Teclistamab for heavily pretreated relapsed/refractory POEMS syndrome

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin lesions)[1] is a rare B-cell lymphoproliferative disorder characterized by monoclonal plasma cell proliferation which belongs to the spectrum of monoclonal gammopathy of clinical significance (MGCS).[2] Diagnosis is based on a combination of clinical, radiological, and biological features, with established major and minor criteria. The diagnosis requires the presence of both polyneuropathy and a clonal plasma cell disorder as mandatory criteria.[3] The most characteristic presentations are the co-existence of demyelinating peripheral neuropathy with monoclonal gammopathy particularly when the light chain isotype is λ, but the diagnosis is still a challenge due to the rarity and the absence of symptomatic malignancy. In Europe the incidence is unknown but estimated to be 1% of multiple myeloma (MM) cases with approximately 50 to 60 new cases per year in France. The pathophysiology of POEMS syndrome is not yet completely established. To date, VEGF is the cytokine that seems most involved in the pathophysiology and activity of the disease.[4] This proangiogenic factor induces a rapid and reversible increase in capillary permeability by binding to endothelial cells. This action results in nerve edema and is probably responsible for neuropathy. The link between the monoclonal gammopathy and elevated vascular endothelial growth factor (VEGF) is not clear. In this MGCS disease, the tumor plasma cells involved is well characterized: in 95% of cases the clonal light chain is of λ isotype with a preferential rearrangement in the variable region (IGVL 1-44 or 1-40).[5] Plasma cell tumor mass, bone marrow infiltration as well as the circulating monoclonal component are often of limited quantity, and sometimes difficult to measure by standard methods.

We describe here the case of a 73-year-old man diagnosed with POEMS syndrome. Written informed consent was obtained from the patient for the publication. He initially presented a sensory-motor polyneuropathy with severe axonal damage secondary to demyelinating lesions, cervical and sub diaphragmatic lymphadenopathy, splenomegaly, hypothyroidism, adrenal insufficiency, gonadotropic insufficiency, skin lesions including angioma, osteosclerotic lesions of the pelvis, edematous syndrome with bilateral pleural effusion, and bilateral papilledema. Free λ light chain was at 180 mg/L in the serum and the bone marrow smear showed 2% of atypical plasma cells without cytogenetic abnormality. The patient initially received high-dose melphalan followed by autologous stem cell transplantation. He then relapsed 3 years later with new adenopathy and bone lesions, and was treated with melphalan orally and dexamethasone for 9 months. He relapsed again after a further 5 years, and he received two cycles of lenalidomide and dexamethasone followed by spinal radiotherapy (40 Gray [Gy]). At his third relapse, 4 years later, he again received lenalidomide dexamethasone and radiotherapy on the sixth thoracic vertebra. Two years later, at the fourth relapse a treatment with daratumumab pomalidomide dexamethasone induced a complete hematological and metabolic response. While still under this regimen at cycle 30, several cervical lymphadenopathies were observed, in association with an increase of both λ free light chain to 120 mg/L (κ 22.4 mg/l, ratio=0.18) as well as VEGF to 2,609 pg/mL in the serum (N <642 pg/mL, measured via enzyme-linked immunosorbant assay (Quantikine®, R&D Systems)[6]). The lymph node biopsy showed the presence of λ-restricted CD138+, CCND1-negative, HHV8/LANA-negative, CD56-negative plasma cells, along with Castleman-like changes. *In situ* hybridization revealed a λ monotype with no expression of heavy chain. We performed a 50 Gy radiotherapy of the cervical and left supraclavicular lymph node without efficacy. On positron emission tomography-computed tomography (PET-CT) post radiotherapy, a progression of the supradiaphragmatic lymph node involvement was observed, together with a heterogeneous infiltration of the axial and proximal appendicular skeleton, with several focal reinforcements (sternum, spine and pelvis).

The patient exhibited a clear re-emergence of clinical and biological disease activity. Clinically, several hallmark features of POEMS persisted, including polyradiculoneuropathy, and endocrinopathy. Notably, pleural effusion and skin changes, previously observed at diagnosis, were absent at this stage (Table 1). This relapse was treated by teclistamab. Teclistamab is a T-cell-redirecting bispecific antibody that targets both CD3 expressed on the surface of T cells and B-cell maturation antigen (BCMA) expressed on the surface of plasma cells. A first dose of 0.06 mg/kg subcutaneously (SC) at C1D1, then 0.30 mg/kg SC C1D4 and 1.50 mg/kg SC at C1D8 was initiated. After premedication with paracetamol 1 g (analgesic/antipyretic), dexchlorpheniramine 5 mg (H1-antihistamine), and dexamethasone 20 mg (corticosteroid), the first cycle was administered during hospitalization, followed by subsequent cycles at 1.50 mg/kg SC weekly in an outpatient setting. A grade 1 cytokine release syndrome (CRS) occurred following the first step-up dose, resolved without the need for tocilizumab, and did not recur with subsequent doses. Substitutive intravenous immunoglobulin was initiated to prevent infectious complications. According to International Myeloma Working Group recommendations,[7] due to the patient's multiple relapses and the initiation of a bispecific anti-BCMA antibodies, prophylactic treatment with amoxicillin, valacyclovir, and trimethoprim-sulfamethoxazole is indicated to prevent bacterial, viral infections and fungal respectively. At C2D1, λ free light chain was unde-

