as a complementary treatment approach to chemoimmunotherapy. Alternative treatment strategies that target different aspects of the amyloidogenesis process should be considered too, and include the stabilization of circulating amyloidogenic FLCs, the inhibition of amyloid fibrils aggregation, and the promotion of amyloid deposits clearance. (Figure 2) Several small molecules and monoclonal antibodies are in development and have been explored in preclinical models, while some have entered phase 3 studies; however, the initial attempts have been disappointing.
Figure 2. Anti-amyloid targeted therapeutic approaches for AL amyloidosis. Created with BioRender.com (accessed on 10 November 2021).

5.1 Targeting Amyloid Formation and Dissolution

Ligands that bind to the native structure of precursor proteins or dimers and kinetically stabilize them can inhibit amyloid formation. Tafamidis is a transthyretin stabilizer that prevents ATTR amyloid formation [114]. There have been efforts to identify stabilizers of amyloidogenic immunoglobulin light chains too. These molecules could provide an accessory treatment option to reduce the amyloid load in vital organs [115]. Coumarin, doxycycline, methylene blue and green tea compound epigallocatechin-3-gallate (EGCG) have been proposed as inhibitors of amyloidogenesis in various laboratory contexts [116,117] and some have ushered in the clinical practice, but no molecule can genuinely inhibit LC aggregation and amyloid formation. The antibiotic doxycycline has shown some activity in a retrospective study but no benefit was observed for Mayo stage IIIB patients [118]. A multi-center, open-label randomized study in patients with Mayo stage II and III failed to demonstrate that doxycycline twice daily could prolong hemPFS (hazard ratio 0.97, 95% CI, 0.59–1.60, p = 0.91) or cardiac PFS (hazard ratio 0.91, 95% CI, 0.54–1.55, p = 0.74) or OS (hazard ratio 1.04, 95% CI, 0.60–1.81, p = 0.89) [119]. An ongoing randomized trial with doxycycline plus standard of care in newly diagnosed patients with cardiac involvement is recruiting (NCT03474458). EGCG has also been used by clinicians, but its efficacy has not been confirmed in a randomized clinical trial (TAME-AL) (NCT02015312). Even if effective stabilizers of light chains are developed, they could not lead to complete hematologic remission because they do not have an effect on amyloid clones. These findings show the complexity of the amyloid formation process and the multiple steps that could be affected by therapeutic interventions.

5.2 Targeting Amyloid Deposits

In the cascade of amyloidogenesis, therapies directed against deposits of LC amyloid are the most elaborated. CAEL-101 (also known as 11-1F4) is a chimeric IgG1κ monoclonal antibody that binds to an epitope of the N-terminal of both κ and λ LC amyloid deposits in the organs, but not with circulating FLCs, and promote amyloid fibril removal by activating phagocytes. An open-label, phase 1a/b study (CAEL101-101) with 27 relapsed or refractory AL amyloidosis patients showed that intravenous administration of CAEL-101 was well-tolerated at the highest tested dose of 500 mg/m² as either single infusion or four weekly infusion schedules. Overall, 63% of evaluable patients manifested organ function improvement (cardiac response in 67% and renal response in 50%), with a median time to response of three weeks [120]. Regarding cardiac involvement, 6 out of 10 patients (60%) achieved a cardiac response. Further improvement in mean GLS 12 weeks after the first infusion, observed in 9 out of 10 patients, showed that CAEL-101 can affect the structural remodeling of the myocardium [121]. CAEL101-203 study demonstrated that the combination of CAEL-101 with a standard of care VCd is safe and determined that
a dose of 1000 mg/m² is the recommended dose for phase 3 studies. At the time, a phase 3, double blinded multicenter study is ongoing and recruiting patients with advanced cardiac disease. The study evaluates the efficacy and safety of CAEL-101 vs placebo in combination with anti-clonal therapy in newly diagnosed patients with Mayo stage IIIA (CAEL101-302) and Mayo IIIB (CAEL101-301) (NCT04512235 and NCT04504825).

Birtamimab (NEOD001) is another humanized IgG1κ moAb designed to target amyloid fibrils, initially developed for AA amyloidosis. It recognizes the C-terminal epitope of amyloid protein, which is similar to both forms of amyloidosis and promotes clearance of amyloid via phagocytosis. In a phase I/II study the drug was well-tolerated while cardiac and renal responses were observed in 57% and 60%, respectively [122]. The randomized phase IIb PRONTO study that evaluated birtamimab in patients with persistent cardiac dysfunction failed to meet its primary endpoint (cardiac response) or secondary endpoints, as a result, all NEOD001 studies were discontinued. However, a post-hoc analysis from the phase III VITAL study, that was prematurely terminated for futility, showed a survival benefit for high-risk patients with Mayo stage IV AL amyloidosis (HR = 0.413, p = 0.025, over nine months). A double-blind, phase 3 study, AFFIRM-AL, of birtamimab (24 mg/kg) every four weeks in combination with bortezomib-based regimens in patients with newly diagnosed Mayo stage IV has been initiated in 2021. The study is designed to evaluate the primary endpoint of all-cause mortality.

