Retrospective cohort study of treatment with BCL-2 inhibitor venetoclax in advanced AL amyloidosis

Venetoclax, an oral Bcl-2 inhibitor, has shown promising results in t(11;14)-positive systemic light-chain (AL) amyloidosis, a translocation found in about half of patients with this condition. In this retrospective single-center study, 44 patients with relapsed or refractory t(11;14)-positive AL amyloidosis after a median of three previous lines of therapy were analyzed. Best hematologic responses (very good partial response [VGPR] or better) occurred in 77% (34/44) of the patients. Estimated event-free survival (EFS) was 86%, 68%, and 53% at 12, 24, and 36 months, respectively; overall survival (OS) was 95%, 81%, and 64%, respectively. Organ responses after 12 months were observed in 39% of cases with cardiac involvement and 62% of cases with renal involvement. Stratification by typical *versus* atypical t(11;14) variants revealed significantly inferior responses at 3 and 6 months for atypical cases. Grade ≥2 adverse events were significantly more frequent in patients with renal impairment (estimated glomerular filtration rate [eGFR] ≤30 mL/min). Venetoclax demonstrates efficacy even in advanced AL amyloidosis but atypical cytogenetic signatures and renal impairment may influence outcome and tolerability.

In AL amyloidosis misfolded light-chain deposits cause progressive organ dysfunction. Many patients relapse or become refractory and are ineligible for intensive treatment regimens.[1] Cytogenetically, t(11;14)(q13;q32.3), juxtaposing *CCND1* and *IGH*, is the most common aberration, observed in approximately 40–60% of AL-patients by interphase fluorescence *in situ* hybridization (FISH). This abnormality induces cyclin D1 overexpression and enhanced BCL-2 activity, creating a biological rationale for venetoclax.[2-4] Overall response rates of up to 90-100% in relapsed/refractory cases have been reported,[5,6] yet, no data exist on the impact of variant translocation patterns or renal impairment.[7]

We analyzed 44 venetoclax-treated patients with biopsy-proven AL amyloidosis and ≥1 prior therapy at the University Hospital Heidelberg (September 2020-May 2023) (Table 1). Written informed consent was obtained from the participants in this study, which was approved by the institutional ethics committee in accordance with the Helsinki Declaration. Outcomes comprised OS, EFS, hematologic and organ responses at baseline as well as 3, 6 and 12 months after treatment initiation, and treatment toxicity, with adverse events graded according to the Common Terminology Criteria for Adverse Events (CTCAE).[8,9] EFS was defined as the time from starting venetoclax until the first event of hematologic relapse and/or progression, initiation of new anticancer therapy or death from any cause. t(11;14) was confirmed by interphase FISH; typical and atypical variants were categorized based on *CCND1:IGH* fusion signal patterns (Figure 1). Venetoclax was predominantly administered as monotherapy (73%) and in 27% with dexamethasone. Doses ranged from 50-400 mg/day (starting dose 100 mg) according to tolerance and response (median 200 mg). Infection monitoring followed standard practice with recommended biweekly complete blood counts. No routine prophylactic antimicrobials were used. Prophylaxis was introduced based on clinical or laboratory signs of infection. In 29 patients (66%) venetoclax dosage was permanently or temporarily reduced; toxicity-driven discontinuation occurred in eight (18%) patients, with two maintaining their response (VGPR, complete response [CR]) after cessation. Twelve patients received additional weekly dexamethasone due to minor responses, impending relapse or treatment tolerability. Dexamethasone was given upfront (25%), within the first 6 months (42%) and added after 8 months in four cases.

Descriptive statistics and Kaplan-Meier analysis were applied, with Fisher exact and Mann-Whitney tests used for categorical and quantitative comparisons (SPSS version 29).

Ninety-five percent of the patients had t(11;14). The median number of prior therapy lines was three. Ninety-five percent of the patients had been exposed to daratumumab (84% refractory), 86% to bortezomib; prior lenalidomide and alkylator treatments were frequent. Venetoclax was started for refractory (34%)/relapsed (23%) disease, or for suboptimal hematologic response to prior lines of therapy (43%). The target dose was 400 mg. Addition of dexamethasone improved hematologic responses in 63% of cases. The overall response rate was 93% with ≥VGPR in 77% (39% CR). The median time to best response (CR, VGPR, partial response, stable disease or progressive disease [PD]) was 3 months; the median duration of response was 21 months. The median EFS and OS were not reached after a median follow-up of 26 months; at cutoff 50% remained on venetoclax, some maintaining their response after discontinuation (*Online Supplementary Figure S1*).

