

Romidepsin is an effective and well-tolerated therapy in CD3⁺CD4⁺ lymphocyte-variant hypereosinophilic syndrome: A case report

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Clinical Implications

- Romidepsin may be an effective and well-tolerated alternative for treatment-refractory lymphocyte-variant hypereosinophilic syndrome.

TO THE EDITOR:

Hypereosinophilic syndrome (HES) is defined by persistent hypereosinophilia (HE), with counts greater than 1.5 G/L associated with eosinophilia-related organ dysfunction or damage.¹ The lymphocyte-variant of HES (L-HES) is considered an indolent clonal T-cell lymphoproliferative disorder. L-HES is characterized by the presence of an abnormal T-cell clone, typically with a CD3⁺CD4⁺ immunophenotype, capable of secreting eosinophilopoietic cytokines, mainly IL-5.^{2,3} Despite the indolent nature of the condition, evolution to T-cell lymphoma has been reported in 2 of 21 cases of L-HES and remains a concern.⁴ Eosinophilia-related organ damage is the most common reason for treatment in most patients. Current management of L-HES is based on long-term systemic corticosteroids, and most patients require steroid-sparing agents.⁵ IFN- α treatment achieves response rates around 50%, but is associated with significant adverse effects. Eosinophil-targeted biotherapeutics such as anti-IL-5 antibodies are effective, but the benefits appear to be short-lived and maintenance therapy is generally required.⁶ Romidepsin has been validated as second-line treatment in patients with cutaneous T-cell lymphoma and peripheral T-cell lymphoma, with nearly 20% of treated patients showing a complete response.⁷ Romidepsin is a selective inhibitor of histone deacetylases. Histone deacetylase inhibitors result in accumulation of acetylated histones, which leads to changes in chromatin structure and transcription factor activation, subsequently inducing cell cycle arrest and apoptosis. Interestingly, romidepsin is also believed to regulate the expression of transcriptional factors involved in cytokine secretion and to induce a switch from T_H2 cells secreting IL-5 toward a T_H1-cell phenotype.⁸ Here, we report 1 patient with refractory L-HES showing a sustained complete response after treatment with romidepsin used as a single agent. A 36-year-old man was referred to our department in 2006 for HE with cutaneous manifestations. He had history of atopic dermatitis in childhood. In 1996, he presented subcutaneous nodules associated with HE (5 G/L) and responded well to corticosteroid treatment. He was lost to follow-up for 10 years, during which time

he remained on steroid therapy. He was seen again in 2006 for painful subcutaneous nodules, pruritus, and episodic angioedema occurring at any attempt of withholding steroids. The examination revealed a slightly enlarged spleen but no lymphadenopathy. Skin biopsies showed a subcutaneous angio-lymphoid infiltration made of small-to medium-sized lymphocytes and numerous eosinophils. The absolute eosinophil count (AEC) was 13.6 G/L, and circulating CD3⁺CD4⁺ T cells (2500/mm³) consistent with L-HES were detected by flow cytometry. IFN- α , cyclosporine, sirolimus, methotrexate, cyclophosphamide, and cladribine failed to taper corticosteroid use below 20 mg/d. Mepolizumab was effective only in decreasing circulating eosinophils but had no effect on clinical symptoms. Alemtuzumab was given from May to July 2014, which led to a complete clinical and biological response but resulted in prolonged pancytopenia and platelet transfusion dependency until October 2014. Steroid treatment was finally stopped in May 2015. In September 2016, the patient presented diarrhea, weight loss, pruritus, arthralgia, and episodic angioedema. A positron-emission-tomography scan revealed diffuse small lymphadenopathies. A biopsy of the axillary lymph nodes revealed dense interfollicular infiltrate comprising atypical monomorphic small-to medium-sized lymphocytes with irregular nucleus. Romidepsin was started in October 2016. Six cycles led to complete clinical and biological remission, defined by normal AEC and undetectable CD3⁺CD4⁺ T cells (Figure 1). Grade III nausea following infusion was the sole reported adverse event. As of December 2018, the patient is still in complete remission.

