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Updated recommendations for the treatment of light-chain amyloidosis from the Swiss Amyloidosis Network

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Summary

Since the publication of the first Swiss recommendations on systemic light-chain amyloidosis in 2020, treatment strategies have evolved. As a result of the third joint meeting of the Swiss Amyloidosis Network, a multidisciplinary and multicentre Swiss clinical consortium, in 2024, recommendations for the treatment of light-chain amyloidosis were updated. They discuss the role of the new standard first-line protocol Daratumumab, Cyclophosphamide, Bortezomib, Dexamethasone (Dara-CyBorD), the timing and indication of high-dose treatment and potential second-line strategies as well as emerging treatment options, with a special focus on multidisciplinary supportive care measures. The update represents a synopsis of current evidence and expert consensus and intends to provide general treatment guidance tailored to the Swiss healthcare system. Nonetheless, treatment decisions should always be personalised and involve a multidisciplinary approach. This update replaces the previous "therapeutic recommendations" while the previous "diagnostic recommendations" remain valid.

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Introduction

Treatment strategies for systemic light-chain amyloidosis (AL) have evolved since the publication of the first consensus recommendations by the experts of the Swiss Amyloidosis Network (SAN) in 2020 [1]. To address and discuss the new aspects, the SAN held its third joint meeting in April 2024 in Zurich, Switzerland. Participants were clinical specialists from all fields of medicine involved in the care of amyloidosis patients. The discussion resulted in an update of the SAN recommendations on light-chain amyloidosis with a particular focus on treatment and supportive care. The following update reflects the available published evidence, including the results of clinical trials and recently published abstracts, as well as existing guidelines from international societies and expert consensus.

The SAN recommendations are tailored to address the structures of the Swiss healthcare system and aim to provide guidance for clinical practitioners in Switzerland. To this end, the manuscript avoids in-depth discussions of the literature and diagnostic considerations, instead concentrating on practical "therapeutic recommendations". This version is not intended to be exclusive, particularly given the anticipation of continued rapid therapeutic advancements.

Methodology

Prior to discussion within the SAN, we performed a PubMed search, focusing on studies published since the release of the first guidelines in 2020. This search included clinical trial publications, treatment recommendations by other societies, review articles as well as published meeting abstracts with high relevance to the field. Relevant publications on light-chain amyloidosis in English were first reviewed and summarised by the first and last author and later discussed, point by point, with experts of the SAN. To increase transparency, the panel used the GRADE approach to assess the underlying level of evidence [2] (table 1).

Where published evidence was limited or insufficient, consensual expert opinions were included in the recommendations. Evaluation of the resulting recommendations was performed by all authors in a stepwise approach. The strength of a recommendation was graded as either strong (Grade A or B; "The SAN recommends…") or conditional (Grade C; "The SAN suggests…"). To strengthen methodological transparency and quality, the final update followed best practice for guideline development according to the principles of AGREE II [3] (Appraisal of Guidelines for Research and Evaluation). The manuscript was finally approved by all active members of the SAN as listed in the author section.

In anticipation of an evolving treatment landscape and more therapeutic advances, the recommendations will be considered current for the following three years or until the publication of an earlier update by the SAN, as future progress may require earlier revisions.

Considerations before and during treatment

Baseline risk stratification and response assessment

The revised Mayo 2004 criteria and its European modification are the two best established staging systems, both including cardiac biomarkers (NT-proBNP, Troponin-T), given that the degree of cardiac involvement has been shown to be the most relevant prognostic factor [4, 5]. For assessment of renal involvement, a separate renal staging system has been developed predicting renal involvement and outcome [6]. Baseline assessment generally also includes evaluation of "fitness" for high-dose (HD) melphalan treatment and autologous stem cell transplantation (ASCT). This initial evaluation is crucial as it affects intensity and sequence of treatment upfront and downstream. Criteria for assessing fitness are subject to ongoing debate. In Switzerland, the criteria proposed by the EHA-ISA working group are the best established [7, 8].

The SAN suggests the use of evaluation criteria for high-dose therapy / autologous stem cell transplantation as proposed by the EHA-ISA working group [7, 8]. *(Grade C, Level III)*

Importantly, although clonal plasma cells are the amyloid-producing cell of origin in most cases, the predominance of lymphoplasmacytic cells should always be excluded in patients with IgM-related amyloidosis, as it modifies the proposed treatment algorithm [9] (see section "IgM-directed treatment"). Organ response remains the ultimate goal of treatment and usually occurs within months after the start of treatment, depending on the speed and depth of the haematological response [10, 11]. Criteria of haematological and organ response have continuously been improved in recent years (table 2). Haematological and organ response should be validated at least at 3 and 6 months after initiation of therapy [12]. However, in routine care, assessments every 1–2 months are an established practice. As the clinical outcome has been shown to be directly related to the depth of response [10], obtaining at least a very good partial response (VGPR) is considered standard. While achievement of a haematological complete response is desirable, assessment of bone marrow minimal residual disease (MRD) is the subject of clinical trials and not yet established as a routine response parameter [13].