tectable in the serum (< 1.47 mg/L) and VEGF level returned to normal (Figure 1). We noticed a clear clinical reduction of tumor syndrome, confirmed on PET-CT after 6 months of treatment with a complete response (standardized uptake value [SUV] normal *vs*. 7.6; Figure 2). After the sixth cycle, the frequency of teclistamab administration was reduced to every 2 weeks until cycle 12, followed by monthly injections until cycle 20, after which teclistamab treatment was discontinued. Since the initiation of teclistamab, the patient has not required rehospitalization for the management of any infection. Currently, 2 years after teclistamab initiation, the patient is regularly monitored through medical consultations, levels of λ free light chain and VEGF both remain normal (Table 1).

The primary goal of treatment in POEMS syndrome is to block the proliferation of monoclonal plasma cells thereby reducing pathogenic free light chains and preventing organ damage. If started before the neurological damage becomes too severe, neurological recovery can be excellent. Fast, deep and sustained hematologic response correlates with improved organ function and survival outcomes. For our reported case, radiotherapy alone did not achieve control of the progressive disease, which is why treatment with teclistamab was initiated. In the event of marrow infiltration and bone lesions, the best treatment is intensive chemotherapy followed by reinjection of autologous hematopoietic stem cells.[8] In relapse setting, there is no consensus on the best treatment to offer although the use of anti-plasma cell agents particularly lenalidomide appears effective.[9,10] However new treatment options for RR POEMS syndrome remain an unmet medical need.

With the recent emergence of highly effective immunotherapies, daratumumab, an anti-CD38 monoclonal antibody, with lenalidomide and dexamethasone was reported for the first time in the context of RR POEMS syndrome in 2018 in a 60-year-old woman who progressed 18 months after therapeutic intensification. At 11 months, the patient was in complete hematological response with neurological improvement.[11] Another POEMS patient was treated with autologous T cells carrying a chimeric receptor for the BCMA antigen (CAR T cells) in 2018, with a complete response at 10 months.[12]

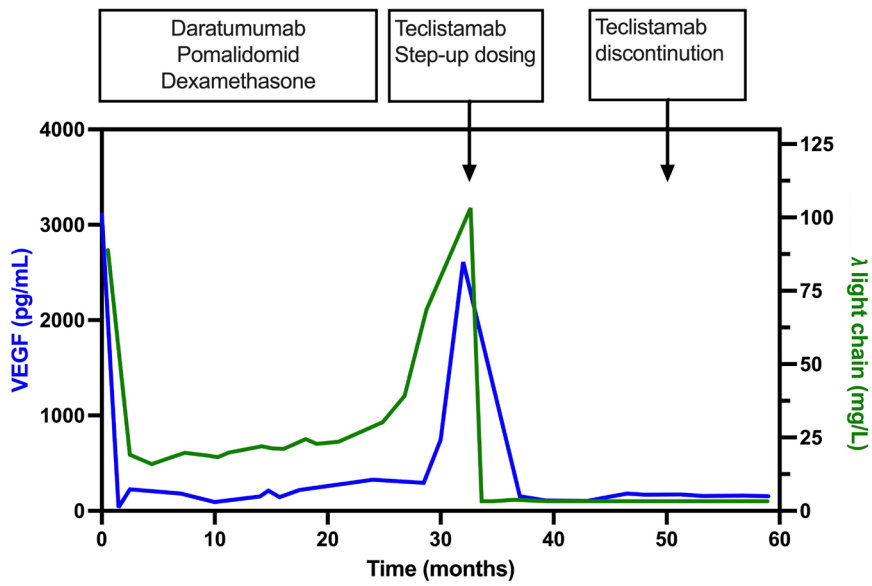

Figure 1. Evolution of vascular endothelial growth factor and free λ light chain under treatment in relapsed/refractory POEMS syndrome. POEMS: polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin lesions; VEGF: vascular endothelial growth factor.

Table 1. Patients characteristics at diagnostic, last relapse and at last follow-up.