We came to use romidepsin in this patient after we observed a dramatic response in another patient presenting with an overlap syndrome between L-HES and T-cell lymphoma. This 27-year-old woman presented in 2005 with a generalized, intensely pruritic papulo-nodular eruption. The AEC was 17 G/L and a CD3⁺CD4⁺ T-cell population was identified (1500/mm³). Skin biopsies revealed a dermal infiltrate of small-to medium-sized lymphocytes, similar to that observed in L-HES, but no eosinophil infiltrate or any eosinophilia-related organ damage. Steroids were effective, but IFN- α treatment failed to improve symptoms and biology after 6 months of therapy. Anthracycline-based chemotherapy, followed by intensive chemotherapy and an autologous stem-cell graft, was performed in March 2007. This treatment led to a complete clinical and biological remission lasting until October 2015. The patient was then treated with romidepsin. Complete response was achieved after 4 cycles (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Grade II nausea and reversible amenorrhea were the only adverse events. As of December 2018, the patient is still in complete clinical and biological remission.

Most therapeutic options available for L-HES do not definitively cure L-HES, but only have a temporary effect on the disease. Here, we report a prolonged effect of romidepsin that led to lasting complete remission despite treatment discontinuation, with no need of maintenance therapy. Romidepsin-related adverse events are generally mild and consist mainly of gastrointestinal disturbances and asthenic conditions. It can also cause

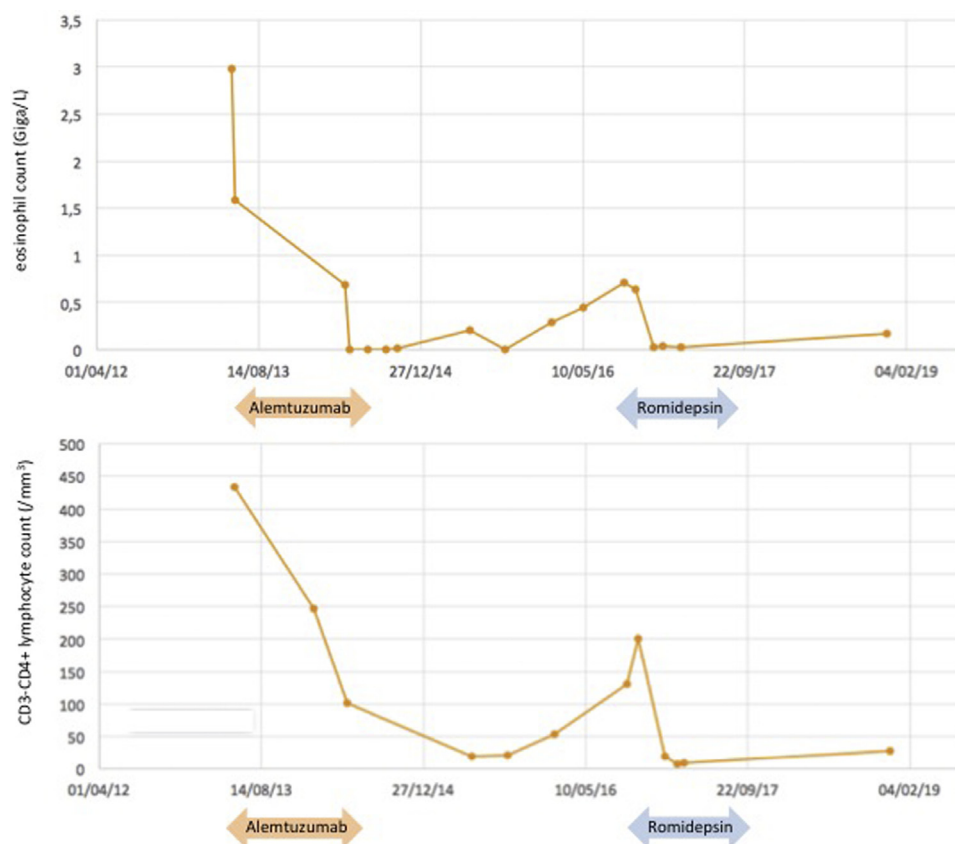


FIGURE 1. CD3⁺CD4⁺ lymphocyte population (/mm³) and eosinophil count (G/L) in case number 1. Rapid decrease after alemtuzumab and prolonged remission after romidepsin therapy (6 cycles).

