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Teclistamab for heavily pretreated relapsed / refractory POEMS syndrome

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Key points: Teclistamab, a bispecific anti-CD3/BCMA antibody demonstrated a complete response in heavily pretreated relapsed/refractory POEMS syndrome, representing the first reported case of its efficacy in this setting.

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 coexistence of demyelinating peripheral neuropathy with monoclonal gammopathy particularly when the light chain isotype is lambda, 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 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 lambda 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 lambda 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 during 9 months. He relapsed again after a further 5 years, and he received 2 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 lambda free light chain to 120 mg/L (kappa 22.4 mg/l, ratio 0.18) as well as vascular endothelial growth factor (VEGF) to 2609 pg/mL in the serum (N< 642 pg/mL, measured via ELISA (Quantikine®, R&D Systems)[6]). The lymph node biopsy showed the presence of lambda-restricted CD138+, CCND1-negative, HHV8/LANA-negative, CD56-negative plasma cells, along with Castleman-like changes. In situ hybridization revealed a lambda monotype with no expression of heavy chain. We performed a 50 Gy radiotherapy of 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 milligrams (mg) /kilograms (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 IMWG 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, lambda free light chain was undetectable in the serum (< 1.47mg/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 6th 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 never required rehospitalization for the management of any infection. Currently, 2 years after teclistamab initiation, the patient is regularly monitored through medical consultations, levels of lambda 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].

Teclistamab, has recently been approved for use in relapsed/refractory MM (RR MM), following the results of a pivotal phase 1–2 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.

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

	Diagnosis	Last relapse	Last follow-up
Age	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 (l/k)	9	5	<0.4
Lambda light chain (mg/L)	180	120	<1.47
VEGF (pg/mL)	1696	2609	133

X: present; O: absent; -: Not done; FLC: free light chain; VEGF: vascular endothelial growth factor

Figure Legends

Figure 1: Evolution of VEGF and free lambda light chain under treatment in RR POEMS syndrome

R/R: relapsed/refractory

POEMS: Polyradiculoneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin lesions

VEGF: vascular endothelial growth factor

Figure 2: 18 FDG PET-CT before and after teclistamab in RR POEMS syndrome

18 FDG PET-CT : 18 Fluorodeoxyglucose Positron Emission Tomography/computed tomography

R/R: relapsed/refractory

POEMS: Polyradiculoneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin lesions

Figure 1: Evolution of VEGF and free lambda light chain under treatment in RR POEMS syndrome

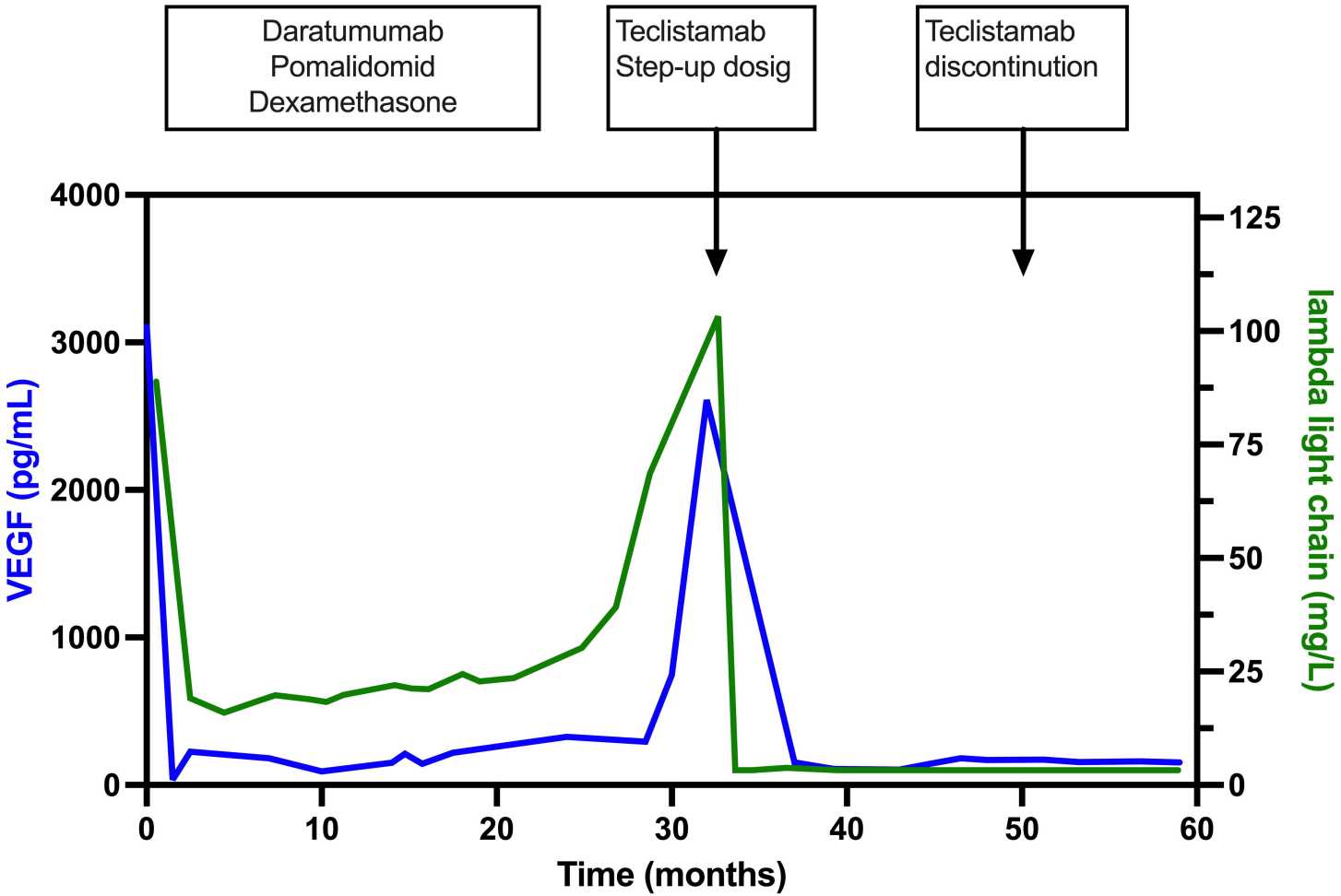
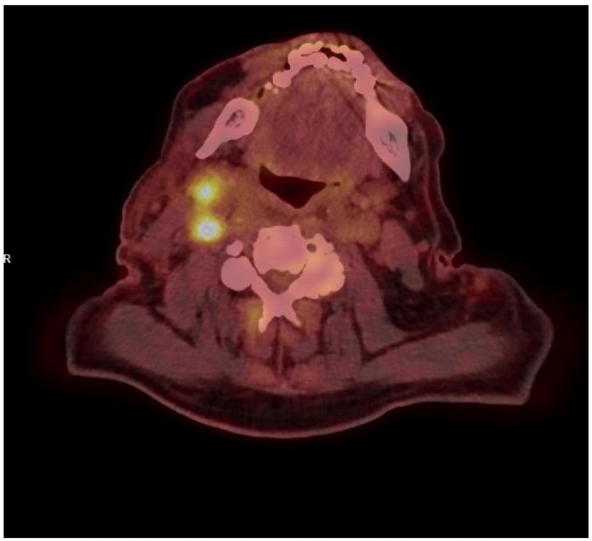


Figure 2: 18 FDG PET-CT before and after teclistamab in RR POEMS syndrome

Before



After