Most patients had multiorgan involvement (89% cardiac, 73% renal, 23% hepatic). Advanced cardiac involvement was evident, with 61% classified as stage IIIa or IIIb according to the European cardiac staging system.[10] After 12 months, organ responses were achieved in 39% of evaluable cardiac, 62% renal, and 37% hepatic cases. Organ improvement paralleled hematologic responses but tended to occur later.

Adverse events included diarrhea, nausea, neutropenia, infections, and fatigue. Grade ≥3 events occurred in 9% of patients (2 hematologic events, 2 infections with pulmonary focus). Dose reductions were frequent and 18% of patients discontinued venetoclax due to toxicity; other reasons for discontinuation were CR (N=2), organ progression, new ma-

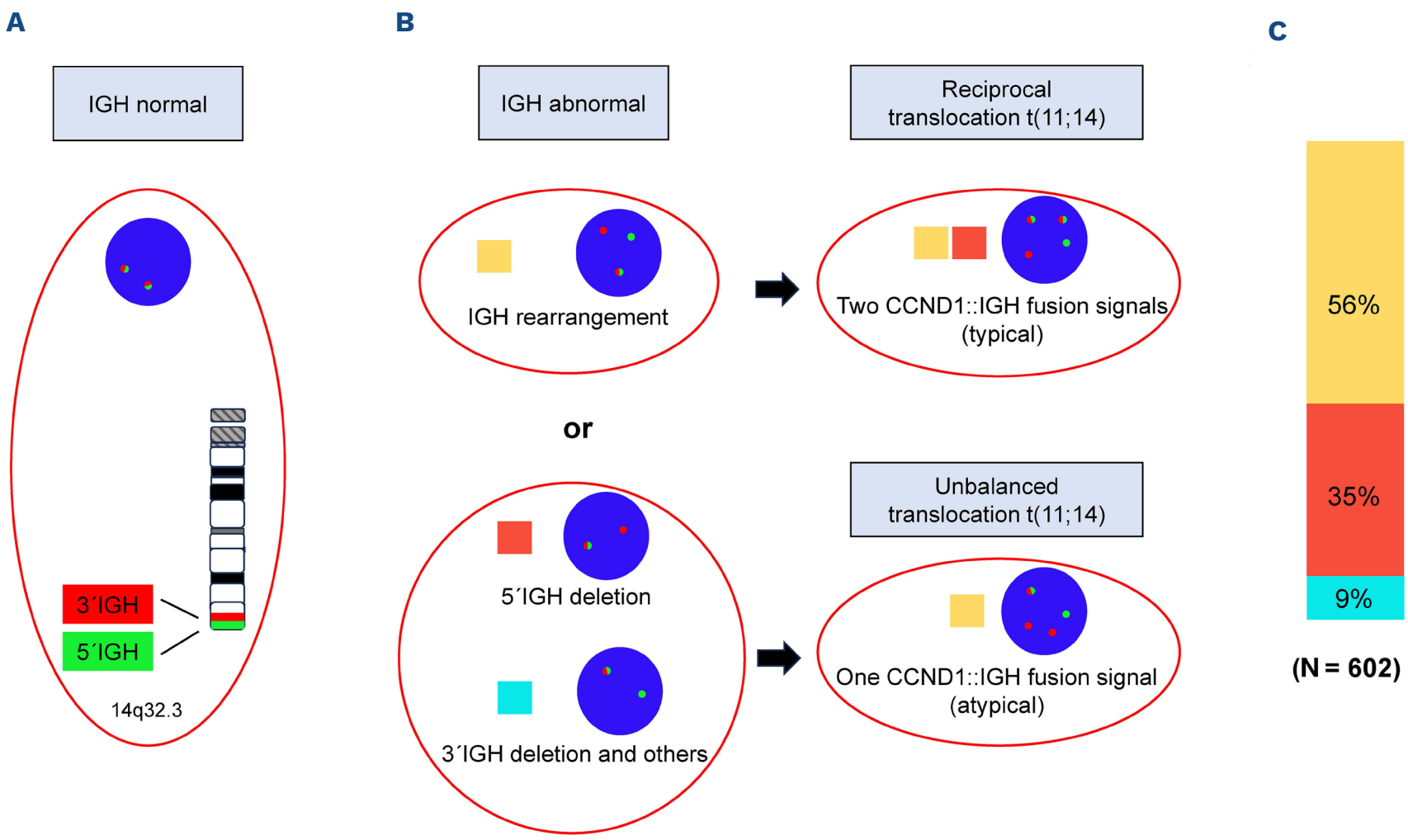

Figure 1. Schematic representation of normal and abnormal *IGH* patterns and t(11;14) signals. (A) IgH break-apart probe: schematic representation of a chromosomal rearrangement involving the heavy chain locus, particularly t(11;14) and normal finding in fluorescence *in situ* hybridization (FISH) diagnostics exhibiting two co-localized signals. (B, C) FISH results of structural abnormalities in the *IGH* gene: most commonly (56%) detection of one fusion signal, one red and one green signal. Below atypical signatures: in 35% one fusion and one red signal suggesting an *IGH* deletion and in 9.5% other variations are found.

lignancies, or evolving plasma-cell clones. Eleven patients discontinued due to progression. Twelve patients died during follow-up, four from AL-related organ failure, one from suicide, one from intestinal ischemia, and six after subsequent therapies. A patient who had previously undergone a heart transplant tolerated venetoclax well and achieved CR. The patients' baseline characteristics, response rates and toxicities are summarized in *Online Supplementary Tables S1* and *S2*.