reversible thrombocytopenia, leukopenia, and anemia. Nonspecific, reversible changes as noted by electrocardiogram readings have been observed in some patients. In our cases, side effects were moderate and reversible. Taken together, romidepsine demonstrated an acceptable safety profile and efficacy as a single agent in relapsing L-HES.

Romidepsin led to complete remission of the lymphoproliferative disorder in both described patients. Even if L-HES is an indolent T-cell lymphoproliferative disorder, evolution to T-cell lymphoma has been reported in few cases.⁸ Treating L-HES by targeting the aberrant T-cell clone may reduce the risk of transformation to lymphoma and is therefore an interesting therapeutic option, as long as risk remains reasonable.

In conclusion, romidepsin may be an attractive salvage alternative for the treatment of refractory L-HES as well as L-HES sharing features with T-cell lymphoma.

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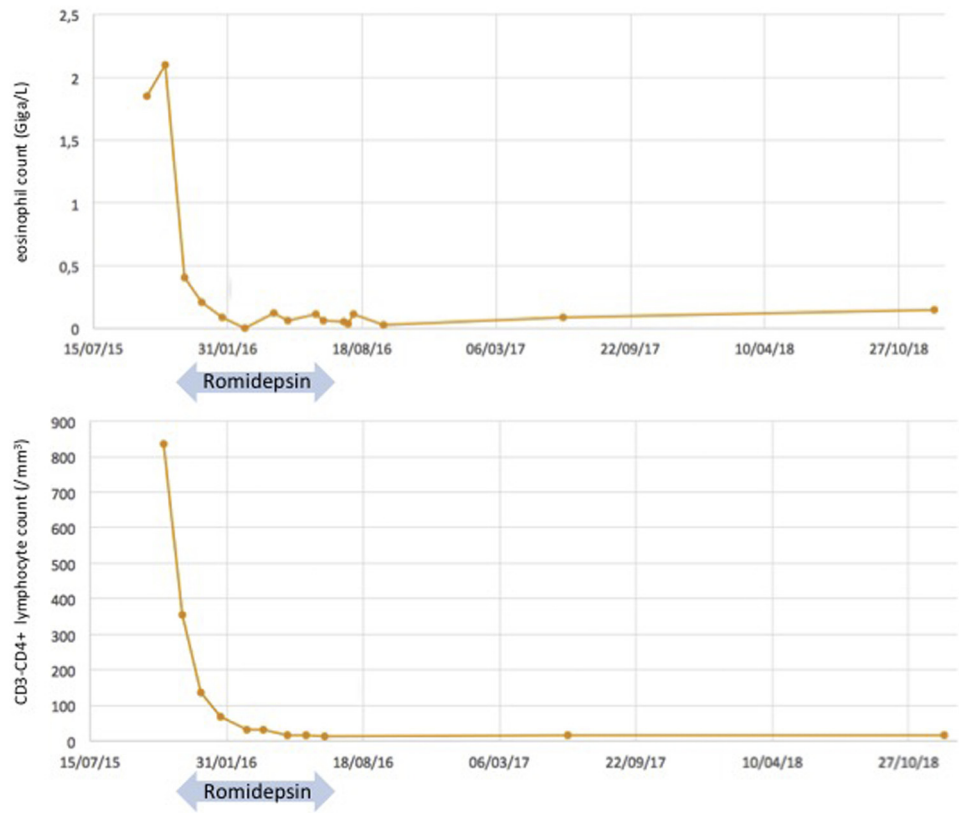


FIGURE E1. CD3⁻CD4⁺ lymphocyte population (/mm³) and eosinophil count (G/L) in patient number 2. Rapid decrease after romidepsin therapy (9 cycles).