The SAN recommends assessment of haematological and organ response at least at the beginning of every cycle and at the end of treatment (every month under treatment,

Table 1:
GRADE levels of evidence.

Grade	Level	Origin of evidence
A	I	(Meta)-analysis of ≥1 randomised controlled trial (RCT)
B	IIA	≥1 non-randomised trial (incl. phase II and case-control)
	IIB	≥1 other prospective non-experimental study (incl. observational studies)
	III	≥1 descriptive study or abstract of meta-analysis and/or randomised controlled trial
C	IV	Expert consensus or opinion statement and/or experience of respected authorities

every 3–6 months under surveillance, respectively). *(Grade B, Level IIB)*

Insufficient response: The SAN suggests change of treatment if no haematological very good partial response is reached within 3–4 months from initiation. *(Grade C, Level IV)*

First-line treatment of light-chain amyloidosis

For patients with rMayo Stage I–IIIa, as represented in the ANDROMEDA trial [17], first-line treatment generally includes induction with Dara-CyBorD (Daratumumab, Cyclophosphamide, Bortezomib and Dexamethasone). The potential benefit of upfront high-dose therapy / autologous stem cell transplantation has not been clearly established yet. The only RCT on this particular matter did not show a survival benefit but was criticised for its unrepresentative inclusion criteria [18]. The ongoing uncertainty has led to country-specific differences in the indication for performing high-dose therapy / autologous stem cell transplantation. In general, given the rarity of the disease and the many unknown variables, if available, treatment in clinical trials should be considered. In Switzerland, treatment with Dara-CyBorD requires prior health insurance approval, which is generally granted. The SAN has agreed on the following recommendations regarding first-line therapy (figure 1):

Patients with Stage I–III/IIIa

The SAN recommends induction with Dara-CyBorD. *(Grade A, Level I)*

– The SAN suggests starting with reduced-dose dexamethasone in patients with cardiac involvement: 10 to 20 mg/dose. *(Grade C, Level IV)*

For patients fit for high-dose therapy / autologous stem cell transplantation, the SAN suggests early stem cell collection after 2–4 cycles of induction. *(Grade C, Level IV)*

– The SAN recommends mobilisation with G-CSF (Grade B, Level IIB) or plerixafor on demand. *(Grade C, Level IV)*

The SAN recommends upfront treatment with high-dose therapy / autologous stem cell transplantation after insufficient haematological response (no very good partial response after 4 months) to induction or in patients with concomitant symptomatic myeloma [8, 19–21]. *(Grade B, Level IIB)*

– The SAN recommends high-dose therapy / autologous stem cell transplantation with standard dose melphalan 200 mg/m^2 rather than dose reduction [8, 22]. *(Grade B, Level IIB)*

– If high-dose therapy / autologous stem cell transplantation is performed, the SAN suggests it is followed by treatment-free surveillance. *(Grade C, Level IV)*

– The SAN does not recommend tandem high-dose therapy / autologous stem cell transplantation in light-chain amyloidosis [23]. *(Grade B, Level III)*

The SAN recommends deferral of high-dose therapy / autologous stem cell transplantation in fit patients who achieve at least very good partial response after 4 induction cycles [24]. *(Grade B, Level IIB)*

If high-dose therapy / autologous stem cell transplantation is not performed or is deferred, the SAN recommends continuation of induction with Dara-CyBorD for a total of 6 cycles followed by 18 cycles of maintenance with daratumumab [17]. *(Grade B, Level IIA)*

Table 2:
Response criteria.

Haematological* [12, 14]		
Complete response (CR)	1. Negative serum and urine immunofixation AND	
	2. Free light-chain ratio within reference range OR uninvolved free light chain > involved free light chain	
Very good partial response (VGPR)	dFLC <40 mg/l	
Partial response (PR)	Decrease of dFLC ≥50%	
No response (NR)	All other	
Organ response [6, 10, 15]		
Complete response (CR)	Heart	NTproBNP: nadir ≤350 ng/l
	Kidney	Proteinuria: nadir ≤200 mg / 24 h
	Liver	Alkaline phosphatase: nadir ≤2 × ULN
Very good partial response (VGPR)	Heart	NTproBNP: decrease >60%, not meeting complete response
	Kidney	Proteinuria: decrease >60% not meeting complete response
	Liver	Alkaline phosphatase: decrease >60% not meeting complete response
Partial response (PR)	Heart	NTproBNP: decrease of 30% to 60%, not meeting complete response
	Kidney	Proteinuria: decrease of 30% to 60% of baseline OR <0.5 g/24 h if >0.5 g/24 h/d at baseline AND no worsening of eGFR >25% of baseline
	Liver	Alkaline phosphatase: decrease ≥50% OR decrease of liver size ≥2 cm
	Peripheral nervous system	Electromyoneurography: any improvement
No response (NR)	None of the response criteria is met	

dFLC: difference involved minus uninvolved free light chain; eGFR: estimated glomerular filtration rate; NTproBNP: N-terminal pro-B-type natriuretic peptide; ULN: upper limit normal.

