Title: Successful desensitization to pomalidomide in a patient with POEMS syndrome with delayed-type hypersensitivity to immunomodulatory imid drugs.

Authors: Grandoni F, Stalder G, Borgeat Kaeser A, Ribi C, Cairoli A, Blum S

Journal: Leukemia amp; lymphoma

Year: 2019 Jun 4

Pages: 1-3

DOI: 10.1080/10428194.2019.1620945

Successful Desensitization to Pomalidomide in a Patient with POEMS Syndrome with Delayed-type Hypersensivity to Immunomodulatory Imide Drugs

Journal:	*Leukemia and Lymphoma*
Manuscript ID	GLAL-2019-0249.R1
Manuscript Type:	Letter to the Editor
Date Submitted by the Author:	02-May-2019
Complete List of Authors:	Grandoni, Francesco; Centre Hospitalier Universitaire Vaudois, Service and Central Laboratory of Hematology Stalder, Grégoire; Centre Hospitalier Universitaire Vaudois, Service and Central Laboratory of Hematology Borgeat Kaeser, Amelie; Centre Hospitalier Universitaire Vaudois, Service of Immunology and Allergology Ribi, Camillo; Centre Hospitalier Universitaire Vaudois, Service of Immunology and Allergology Cairoli, Anne; Centre Hospitalier Universitaire Vaudois, Service and Central Laboratory of Hematology Blum, Sabine; Centre Hospitalier Universitaire Vaudois, Service and Central Laboratory of Hematology
Keywords:	desensitization, hypersensitivity, lenalidomide, poems, pomalidomide

Successful Desensitization to Pomalidomide in a Patient with POEMS Syndrome with Delayed-type Hypersensitivity to Immunomodulatory Imid Drugs

F. Grandoni[1], G. Stalder[1], A. Borgeat Kaeser[2], C. Ribi[2], A. Cairoli[1], S. Blum[1]

[1]Service and Central Laboratory of Hematology, Centre Hospitalier Universitaire Vaudois, rue du Bugnon 46, CH-1011 Lausanne, Switzerland

[2]Service of Immunology and Allergology, Centre Hospitalier Universitaire Vaudois, rue du Bugnon 46, CH-1011 Lausanne, Switzerland

Corresponding author: Gregoire Stalder

Service and Central Laboratory of Hematology

Centre Hospitalier Universitaire Vaudois

CH-1011 Lausanne, Switzerland

Phone: +41 79 556 86 16

e-mail: gregoire.stalder@chuv.ch

Declaration/disclosure: All authors declare that they have no conflict of interest.

Acknowledgments: The authors thank Margaret McLauchlan for her support with language editing.

Keywords: desensitization, hypersensitivity, lenalidomide, poems, pomalidomide

Dear Editor,

We report the management of a patient treated for POEMS syndrome who developed hypersensitivity reactions to both lenalidomide and pomalidomide.

A 70-year-old caucasian female patient known for hypertension without vascular complications and a history of autoimmune thyroiditis, as well as hyperprolactinemia secondary to metoclopramide use. In March 2015, she developed distal paraesthesia of the upper and lower limbs, which evolved into a distal paresis within two months, requiring the use of crutches. Six months later, she presented with night sweats and weight loss of eight kilograms. Additionally, cutaneous angioma and sclerodactylia appeared. Initially, nerve conduction studies were consistent with chronic demyelinating inflammatory polyradiculoneuritis (CIDP). However, treatment with intravenous polyclonal immunoglobulins proved unfavourable. Repeated immunosubtraction in serum and urine failed to reveal a monoclonal component, even 8 months after presentation, when a slight elevation of serum VEGF (343 pg/ml for a cut-off < 200 pg/ml) was observed.

Monoclonal IgA lambda gammopathy was finally detected by immunofixation analysis 14 months after the appearance of the first symptoms. Full blood count revealed a thrombocytosis of $457x10^9$/l as the only anomaly. At the same time, VEGF levels further increased to 917 pg/ml. A total body MRI demonstrated the presence of a splenomegaly (140 mm on the main axe) and a higher intensity of the bone marrow in comparison to the normal kidney parenchyma. Bone marrow tap revealed 8% of monoclonal plasma cells. An endocrinological workup excluded a clinically relevant endocrinopathy, aside from the pre-existing subclinical hypothyroidism. A cutaneous biopsy showed glomerular haemangioma.