Characteristics	Diagnosis	Last relapse	Last follow-up
Age, years	54	71	73
Treatment	Melphalan HD	Teclistamab	None
Polyradiculoneuropathy	X	X	X
Organomegaly	X	X	0
Endocrinopathy	X	X	X
Monoclonal gammopathy	X	X	0
Skin lesions	X	0	0
Osteosclerotic lesions	X	X	0
Pleural effusion	X	0	0
Bilateral papilledema	X	-	-
Blood count			
Hemoglobin, g/L	137	112	124
Platelets, $\times 10^9$/L	238	277	152
Neutrophils, $\times 10^9$/L	4.9	1.5	1.9
Lymphocytes, $\times 10^9$/L	1.2	1.3	0.9
Creatinine, μmol/L	99	92	62
FLC ratio, λ/κ	9	5	<0.4
λ light chain, mg/L	180	120	<1.47
VEGF, pg/mL	1,696	2,609	133

X: present; O: absent; -: not done; FLC: free light chain; HD: high dose; VEGF: vascular endothelial growth factor.

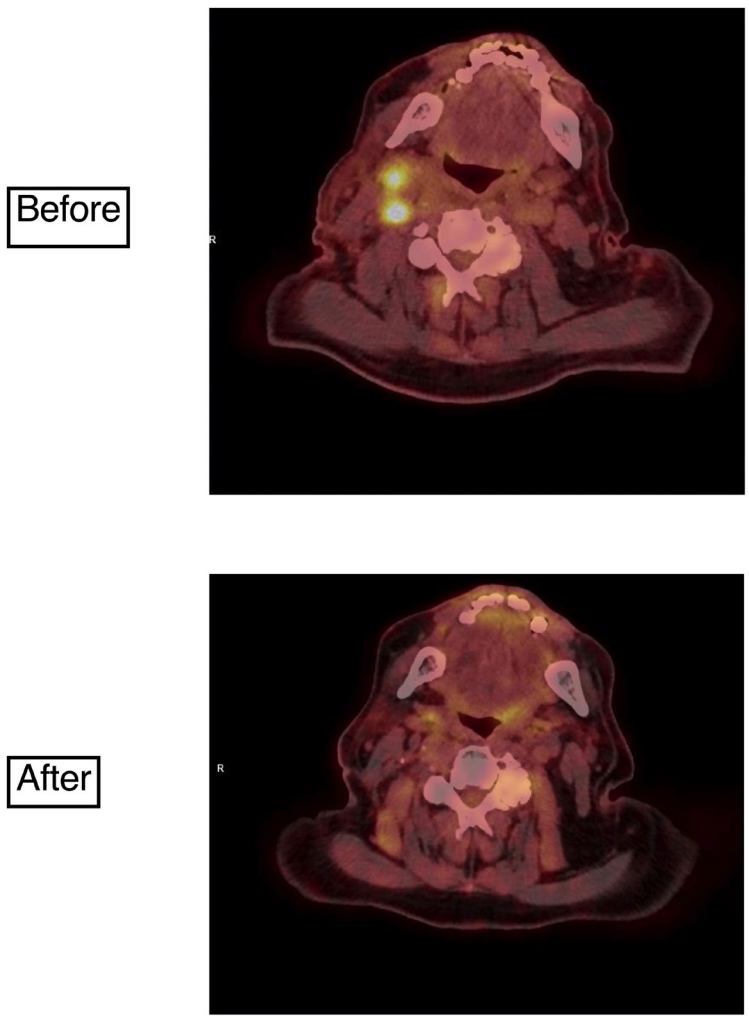

Figure 2. ^{18}FDG positron emission tomography/computed tomography before and after teclistamab in relapsed/refractory POEMS syndrome. (A) Positron emission tomography/computed tomography image prior teclistamab treatment and after 6 months of treatment with complete response. (B) Clear clinical reduction of tumor syndrome is visible. ^{18}FDG: 18 fluorodeoxyglucose; POEMS: polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin lesions.

Teclistamab, has recently been approved for use in relapsed/refractory MM (RR MM), following the results of a pivotal phase I-II study (MajesTEC-1) involving 165 patients with triple-class-exposed RR MM.[13] Teclistamab showed promising efficacy, with 65% of patients having a partial response or better. The progression-free survival was 11.3 months and 39.4% of patients had a complete response or better, with 26.7% reaching MRD negativity despite a history of extensive previous treatments and a disease that was refractory to currently available therapies. The main safety concerns are mostly grade 1/2 infections, but also the occurrence of CRS or immune cells associated neurological symptoms (ICANS).[14] Teclistamab has already been used successfully in other types of MGCS. For RR AL amyloidosis patients, teclistamab showed promising results in a recent series of 17 patients, with very good partial response or better in 88% of patients, involved free light chain <10 mg/L in 76%, with a 35% rate of severe infections and no cardiac or kidney related events.[15] Most responses appeared from the first cycle of treatment. This case describes a 73-year-old patient with a 20-year course of POEMS syndrome with heavily pretreated relapsed/refractory who achieved a rapid and durable complete remission 6 months after last bispecific injection, highlighting its potential efficacy and safety in this rare plasma cell disorder. In patients with MGCS and low tumor burden, bispecific anti-BCMA antibodies may offer effective treatment with a shorter duration. This approach could reduce treatment-related complications while maintaining disease control, warranting further investigation. This case suggests that bispecific anti-BCMA antibodies may offer a valuable treatment option in refractory POEMS syndrome, supporting their consideration in future clinical practice.