* Adapted criteria for patients with low baseline free light-chain burden (<50 mg/l) [16].

Patients unfit for high-dose therapy / autologous stem cell transplantation and/or Stage IV/IIIb

In Stage I–IIIa unfit for high-dose therapy; the SAN recommends induction with 6 cycles of Dara SC-CyBorD followed by 18 cycles of daratumumab maintenance [17]. *(Grade A, Level I)*

In Stage IIIb/IV with advanced cardiac involvement; the SAN recommends a daratumumab-based induction treatment, i.e. as monotherapy, in combination with dexamethasone [25], or as a modified, dose-reduced Dara-CyBorD protocol [26]. *(Grade B, Level III–IV)*

- The SAN suggests to start with bortezomib at an attenuated dose (0.7 mg/m^2) followed by an increase every two weeks (+0.3 mg/m^2) if tolerated. *(Grade C, Level IV)*
- The SAN suggests to start with reduced-dose dexamethasone (4–10 mg). *(Grade C, Level IV)*

IgM-directed treatment

In IgM-type amyloidosis, non-Hodgkin's lymphoma (NHL) clonal B cells (less commonly plasma cells) are usually at the origin of the disease. When clonal B cells are identified, rituximab-based treatment regimens are established first-line therapies [9, 27, 28], combinations with Bruton's tyrosine kinase (BTK) inhibitors [29], bendamustin, cyclophosphamide, chlorambucil, bortezomib and systemic corticosteroids may be appropriate depending on the biology of the underlying clone [27, 29, 30]. Plasma cell-directed treatment may also be appropriate if plasma cells are (part of) the identified clonal population.

The SAN recommends rituximab-based induction therapy in the treatment of IgM-associated amyloidosis. *(Grade B, Level IIB)*

Second-line treatment of relapsed/refractory light-chain amyloidosis

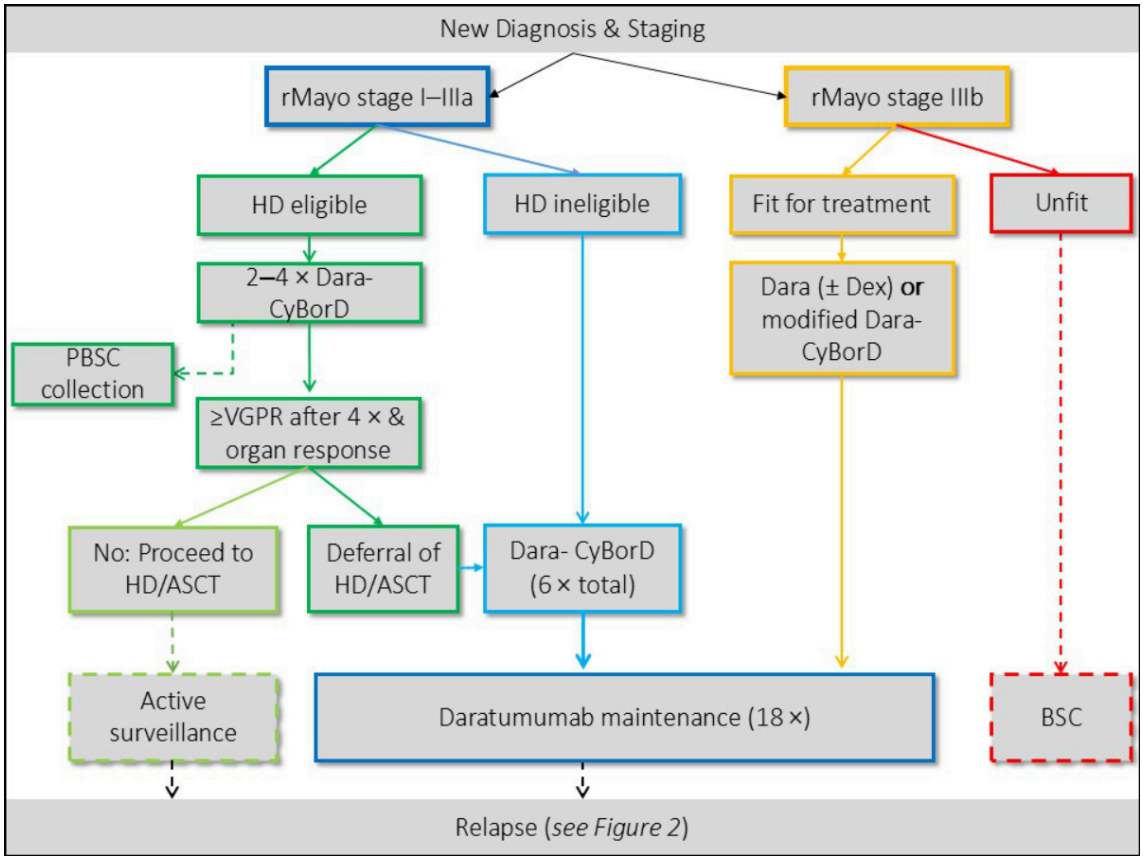
Although the pathological plasma cell clone is generally responsive to multiple treatment options, many therapeutic agents are poorly tolerated and disease- and treatment-related morbidity and mortality may be significant, especially at the beginning of treatment. Multidisciplinary evaluation and frequent adjustment of the therapeutic regimen are common, and individualised symptom management is an integral part of therapy (figure 2).

Timing of relapse treatment

The optimal timing of second-line treatment initiation is a matter of debate [31], weighing the apparent benefits (prevention of organ deterioration) against potential therapy-associated side effects. Palladini et al. suggested treatment restart at high risk for progression, defined as a dFLC of >20 mg/l, a level >20% of baseline and a >50% increase from the lowest value reached [32].

The SAN recommends initiation of rescue therapy in haematological relapse as proposed by Palladini et al. [32]. *(Grade B, Level IIB)*

Figure 1: First-line treatment algorithm as proposed by the Swiss Amyloidosis Network (SAN). ASCT: autologous stem cell transplantation; BSC: best supportive care; CyBorD: cyclophosphamide-bortezomib-dexamethasone; Dara: daratumumab; Dex: dexmethasone; HD: high-dose therapy; PBSC: peripheral blood stem cells; rMayo: revised Mayo stage; VGPR: haematological very good partial remission.



– Criteria: dFLC of >20 mg/l AND >20% of baseline AND >50% increase from the lowest value reached.

The SAN recommends earlier initiation (at biochemical loss of response) of rescue therapy in patients with cardiac involvement to prevent cardiac deterioration [32]. *(Grade B, Level III)*

Treatment options

In the relapsed/refractory setting, a variety of possible treatment options are available, most of which are derived from myeloma treatment [31]. The optimal type and intensity of treatment depends on previous exposure and response, time to relapse and current disease stage/comorbidities. Access to treatment can be challenging however, as there is no guaranteed reimbursement beyond first-line treatment in the absence of plasma cell myeloma in Switzerland. Requests for cost coverage must be justified in accordance with Article 71 of the Health Insurance Act [33].

The SAN recommends r/r treatment with an anti-CD38-Ab and/or a proteasome inhibitor, if not already included in previous therapy [34, 35]. *(Grade B, Level IIB)*

The SAN suggests retreatment with the initial regimen in patients with good initial response and tolerance of first-line and after at least 24 months of treatment-free remission. *(Grade C, Level IV)*

If relapse occurs after the current standard-of-care, Dara-CyBorD or similar protocols including an anti-CD38-Ab and proteasome inhibitor, there is no universal standard for further-line therapy and the available evidence is often limited to registry data and small case series. Therefore, the following options are Grade B or C recommendations and are based on expert consensus within the SAN.

Venetoclax: translocation t(11;14)

Venetoclax is a B-cell lymphoma-2 (BCL-2) inhibitor active in plasma cell neoplasia such as myeloma (PCM), particularly those harbouring t(11;14), which is associated with high BCL-2 expression [36–38]. Approximately 50% of patients with light-chain amyloidosis show t(11;14) [39, 40], making venetoclax a valuable option. Growing evidence in a heavily pretreated patient population demonstrates efficacy as a single agent or in combination with an acceptable safety profile, with tumour lysis syndrome (TLS) being rare [36, 37]. If not already performed at diagnosis, an iFiSH and/or BCL-2 expression analysis is a prerequisite for treatment with venetoclax.

The SAN recommends second-line treatment with venetoclax in patients with t(11;14) and previous exposure to an anti-CD38-Ab. *(Grade B, Level IIB)*

– The SAN suggests a target dose of 400 mg/d, consider ramp-up over 3 days with a starting dose of 100 mg/d under TLS monitoring. *(Grade B, Level III)*

The SAN suggests venetoclax in patients with t(11;14), as monotherapy or in combination with an anti-CD38-Ab and/or a proteasome inhibitor in case of no pre-exposure. *(Grade C, Level IV)*