Renal dysfunction (eGFR ≤30 mL/min) was present in 32% of the patients. These patients required more frequent dose reductions (71%; eGFR ≤30 mL/min observed in 14/44: venetoclax range: 50-400 mg, median 200 mg; eGFR >30 mL/min observed in 30/44: range 100-400 mg, median 300 mg) and represented 75% of grade ≥3 toxicities. Hemodialysis was required in five cases at baseline and in two more patients during therapy, who both died due to advanced AL organ progression. Adverse events grade ≥2 were significantly more frequent in this subgroup (P=0.048) (Figure 2). Impaired renal filtration was associated with higher N-terminal pro B-type natriuretic peptide levels, reflecting decreased clearance and advanced systemic disease.

Typical t(11;14) was present in 63% and atypical variants in 36% (42/44 cases evaluable). Atypical cases, showing deletions of either *IGH* signal, were more frequent among males and affected patients presented with higher baseline organ burden and poorer hematologic status. EFS was numerically longer for patients with typical translocations (29 *vs*. 25 months, P=0.285) (Figure 3A). The median OS did not differ significantly, but response depth did: non-responders occurred only in the group with atypical translocations. Early response rates (at 3 and 6 months) were significantly inferior in the group with atypical variants. After 3 months, responses among the group with the typical translocation were VGPR+CR 57% and no PD compared to VGPR+CR 75% and PD 17% among those with atypical variants (P=0.027). After 6 months the response rates were VGPR+CR 65% and no PD for patients with the typical translocation *versus* VGPR+CR 70% and PD 20% for those with atypical variants (P=0.03). Significance was lost by month 12, likely due to small cohort size (Figure 3B, C). The overall response rate was 100% for patients with the typical t(11:14) and 79% for those with atypical patterns, with a median duration of response of 21 *vs*. 19 months, respectively. Patients with amplification of 1q21 (11%) showed heterogeneous outcomes (2 CR, 2 VGPR, 1 PD). Response and survival were not associated with hematologic status

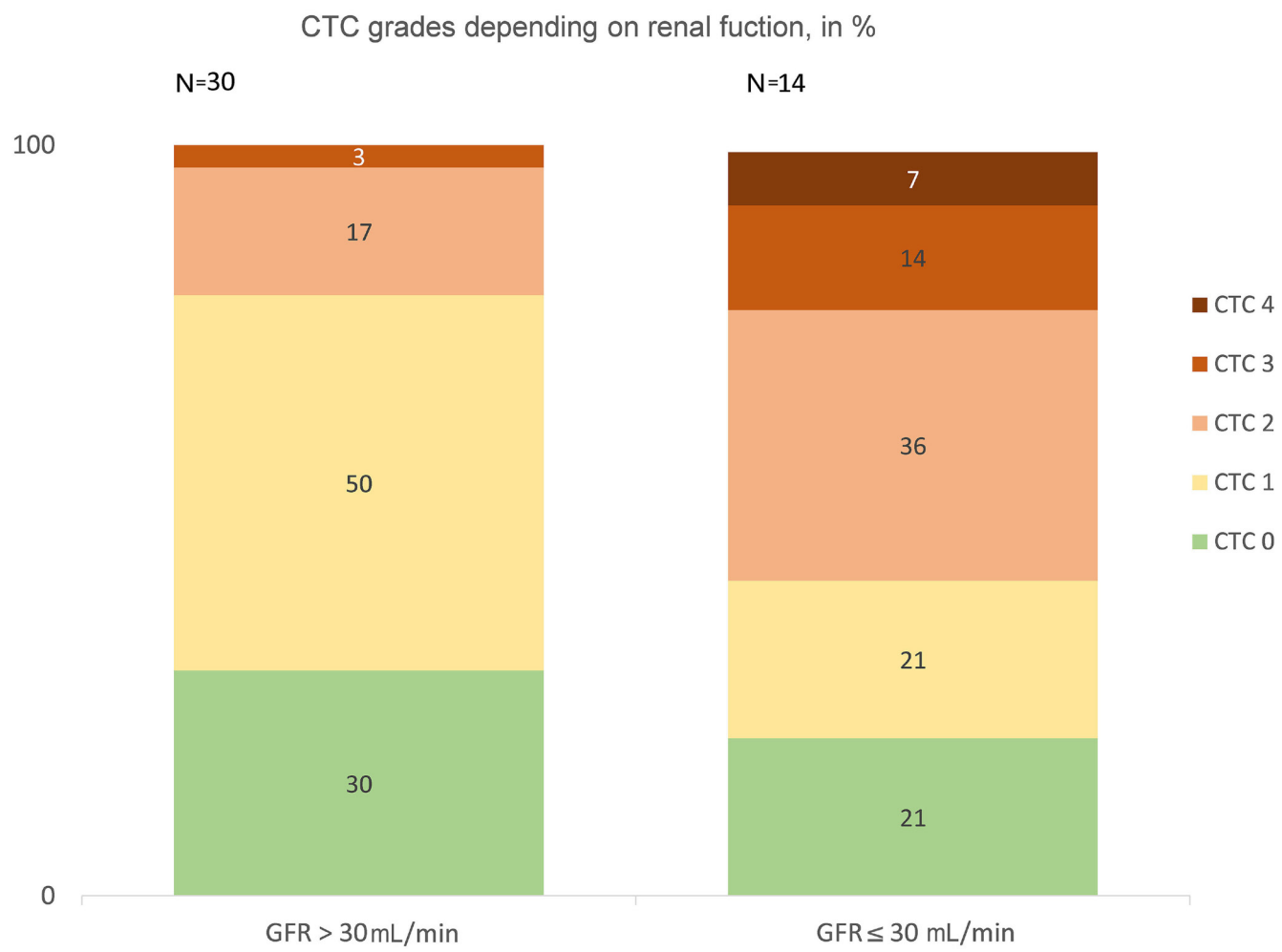

Figure 2. Comparison of grades of adverse events for the cohort segregated depending on renal function. Grades of adverse events according to Common Toxicity Criteria (CTC) for the subgroup of patients with estimated glomerular filtration rate (eGFR) >30 mL/min, N=30 compared to CTC grades for the subgroup with eGFR ≤30 mL/min, N=14. CTC grades differ significantly between groups (GFR ≤30 mL/min *vs*. >30 mL/min), *P*=0.048, with more higher-grade adverse events in the subgroup of patients with eGFR ≤30 mL/min.

at the start of venetoclax therapy.