According to the International Myeloma Working Group criteria, the diagnosis of POEMS syndrome was made (two mandatory criteria: polyneuropathy and monoclonal plasma cell

disorder; one major criterion: VEGF elevation; three minor criteria: splenomegaly, skin lesions (glomerular haemangioma and sclerodactily) and thrombocytosis) [1].

The patient was treated with lenalidomide (25 mg/d, d1-d21) and dexamethasone (40 mg/weekly) [2], together with fondaparinux (2.5mg/d). The patient was already on candesartan, hydrochlorothiazide and amitriptyline (introduced one year before to control neuropathic pain) for several years. Six days after starting lenalidomide, she developed a cutaneous grade 3 (according to CTCAE v4.03) maculo-papular rash with a moderate eosinophilia ($0.97x10^9$/l)without fever, renal or hepatic involvement. The lenalidomide treatment was interrupted and topical betamethasone was administered. One month later, after full resolution of the rash and of eosinophilia, an attempt to re-introduce a lower dose of lenalidomide (15 mg/d) associated with prednisone (20 mg/d) provoked the reoccurrence of the rash (grade 3) without eosinophilia. Lenalidomide treatment was interrupted, topical treatment with betamethasone was reintroduced and oral prednisone was slowly tapered. Two weeks later, the rash completely resolved. Because of the severity of the rash and its reoccurrence despite a concomitant treatment with oral prednisone, no desensitization for lenalidomide was attempted and the treatment was definitively interrupted.

Six weeks thereafter, lenalidomide was replaced by pomalidomide (4 mg/d) in combination with dexamethasone (40 mg/weekly). Two days after the treatment start, a grade 3 maculo-papular rash recurred, without eosinophilia. Delayed hypersensitivity to both lenalidomide and pomalidomide was diagnosed.

In analogy to a desensitization schedule for lenalidomide published in 2014 by Lee and colleagues [3], a desensitization for pomalidomide was started in October 2016 following a schedule summarized in table 1. The treatment with dexamethasone (40mg/weekly) was continued.

The patient reached the target dose of 2 mg/d after 5 weeks without re-occurrence of adverse events.

The clinical as well as the biological evolution was favorable after three 28-days cycles associating pomalidomide and dexamethasone. The patient described a general improvement of her condition and a weight gain. She was able to walk short distances without assistance. The overall disability sum score (ODSS) [4] was 2 for the superior members and 3 for the inferiors members, as compared to 4 before the treatment. The monoclonal IgA lambda component disappeared in the blood immunofixation with a 50% decrease of the IgA level. VEGF normalised (88 pg/ml). However, ENMG analysis did not demonstrate any improvement of the demyelinizating signs.

A peripheral blood stem cell collection was performed after four cycles of pomalidomide/dexamethasone. A total of six cycles were given. The patient was then treated with high-dose melphalan (200 mg/m^2) followed by an autologous stem cell transplantation 26 months after presentation.

The day 100 control was consistent with a complete response. One year after the autologous stem cell transplantation, the patient is still in ongoing response with a continuous neurological improvement.

Pomalidomide is an immunomodulatory agent approved for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) [5].

The Food and Drug Administration (FDA) approved pomalidomide for single use in the United States in February 2013, and the European Medicines Agency (EMA) for use in combination with dexamethasone in patients with MM who have received at least two prior therapies including lenalidomide and bortezomib in August 2013. The molecule is structurally related to lenalidomide and thalidomide.