Immunomodulatory agent-based treatment: no t(11;14) and adequate organ function

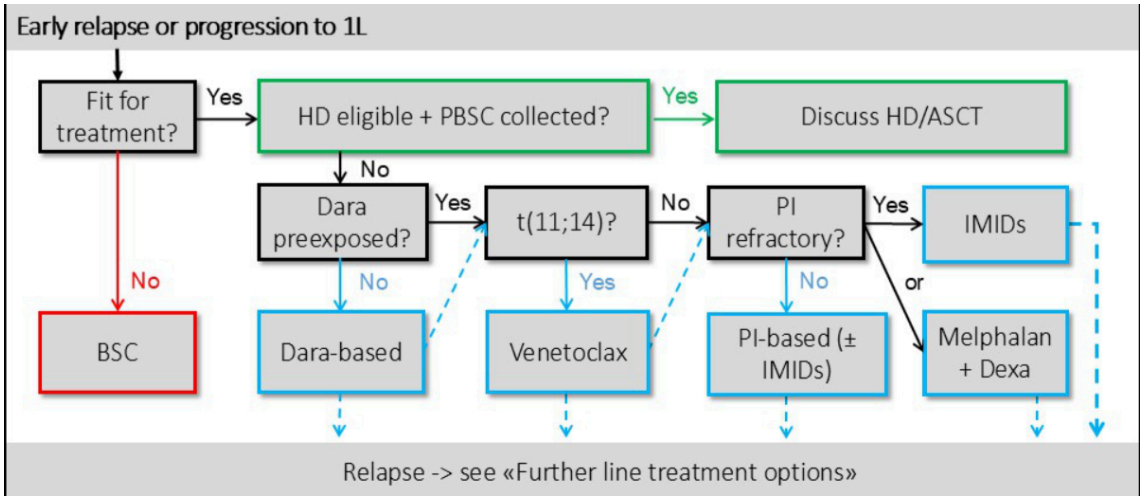
Various case series and phase II trials report the efficacy of immunomodulatory agents (IMIDs) in pretreated patients. However, unlike plasma cell myeloma, the tolerability of immunomodulatory agents in light-chain amyloidosis is poor, the discontinuation rate is high (>40%) and reduced cardiac and renal function as well as possible cytopenia are major limiting factors [41]. Published evidence favours pomalidomide over lenalidomide due to better tolerability [41, 42]. Potential effects on volume homeostasis, cardiac function (biomarkers/rhythm) and renal function should be closely monitored.

In patients with progression to standard treatment, adequate organ function and without t(11;14), the SAN recommends treatment with immunomodulatory agents ± dexamethasone as second-line treatment [43, 44]. *(Grade B, Level IIB)*

– The SAN recommends a preferential use of pomalidomide over lenalidomide [42, 45]. *(Grade B, Level III)*

– The SAN suggests starting immunomodulatory agent treatment in reduced doses (pomalidomide; start at 1

Figure 2: Treatment algorithm for r/r light-chain amyloidosis (AL) as proposed by the SAN (SAN). ASCT: autologous stem cell transplantation; BSC: best supportive care; Dara: daratumumab; Dexa: dexamethasone; HD: high-dose therapy; IMIDs: immunomodulatory agents; PBSC: peripheral blood stem cells; PI: proteasome inhibitor; r/r: relapsed/refractory; t(11;14): translocation 11;14; 1L: first-line treatment.



mg/d, lenalidomide; start at 5 mg/d) and subsequent dose escalation, if tolerated. *(Grade C, Level IV)*

Oral melphalan + dexamethasone: no t(11;14) and immunomodulatory agents not feasible

Melphalan alone or in combination with dexamethasone (MelDex) has been studied quite extensively in the field of light-chain amyloidosis. In selected patients, without significant comorbidities or advanced cardiac involvement, it has been shown to be effective but is associated with relevant toxicity [46, 47].

The SAN recommends treatment with melphalan/dexamethasone (MEL 0.22 mg/kg/d and Dex 20–40 mg/d , d1–4 every 28 days [46]) in patients without significant cardiac involvement (<revised Mayo Stage III) and not qualifying for the other therapeutic options. *(Grade A, Level I)*

High-dose therapy melphalan and autologous stem cell transplantation: only selected patients in the r/r setting

If not already performed upfront, in patients considered medically fit according to the proposed criteria (see above, "Considerations before and during treatment") and when autologous stem cells are available, high-dose therapy and autologous stem cell transplantation may be considered at relapse [24].

The SAN recommends early consideration of high-dose therapy / autologous stem cell transplantation as part of relapse treatment for eligible patients. *(Grade B, Level III)*

Prior reinduction is optional. *(Grade C, Level IV)*

Ixazomib: if bortezomib is not feasible

Ixazomib-dexamethasone was evaluated in a phase III study [48] (Tourmaline) where it showed no advantage in haematological response over physician's choice. As the proteasome-inhibitor bortezomib is often part of first- or second-line treatment, an additional benefit of ixazomib at later time points is expected only in very specific scenarios, i.e. if tolerability is of higher priority [49] (see below, "Supportive care and treatment in advanced organ involvement").

The SAN recommends treatment with ixazomib only in selected scenarios and if bortezomib is not feasible. *(Grade A, Level 1)*

Further-line treatment options

If patients progress after the proposed second-line options and do not qualify for retreatment, the optimal treatment will again depend on prior exposure, comorbidities and potential access to novel therapies, which is often limited to patients with associated symptomatic myeloma.

Bispecific T-cell engagers (BiTe) and chimeric antigen receptor T-cells (CAR-T)

Early retrospective studies have been published demonstrating efficacy and good tolerability of BCMA-directed bispecific antibodies [50, 51]. Given the often low plasma cell burden in light-chain amyloidosis and the therefore high "effector to target" ratio, they potentially reflect a very effective, well-tolerated and promising treatment option.