Venetoclax demonstrated robust activity in heavily pretreated AL amyloidosis (e.g., 86% of the patients were daratumumab refractory), providing sustained hematologic control and clinically relevant organ improvement. The 93% overall response rate and 70% ≥VGPR align with previous reports and confirm that BCL-2 inhibition effectively targets the t(11;14)-positive clone.[9,11-15] The median EFS and OS were not reached and estimated 3-year survival above 60% suggests long-lasting benefit. The safety profile was favorable, with few grade 3-4 events despite extensive prior treatments and organ impairment,[6] although mortality was non-negligible and mainly linked to underlying disease and infections, emphasizing the need for vigilant supportive care.

This analysis is, to our knowledge, the first to explicitly evaluate toxicity by kidney function. The significant association between renal impairment and higher-grade adverse events suggests altered metabolism or delayed drug clearance. Clinically, reduced renal capacity should prompt cautious dose titration and close laboratory and clinical monitoring. A lower target dose (200 mg *vs*. 400 mg) might optimize the safety/efficacy balance in this subgroup.

Glucocorticoid co-medication appeared beneficial in a subset of patients suggesting possible synergism. In myeloma, venetoclax + daratumumab or bortezomib have yielded exceptional response rates, and these findings are mirrored in small AL cohorts.[5,6] Given the strong efficacy of venetoclax as a monotherapy, combination approaches may be reserved for relapse or suboptimal responders, balancing toxicity risks.

Our study suggests that not all t(11;14) translocations are biologically equivalent. Atypical variants with single fusion signals may represent unbalanced translocations leading to altered BCL-2 dependence or expression, potentially explaining inferior early response kinetics.[13] Our data support a refined cytogenetic classification of AL amyloidosis that integrates variant signal patterns. This could change the selection of patients for venetoclax-based therapy and might explain inter-individual differences in sensitivity. The role of overlapping genomic alterations such as 1q21 amplification also deserves exploration since it may modify apoptotic mechanisms.

In the evolving therapeutic landscape – including bispecific antigens targeting B-cell maturation antigen and chimeric antigen receptor T-cell products – venetoclax retains specific importance for t(11;14) carriers.

Limitations of this study included its retrospective character, small subgroup sizes, and reliance on clinical chart documentation for adverse event grading. The heterogeneity

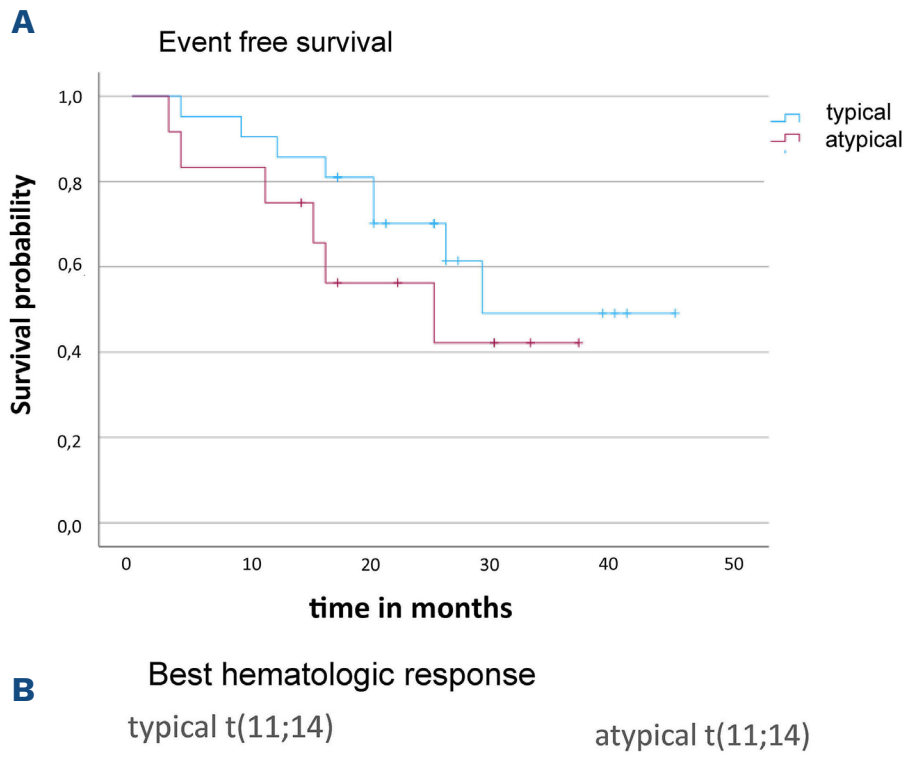

Figure 3. Venetoclax in typical *versus* atypical t(11;14)-positive AL amyloidosis. (A) Kaplan-Meier curves for event-free survival (EFS) in the patients divided according to whether they had typical (blue) or atypical (purple) t(11;14) with the median EFS being 29 and 25 months, respectively (P=0.285). Progression, relapse or death of any cause counted as an event. (B) Best hematologic responses for the segregated cohorts: typical t(11;14) *versus* atypical t(11;14). Fourteen percent of patients in the atypical t(11;14) cohort had primary refractory disease. (C) Comparison of hematologic response rates for patients with typical or atypical t(11;14) after 3, 6 and 12 months. After 3 and 6 months the distribution of hematologic response rates between the two groups was statistically significantly different, indicated by the star (3 months: *P*=0.05; 6 months: *P*=0.027) but not at 12 months (*P*=0.31). CR: completre response; PD: progressive disease; PR: partial response; SD: stable disease; VGPR: very good partial response.

of doses and the use of combination treatments preclude a standardized toxicity-efficacy correlation. The study's strengths lie in detailed cytogenetic and renal stratification and the longest follow-up in the largest single-center study in a real-world cohort.

Our investigation confirms that venetoclax provides substantial and durable responses in relapsed or refractory t(11;14)-positive AL amyloidosis with manageable toxicity. The findings encourage integration of venetoclax earlier in therapy algorithms and emphasize the need to individualize dosage and monitoring, particularly in patients with renal dysfunction. Differences between typical and atypical t(11;14) signatures may influence early response and outcome, advocating inclusion of variant analysis in future studies. Prospective trials are warranted to define standardized dosing strategies, explore optimal combination regimens and evaluate predictive biomarkers. Venetoclax thus represents a significant advance in AL amyloidosis therapy, offering targeted disease control and paving the way for precision-based treatment approaches.

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KV, TD, AJ, and MG have no conflicts of interest to disclose. CK has been a member of advisory boards for Amgen, AstraZeneca, Gilead, GSK, Janssen, Oncopeptides, Pfizer, Sanofi-Aventis, Sobi, and Takeda; has received financial support for congress participation from Amgen, AstraZeneca, Gilead, GSK, Janssen, and Sanofi-Aventis; and has received travel grants from Gilead and Janssen, Incyte, BMS, Oncopeptides, and AbbVie. UH has received honoraria for talks from Janssen, Pfizer, Alnylam, Prothena, and AstraZeneca; has received financial support for congress participation from Janssen, Prothena, and Pfizer; has participated in advisory boards for Pfizer, Prothena, Janssen, Alexion, Alnylam, and Neurimmune; and has obtained financial sponsoring of the Amyloidosis Registry from Janssen. MSR has received honoraria from BMS, Amgen, Janssen, Sanofi, AbbVie, and Oncopeptides for lectures or presentations; honoraria for advisory board participation from GSK, Pfizer, and Takeda; research support from BMS, Janssen, and Heidelberg Pharma; and travel grants from BMS, Amgen, Janssen, and Oncopeptides. SS has acted as a consultant/adviser for and received travel grants, honoraria, and research funding from Janssen and Prothena; has received research funding from Sanofi; has received honoraria from Pfizer and Takeda; is an adviser for Telix; and has received travel grants from Binding Site, Celgene, and Jazz.

Contributions

KV conceived the study, was responsible for the curation, analysis and visualization of the data, and prepared the original draft of the manuscript. SS and UH conceived the study and curated the data. All authors were involved in the interpretation of data, and critical review and editing of the manuscript.

Artificial intelligence

We used language editing tools, including OpenAI's ChatGPT and DeepL Write, to assist with the grammar and style refinement of this article.

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Data-sharing statement

The datasets are available from the corresponding author upon reasonable request.

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