Other fibril-directed therapies that have been tested in AL amyloidosis patients include the anti-serum amyloid P (anti-SAP) antibody, dezamizumab in combination with miridesap (CPHPC), a molecule that depletes SAP from circulation, are no longer in development based on their risk and benefit profile.

6. Future Combinations and Treatment Algorithms

The results of the ANDROMEDA study introduced DaraVCd as the new standard of care for the treatment of newly diagnosed AL amyloidosis and redefined the optimal goal of therapy. We expect, however, to see optimizations of this quadruplet regimen given the expanding treatment landscape and increased understanding of the characteristics of the plasma cell clone, the signaling pathways involved in the disease, and the mechanisms involved in amyloid formation, deposition, and degradation. Respectively, we expect therapeutic advances to be applied in the relapse setting.

Future combinations will become increasingly risk-adapted; a thorough assessment of the type, number, and extent of organ involvement in addition to co-existing comorbidities will guide therapeutic algorithms. For example, an ongoing trial is assessing the safety and efficacy of Daratumumab monotherapy in previously untreated AL amyloidosis patients with stage 3B disease (NCT04131309). Given the very frail profile of this subgroup of patients, daratumumab monotherapy might prove to be the treatment of choice given the excellent safety profile and tolerance of this agent.

The role of chemotherapy, such as cyclophosphamide and melphalan, in triplet or quadruplet combinations, will most likely be challenged given the associated myelotoxicity. It is unclear what is the added benefit of cyclophosphamide in the DaraVCd combination. A head-to-head comparison is not likely, but we expect future clinical trials to not include cyclophosphamide, particularly if another agent (monoclonal antibody, anti-amyloid antibody, etc.) is added to the DaraBorD combination. Combination of immunotherapies is another likely approach (for example daratumumab or isatuximab with a bispecific, or with amyloid-targeting immunotherapy). It is also likely that the place of proteasome inhibitors, especially bortezomib, will be challenged, at least for some patient groups.

What has become increasingly evident is that anti-clonal treatment does not suffice, particularly in patients with advanced organ damage, to alter the prognosis and outcome of AL amyloidosis patients. Elimination of the plasma cell clone is only the first of two necessary steps. Antiamyloid agents that rapidly eliminate amyloid deposits or engage the immune system to increase the rate of elimination are necessary and will act in a complementary manner to anti-clonal treatment. Amyloid targeting treatments could
change the natural history of the disease. Dual monoclonal antibody treatment that targets the plasma cell clone and amyloid deposits concurrently, in the frontline and relapse setting, is expected to become standard of care and to change the disease outcome. Clinical trials assessing the combination treatment of CAEL-101 with VCd and daratumumab are currently ongoing. Introducing dual antiamyloid and anti-clonal treatment shifts the focus to include not only hematological but also organ responses as organ function recovery could be more dependent on amyloid fibril targeting, which reduces direct toxicity and enhances tissue clearance.

Other combinations that are expected to emerge are combinations of anti-clonal monoclonal antibodies, pathway inhibitors, RNA interference, and agents that engage the immune system. The key to future treatments is the rationalization behind the choice of combination treatments in a manner that the agents used act synergistically and have complementary actions. Pathway inhibitors could prevent or overcome the development of resistance to anti-clonal agents and could be combined with PIs, ImiDs, and clonal plasma cell-directed antibodies. Antibody–drug conjugates are another promising class of agents. Belantamab mafodotin is currently being assessed for safety and efficacy in combination with different anti-clonal agents (IMiDs, daratumumab, other anticd38 antibodies, and PIs) in a number of clinical trials in the MM setting. The role of CAR-T cells in the AL amyloidosis setting remains to be seen. As CAR-T cell treatment evolves it is expected to become safer and there is perhaps a place for this treatment for lower-risk or IgM-Amyloidosis patients.

7. Conclusions

The ever-evolving therapeutic field in multiple myeloma offers a preview of what is to come in the treatment of AL amyloidosis, in an adapted manner nonetheless. One of the major concerns regarding novel anti-clonal regimens, key pathway inhibitors, and immune system engagers remains their associated toxicity. Risk-assessment and treatment tailoring in combination with the provision of specialized supportive care will therefore remain key to the management of this unique patient population. Anti-clonal agents need to be assessed in the AL amyloidosis setting and specifically for different patterns of organ involvement and levels of organ dysfunction. Finally, it will become clear that the effective elimination of the plasma cell clone makes up only one part of the rationale behind the treatment of AL amyloidosis. Targeting and effective clearance of the amyloid deposits is expected to become a necessary part of future treatment combinations. Adopting and adapting is therefore key for the future of the therapeutic field in AL amyloidosis.

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