The SAN suggests treatment with BCMA-BiTe in eligible patients, relapsed/refractory or not qualifying to all other established 2nd line treatment options. *(Grade C, Level III)*

Preliminary data on successful CAR-T cell treatment has recently been published in a very selected patient population [52–54]. Given its potential side effects in patients with severe organ involvement and its financial burden, CAR-T cells are not yet established outside of clinical trials and rather reflect a potential future option.

So far, the SAN does not recommend treatment with CAR-T cells outside clinical trials. *(Grade B, Level IIB)*

Treatment options currently not recommended by the SAN

Carfilzomib has been shown to be associated with a high rate of severe adverse events in patients with light-chain amyloidosis, especially resulting from its potential cardiac toxicity [55].

If other options are available, the SAN does not recommend carfilzomib-based treatment. *(Grade B, Level IIA)*

Various light-chain amyloid-targeting agents have been developed. To date, none of them has been translated into clinical practice. A phase III study with birtamimab, a humanised IgG1 binding circulating and deposited light-chain fibrils, is currently recruiting (AFFIRM-AL). Prior phase I/II studies have shown somewhat inconsistent results [56–59].

Treatment of localised light-chain amyloidosis

Localised amyloidosis, if not involving a critical site, generally does not impair survival of affected patients and almost never progresses to a systemic disease [60]. The treatment of "amyloidoma" is therefore reserved for symptomatic disease and usually involves surgical excision whenever possible (although evidence is sparse) [61, 62]. In selected cases where surgery is not feasible, radiotherapy or laser treatment can be an alternative local treatment options [63].

The SAN recommends local treatment (such as surgical resection) of localised light-chain amyloidosis in symptomatic patients. *(Grade B, Level III)*

If local treatment is not feasible and need for therapy is high, an individualised approach with systemic treatment may be considered. *(Grade C, Level IV)*

The SAN recommends annual follow-up to screen for local recurrence [64]. *(Grade B, Level III)*

During follow-up, the SAN generally suggests not to perform repetitive extensive evaluation for systemic involvement, but to perform a regular basic screening with NT-proBNP and albuminuria measurements. *(Grade B, Level III)*

Supportive care and treatment in advanced organ involvement

Monitoring during follow-up

Supportive care requires a multidisciplinary approach. Monitoring of organ function includes repetitive assess-

ment of involved organs and screening of new potential end-organ disease [65]. The SAN suggests the following approach [66–68]:

The SAN suggests a comprehensive cardiac assessment every 6–12 months (cardiac biomarkers, ECG, Holter ECG, echocardiography, MRI if image quality is poor).

The SAN suggests routine renal assessment at least every 3 months with standard measurements (eGFR, proteinuria in spot urine) and a more comprehensive assessment every 6–12 months in case of significant renal involvement or treatment toxicity.

The SAN suggests assessment of liver enzymes at least every 3 months and a more comprehensive assessment every 12 months (sonography, liver stiffness) in case of involvement or associated toxicity.

The SAN suggests clinical screening for polyneuropathy at least every 3 months and a comprehensive assessment (clinical examination, autonomic testing and ENMG) every 12 months in case of organ involvement or significant treatment-related neuropathy. Additional skin biopsy for assessment of small-fibre neuropathy can be considered [69, 70].

General measures of supportive care and disease-modifying therapy

Supportive care includes symptom management; anti-infective strategies; management of cardiac and renal involvement, neuropathy and GI dysfunction; and treatment of potential therapy-induced toxicities [65, 71]. Optimal supportive care is achieved through multidisciplinary care, preferably within the SAN. Due to the rarity of the disease and the heterogeneity of the clinical picture, studies focusing on supportive measures are rare. Therefore, many of the following recommendations are extrapolated from similar scenarios in other diseases. The few supportive care drugs that have been studied specifically in light-chain amyloidosis include doxycycline and Epigallo-Catechin-Gallat (EGCG). However, after promising early-phase study results, doxycycline failed to show significant benefit in a phase III trial and should therefore no longer be part of supportive care in light-chain amyloidosis [72]. Similarly, although often associated with much patient hope, there is only insufficient evidence to support the use of Epigallo-Catechin-Gallat or other green tea extracts [73, 74]. Patients should be advised not to co-administer Epigallo-Catechin-Gallat with immunochemotherapy agents due to potential interactions.

The SAN recommends against the use of doxycycline as a supportive agent in light-chain amyloidosis. *(Grade A, Level I)*

The SAN suggests not to use Epigallo-Catechin-Gallat in light-chain amyloidosis during chemo-immunotherapy. *(Grade C, Level IV)*

Cardiovascular care

The most common early clinical manifestations of cardiac involvement in light-chain amyloidosis are heart failure with preserved ejection fraction (HFpEF), with predominant diastolic dysfunction and its consequences. Fluid retention with elevated filling pressures together with structural alterations in the atria increase the likelihood for atrial fibrillation and thromboembolic stroke. Amyloid deposition can also lead to heart block and arrhythmia such as ventricular tachycardia.