In the multiple myeloma MM-003 study, cutaneous reactions were reported in less than 10% of patients treated with pomalidomide and low-dose dexamethasone [5]. Rash appeared to be less common with pomalidomide than with lenalidomide [6,7]. The structural similarity of both molecules suggests a potential for cross-sensitization. Because of this theoretical concern, patients having experienced hypersensitivity to immunomodulatory imid drugs were excluded from trials with pomalidomide [8]. Thus, clinical data regarding safety of pomalidomide in patients having experienced hypersensitivity reactions to lenalidomide are lacking. As proposed by an expert panel [9], pomalidomide should be used with caution in patients who developed a rash during prior treatment with lenalidomide or thalidomide. In patients developing mild-to-moderate maculopapular eruption or erythema, a treatment with low-dose prednisone and antihistamines may be adequate. In patients presenting with more severe reactions, the pomalidomide dose should be reduced or interrupted [9]. A desensitization procedure may be attempted in hypersensitive patients to whom no alternative treatment is available, if the reaction was not life threatening. One case report describes the rapid desensitization procedure to pomalidomide in a patient with relapsing myeloma and previous grade 3 rashes to both thalidomide and lenalidomide, in order to avoid potential cross-reactivity [10]. However, it is unknown whether the abovementioned patient would have reacted if exposed to standard-dose pomalidomide. In contrast, our patient presented with a grade 3 rash to both lenalidomide and pomalidomide. We used a slow desensitization protocol to avoid hospitalization and an individual pharmacy preparation (magistral preparation produced by the hospital pharmacy containing only a small amount of the active principle not industrially available, i.e. 0.00025 mg or 0.00125 mg). During the desensitization procedure, our patient was followed on a weekly basis with a clinical examination and laboratory screening. The

rash did not re-occur and no other adverse events were observed, while the patient continued her treatment as planned.

Our case demonstrates that a slow desensitization procedure to pomalidomide may be performed safely in an outpatient setting after grade 3 rash to both pomalidomide and lenalidomide. Furthermore, to the best of our knowledge, this is the first description of the use of pomalidomide in POEMS.

In conclusion, pomalidomide may be considered an effective alternative to lenalidomide in patients with POEMS having experienced non-severe delayed skin reaction but carries the risk of recurrent rash. For patients with non-life-threatening delayed hypersensitivity to pomalidomide, a slow desensitization procedure may be attempted. Further studies are needed to assess the efficacy of pomalidomide in POEMS and its safety in case of hypersensitivity to other immunomodulatory imid drugs.

Consent

Signed informed consent from the patient was obtained for the off-label use of pomalidomide as well as for the publication of her case.

References

[1] Dispenzieri A. POEMS syndrome: 2017 Update on diagnosis, risk stratification, and management. Am. J. Hematol. 2017;92:814–829.

[2] Zagouri F, Kastritis E, Gavriatopoulou M, et al. Lenalidomide in patients with POEMS syndrome: a systematic review and pooled analysis. Leuk. Lymphoma. 2014;55:2018–2023.

[3] Lee MJ, Wickner P, Fanning L, et al. Lenalidomide desensitization for delayed hypersensitivity reactions in 5 patients with multiple myeloma. Br. J. Haematol. 2014;167:127–131.

[4] Merkies ISJ, Schmitz PIM, van der Meché FGA, et al. Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies. J. Neurol. Neurosurg. Psychiatry. 2002;72:596–601.

[5] Miguel JS, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14:1055–1066.

[6] Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N. Engl. J. Med. 2007;357:2123–2132.

[7] Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N. Engl. J. Med. 2007;357:2133–2142.

[8] POMALYST_Product_Monograph_English_Version.pdf [Internet]. [cited 2018 Sep 19]. Available from: http://media.celgene.com/content/uploads/sites/23/POMALYST_Product_Monograph_English_Version.pdf.

[9] Dimopoulos MA, Leleu X, Palumbo A, et al. Expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma. Leukemia. 2014;28:1573–1585.

[10] Seki JT, Sakurai N, Lam W, et al. Pomalidomide desensitization in a patient hypersensitive to immunomodulating agents. Curr Oncol. 2017;24:e328–e332.

Table

Table 1. Desensitization schedule to pomalidomide (target dose of 2 mg/d)

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week 1	1 mg						
Week 2	1 mg			1 mg			1 mg
Week 3		1 mg		1 mg		1 mg	1 mg
Week 4	1 mg	1 mg	1 mg	2 mg	1 mg	2 mg	1 mg
Week 5	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg