METABOLISM CLINICAL AND EXPERIMENTAL 69 (2017) 107–111

Available online at www.sciencedirect.com

Metabolism

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Brief Report

Denosumab for the treatment of adult multisystem Langerhans cell histiocytosis

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ARTICLE INFO

Article history:
Received 18 December 2016
Accepted 6 January 2017

Keywords:
Langerhans cell histiocytosis
Treatment
Denosumab
RANKL

ABSTRACT

Purpose. An etiological treatment is currently lacking for Langerhans Cell Histiocytosis (LCH). Receptor activator of nuclear factor κB ligand (RANKL) appears to play a central role in the lesional immunological process inducing compensatory osteoprotegerin (OPG) activation. In a preliminary study we aimed to evaluate for the first time the use of denosumab, a RANKL inhibitor, as a targeted treatment strategy in LCH in order to support and enhance endogenous OPG action in order to control or alter the lesional immunological process.

Procedures. Two adult female patients with painful osteolytic bone lesions and concomitant pulmonary involvement received bimonthly denosumab 120 mg in a total of 4 doses.

Results. Both patients reported an immediate pain relief within the first two weeks following the 1st dose of denosumab. One month following the last dose an almost full remission of the initial osteolytic and lung lesions was observed, although an apparent new bone lesion was detected in one patient that was treated with a single intralesional steroid injection. No adverse events were recorded throughout the treatment period. Both patients have no active disease 6 months following the last denosumab dose.

Conclusions. Denosumab could be considered an effective treatment option in adults with multisystem LCH also exerting a significant analgesic effect in bone lesions, warranting further investigation.

Abbreviations: LCH, Langerhans cell histiocytosis; LCs, Langerhans cells; NSAIDs, non-steroidal anti-inflammatory drugs; CT, computed tomography; MRI, magnetic resonance imaging; 18-FDG PET, 18-fluorodeoxyglucose positron emission tomography; SUVmax, maximum standardized uptake value; IRB/EC, institutional review board and ethics committee; ESR, erythrocyte sedimentation rate; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor κB ligand; NFκB, nuclear factor κB ligand; Q8W, every 8 weeks; Q4W, every 4 weeks.

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http://dx.doi.org/10.1016/j.metabol.2017.01.004
0026-0495/

1. Introduction

Langerhans Cell Histiocytosis (LCH) is a disease of unknown etiology exhibiting a variable clinical course that is characterized by the abnormal accumulation and/or proliferation of specific dendritic cells resembling normal epidermal Langerhans cells (LCs) [1,2]. LCH is rare in adults, and is regarded as an "orphan disease" [3]. As there is still no etiological treatment, systemic chemotherapy is administered in patients with multisystem disease and single system disease with multiple lesions and/or involvement of high risk organs (bone marrow, liver, spleen, central nervous system) [2]. Cessation of smoking is mandatory in pulmonary involvement leading to spontaneous regression in up to 50% of cases [4,5].

We herein report for the first time, the response to treatment with denosumab in two adults with multisystem LCH.

2. Description of Cases

2.1. *Patient 1*

A 38-year-old female physician developed a blunt, continuous, nocturnal pain at her right hip on May 2015, partially responding to nonsteroidal anti-inflammatory drugs (NSAIDs). Computed tomography (CT) scan and a subsequent magnetic resonance imaging (MRI) revealed a 1.5 × 0.8 cm circumscribed osteolytic lesion at the inner section of the right acetabulum with associated surrounding edema which had a moderate intensity signal in T1 and a high intensity signal in T2 weighted sequences. CT-guided biopsy showed microscopic appearance of LCH with positive immunohistochemical staining for CD1a and S100. Systemic evaluation and staging [2] revealed multiple micronodular lesions in the middle and upper lungs albeit with no effect in lung function tests. An 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) CT scan showed that the osteolytic lesion of the right acetabulum was intensely hypermetabolic with a maximum standardized uptake value (SUVmax) of 7.1, while the multiple micronodular lung lesions had a mild activity of up to 3 (Fig. 1). The patient was initially reluctant to be treated with the recommended treatment including methotrexate and/or azathioprine [2] because of a future prospect of pregnancy. However, as her symptoms persisted, she gave informed consent to be treated with denosumab for an initial period of 6 months, as she considered that denosumab presented a safer option. The treatment plan was approved by the institutional review board and ethics committee (IRB/EC) of the 251 Hellenic Air Force & VA General Hospital of Athens, Greece and by the committee for the off label use of medicinal products of the Greek National Drug Agency. Prior to treatment initiation the patient's right hip was