Heart failure and fluid management

As early mortality is high in patients with advanced cardiac involvement (revised Mayo Stage IV / European modification Stage IIIb), immediate initiation of plasma cell-directed therapy is crucial. Treatment requires close collaboration with heart failure specialists and may even require in-hospital monitoring during the first days of treatment. Daratumumab alone or in combination with dexamethasone has been shown to be safe and effective as initial treatment [25] (see section “First-line treatment of light-chain amyloidosis”).

In advanced cardiac involvement (rMayo IV), the SAN suggests in-hospital monitoring during initiation of treatment. *(Grade C, Level IV)*

Administration of diuretics is often required (furosemide or torasemide ± spironolactone). However, careful dose titration is advised to avoid symptomatic hypotension and significant reduction of preload, which may further deteriorate cardiac function. Potential potassium supplementation and restriction of salt and volume intake may be advisable [67].

Standard heart failure therapy including beta-blockers, RAAS inhibitors and calcium-channel blockers should be used with great caution as they are often not well tolerated and may worsen clinical symptoms (orthostatic hypotension, volume overload) [75].

The SAN suggests initiation of loop diuretics in patients with volume overload (low starting dose, e.g. torasemide 5–10 mg). *(Grade C, Level IV)*

The SAN suggests that calcium-channel blockers should generally be avoided. RAAS inhibitors and beta-blockers should only be used in selected cases and with great caution [76, 77]. *(Grade C, Level IV)*

The SAN cannot recommend for or against treatment with SGLT2 inhibitors due to insufficient evidence. *(Grade C, Level IV)*

Heart transplant is an option for eligible patients in the absence of severe other organ involvement [78, 79]. It should always be followed by very close monitoring of haematological response and a low threshold for light-chain amyloidosis directed treatment.

The SAN recommends evaluation of heart transplantation in young patients. *(Grade B, Level IIb)*

Arrhythmia

Due to its frequency, arrhythmia should be actively screened for (see section “Monitoring during follow-up” above). Antiarrhythmic therapy should generally be limited to amiodarone. Rate control with a beta-blocker is also an option, but heart rate should not be lowered too much as cardiac output depends on heart rate with stroke volume fixed due to amyloid deposition [80].

If required, the SAN suggests pharmacological antiarrhythmic therapy preferably with amiodarone [80, 81]. *(Grade C, Level IV)*

With cardiac involvement, all patients with atrial fibrillation (Afib) are at very high risk of thromboembolic events [82]. Oral anticoagulation, irrespective of the CHA_2DS_2-VA score, is therefore generally advisable in the absence of overt bleeding or amyloidosis-associated coagulopathies. Particular attention should also be given to ventricular arrhythmias with the risk for sudden cardiac death [83]. Although an implanted cardiac defibrillator (ICD) may potentially be life-saving, its long-term benefit on mortality has not yet been proven in cardiac light-chain amyloidosis [84].

The SAN suggests oral anticoagulation irrespective of CHA2DS-VA in patients with cardiac involvement and Afib (unless there is significant coagulopathy). *(Grade C, Level IV)*

In selected patients with atrial mechanical dysfunction and restrictive filling pattern (severe diastolic dysfunction), anticoagulation can be evaluated in the absence of Afib. *(Grade C, Level IV)*

The SAN suggest the use of ICD in cardiac amyloidosis only in selected cases and after interdisciplinary discussion [85–87]. *(Grade B, Level IIa)*

The SAN cannot recommend for or against catheter ablation or LAA-occlusion in patients with cardiac light-chain amyloidosis. *(Grade C, Level IV)*

Renal support

Nephrotic syndrome

Fluid management and diuretic therapy (preferably loop diuretics, may be combined with thiazides and/or spironolactone in diuretic resistance) are among the mainstays of treatment. To date, evidence to support albumin infusions is insufficient. In patients with progressive hypoalbuminaemia, management of haemostasis can be particularly challenging (see section “Management of gastrointestinal involvement and haemostasis”).

The SAN does not generally suggest prophylactic anticoagulation in severe nephrotic syndrome with serum albumin <25 g/l due to the potentially increased risk of bleeding. *(Grade C, Level IV)*

In patients with renal light-chain amyloidosis and proteinuria, the SAN does not recommend anti-proteinuric treatment with RAAS-blocking agents, as their potential harm in co-existing autonomic dysfunction and cardiac amyloidosis may outweigh the potential benefits [88–90]. *(Grade B, Level IIb)*

The SAN suggests salt and fluid restriction in resistant oedema. *(Grade C, Level IV)*

End-stage renal disease (ESRD)

RAAS-blocking agents may be introduced, but caution is advised concerning hypotension and autonomic dysfunction (see above). Optimal control of independent cardiovascular risk factors is recommended. Dialysis has been shown to improve survival particularly in patients without end-stage heart disease [91–94]. Peritoneal dialysis may be preferable over haemodialysis in end-stage renal disease and heart failure, given its superior haemodynamic tolerance [95]. Standard first-line Dara SC-CyBorD can be safely administered to patients with end-stage renal disease with or without dialysis. However, many other light-chain amyloidosis treatment options should be dose-reduced or omitted in patients with end-stage renal disease.