Authors

Alexis Talbot,[1,2] Nathalie Forgeard,[1] Tristan Vaugeois,[1] Floriane Theves,[1] Sabrine Dimassi,[1] Bruno Royer,[1] Pierre-Edouard Debureaux,[1] Véronique Meignin,[3] Laetitia Vercellino,[2,4] David Boutboul,[1,2] Bertrand Arnulf[1,2] and Stéphanie Harel[1]

[1]Immuno-Hematology, Saint Louis Hospital, AP-HP; [2]Université Paris Cité; [3]Department of Pathology, Saint-Louis Hospital, AP-HP and [4]Department of Nuclear Medicine, Saint Louis Hospital, AP-HP, Paris, France

Correspondence:
A. TALBOT - alexis.talbot@aphp.fr

https://doi.org/10.3324/haematol.2025.287606

Received: February 18, 2025.
Accepted: June 20, 2025.
Early view: July 3, 2025.

Disclosures

AT discloses advisory boards at Janssen, BMS, Takeda, Amgen, Sanofi, and Pfizer BA; research funding (to the institution) from BMS and Janssen; honoraria fom Janssen, BMS, Sanofi and GSK; travel funding from Janssen, BMS, Sanofi and Amgen. All other authors have no conflicts of interest to disclose.

Contributions

AT, SH and BA designed the study and analyzed the data. AT wrote the paper. All authors revised and approved the final manuscript.

Acknowledgments

We acknowledge and appreciate the participation of the patient affected by POEMS syndrome.

Data-sharing statement

The data supporting the findings of this case report are available from the corresponding author upon reasonable request.

References

1. Bardwick PA, Zvaifler NJ, Gill GN, Newman D, Greenway GD, Resnick DL. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS Syndrome: report on two cases and a review of the literature. Medicine (Baltimore). 1980;59(4):311-322.
2. Fermand JP, Bridoux F, Dispenzieri A, et al. Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications. Blood. 2018;132(14):1478-1485.
3. Dispenzieri A. POEMS syndrome: update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(12):1934-1950.
4. Watanabe O, Arimura K, Kitajima I, Osame M, Maruyama I. Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. Lancet. 1996;347(9002):702.
5. Bender S, Javaugue V, Saintamand A, et al. Immunoglobulin variable domain high-throughput sequencing reveals specific novel mutational patterns in POEMS syndrome. Blood. 2020;135(20):1750-1758.
6. Wang C, Huang XF, Cai QQ, et al. Remarkable expression of vascular endothelial growth factor in bone marrow plasma cells of patients with POEMS syndrome. Leuk Res. 2016;50:78-84.
7. Raje NS, Anaissie E, Kumar SK, et al. Consensus guidelines and recommendations for infection prevention in multiple myeloma: a report from the International Myeloma Working Group. Lancet Haematol. 2022;9(2):e143-e161.
8. Li J, Duan MH, Wang C, et al. Impact of pretransplant induction therapy on autologous stem cell transplantation for patients with newly diagnosed POEMS syndrome. Leukemia. 2017;31(6):1375-1381.
9. Royer B, Merlusca L, Abraham J, et al. Efficacy of lenalidomide in POEMS syndrome: a retrospective study of 20 patients. Am J Hematol. 2013;88(3):207-212.
10. Li J, Huang XF, Cai QQ, et al. A prospective phase II study of low dose lenalidomide plus dexamethasone in patients with newly diagnosed polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. Am J Hematol. 2018;93(6):803-809.
11. Dima D, Valent J, Khouri J. Daratumumab monotherapy for relapsed POEMS syndrome. Am J Hematol. 2023;98(11):E291-E294.
12. Xu J, Wang Q, Xu H, et al. Anti-BCMA CAR-T cells for treatment of plasma cell dyscrasia: case report on POEMS syndrome and multiple myeloma. J Hematol Oncol. 2018;11(1):128.
13. Usmani SZ, Garfall AL, van de Donk NWCJ, et al. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet. 2021;398(10301):665-674.
14. Moreau P, Garfall AL, Van De Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2022;387(6):495-505.
15. Forgeard N, Elessa D, Carpinteiro A, et al. Teclistamab in relapsed or refractory AL amyloidosis: a multinational retrospective case series. Blood. 2024;143(8):734-737.