The SAN recommends evaluation of dialysis in end-stage renal disease. *(Grade B, Level IIB)*

Kidney transplantation has been shown to have similar outcomes in renal light-chain amyloidosis compared to other causes of end-stage renal disease [92, 96]. An adequate haematological response (very good partial response or better) to light-chain amyloidosis treatment and/or promising further therapies are prerequisites, as local recurrence is otherwise foreseeable.

The SAN recommends evaluation of kidney transplantation in selected patients. *(Grade B, Level IIB)*

Management of gastrointestinal involvement and haemostasis

Management of gastrointestinal complaints is challenging and often focuses on symptomatic treatment [97]. Malnutrition may require nutritional counselling; evidence on parenteral nutrition is very sparse. Patients with high bilirubin represent a particular challenge because liver-specific dose modification for many established amyloidosis-directed treatment options remains poorly studied.

In advanced amyloidosis, bleeding potentially complicates severe hepatic failure or may be associated with amyloid vasculopathy, factor X deficiency, hypofibrinogenaemia or other clotting factor deficiency [98]. However, risk of thrombosis may also be relevant due to the disease-associated immobility, therapy (e.g. immunomodulatory agents) or possible nephrotic syndrome. The optimal strategy for managing haemostasis therefore requires an individualised, multidisciplinary consensus.

Polyneuropathy

Supportive care measures focus on symptom management and prevention of further treatment-related damage. In patients with neuropathic pain associated with peripheral neuropathy, symptomatic treatment is essential. First-line treatments include serotonin-noradrenaline reuptake inhibitors and gabapentinoids. Second-line treatments include tramadol, tricyclic antidepressants (beware of hypotension), combinations and adjunctive psychotherapy. Autonomic neuropathy presents a particular challenge (postural hypotension) and may also require symptomatic treatment [99].

Amyloidosis-directed treatment in patients with significant neuropathy should not include bortezomib. Daratumumab, alone or in combination with cyclophosphamide and/or dexamethasone, as well as immunomodulatory agents are feasible. In this specific patient population, the SAN also considers ixazomib a reasonable alternative when bortezomib is not feasible [48].

The SAN recommends initial treatment with single-agent daratumumab in patients with severe polyneuropathy (CTCAE grade III). *(Grade C, Level IV)*

The SAN suggests symptomatic treatment of peripheral nervous system involvement with gabapentin (start dose 100 mg 3 ×/d, ramp up to max. 1200 mg 3 ×/d) and/or

duloxetine (start dose 30 mg/d, ramp up to max. 120 mg/d) under close blood pressure monitoring [81]. *(Grade C, Level IV)*

In symptomatic hypotension, pressure stockings, abdominal binders and midodrine are valuable options [100] (starting dose 3 × 2.5 mg/d and escalation to a max. of 10 mg 3 ×/d). *(Grade C, Level IV)*

Infection prevention

Many forms of amyloid- and/or plasma cell-directed treatment, particularly daratumumab, often cause profound hypogammaglobulinaemia, increasing the risk of infections. Immunoglobulin substitution may be beneficial; it is reimbursed in Switzerland in cases of total IgG <4 g/l and repetitive infections or inadequate antibody response to vaccination [101].

The SAN suggests immunoglobulin substitution in patients with total serum IgG <4 g/l and infectious complications. *(Grade C, Level IV)*

The SAN recommends seasonal vaccination against influenza and COVID infections during treatment and pretherapeutic invasive pneumococcal disease vaccination. *(Grade B, Level III)*

The SAN suggests Varicella zoster virus-reactivation prophylaxis in light-chain amyloidosis patients undergoing plasma cell-directed treatment; PJP prophylaxis may be considered. *(Grade C, Level IV)*

Conclusion

Fortunately, the evidence for upfront management of patients with light-chain amyloidosis has improved significantly in recent years. However, management in the relapsing/remitting setting, in patients with more significant comorbidities or in those with very advanced disease, still requires expert consensus, as the available evidence is limited to small prospective phase II or observational studies. Supportive care should always involve a multidisciplinary team, as patterns of organ involvement and clinical presentation are very heterogeneous. In particular, management of the most advanced and morbid patients requires a comprehensive care approach. Whenever possible, patients should be considered for clinical trials.

Author contributions

Conceptualisation: Rahel Schwotzer, Max Rieger, Bernhard Gerber. Data curation, investigation and methodology: Rahel Schwotzer, Max Rieger. Funding acquisition: Rahel Schwotzer. Drafting of the original manuscript, project administration: Max Rieger, Rahel Schwotzer. Revision and Editing: All authors. Visualisation: Max Rieger, Rahel Schwotzer. Administrative, technical and material support: Max Rieger, Rahel Schwotzer. Supervision and validation: Rahel Schwotzer, Bernhard Gerber.

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