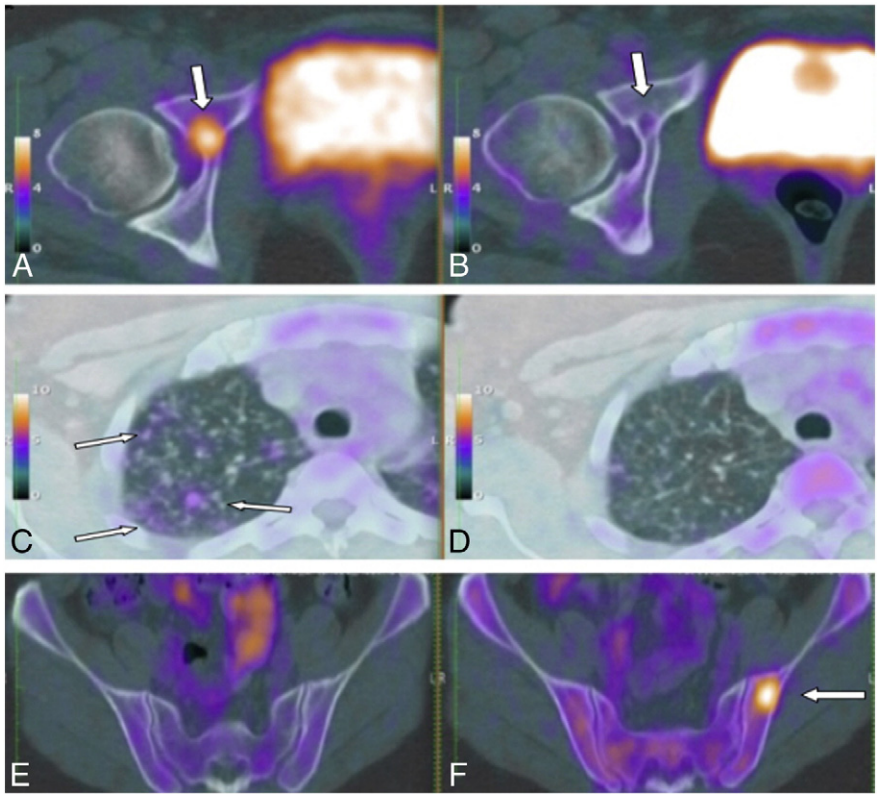

Fig. 1 – Patient 1; Shown is the pre-treatment hypermetabolic appearance in 18-FDG PET CT scan of the osteolytic lesion at the inner section of the right acetabulum (intense yellow signal; panel A) and of the micronodular lung lesions (scattered purple signal; panel C) in contrast with the reciprocal post-treatment appearance lacking any metabolic activity at both the bone (panel B) and lung (panel D) lesions following 1 month after the last dose of denosumab. The new hypermetabolic lesion at the left iliac bone (intense yellow signal; panel F) is depicted in contrast with the pre-treatment appearance (panel E).

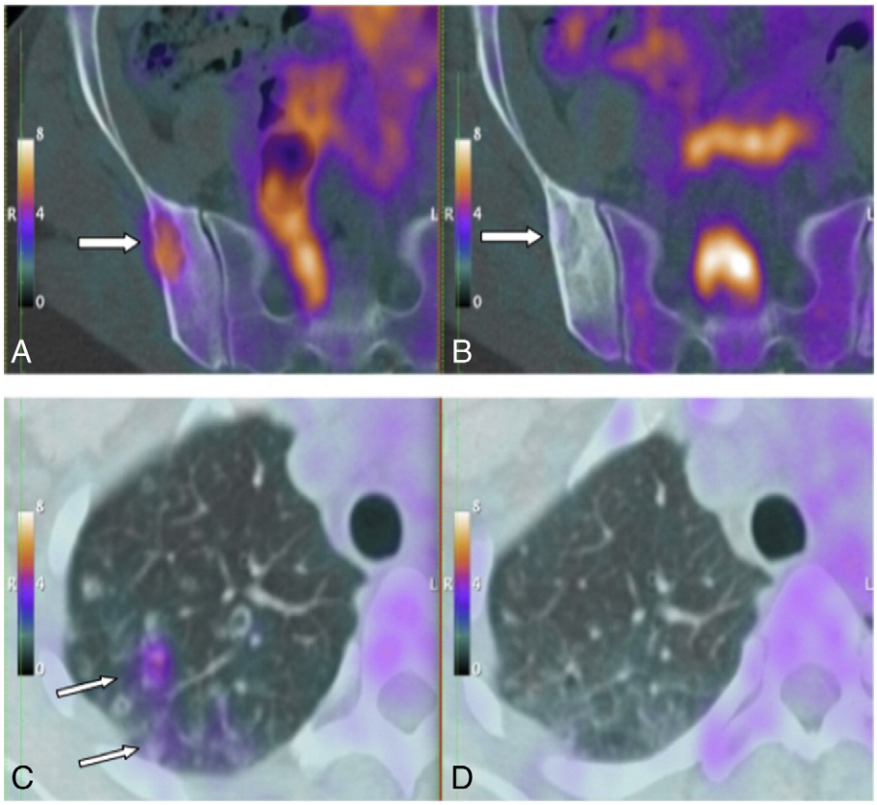

Fig. 2 – Patient 2; Shown is the hypermetabolic appearance in 18-FDG PET CT scan of the osteolytic lesion at the right iliac bone (intense yellow/purple signal; panel A) and of the micronodular lung lesions (scattered purple signal; panel C) before treatment. One month following the last denosumab dose no hypermetabolic activity is confirmed at both the osseous (panel B) and lung lesions (panel D).

extremely painful affecting her gait and was partially controlled with NSAIDs. With the exception of ESR 39 mm/h (normal range: 0–20 mm/h) all the remaining laboratory results were normal. She was treated with bimonthly s.c. denosumab 120 mg for a total of 4 doses along with supplementary calcium and vitamin D to avoid hypocalcaemia. The patient reported an immediate pain relief 10 days after the 1st denosumab dose leading to discontinuation of NSAIDs. An intermediate evaluation of the systemic LCH involvement one month after the 2nd dose of denosumab revealed a significant reduction of the surrounding edema of the osteolytic lesion and amelioration of the lung lesions, supporting the continuation of the therapeutic protocol. Although she was advised to quit smoking (10 pack-years at baseline), she failed to comply throughout the treatment period. A subsequent 18-FDG PET CT scan in June 2016, one month after the last denosumab injection, showed a significant reduction of the uptake at the right acetabulum with sclerotic margins. In addition, a complete remission of the previously noted hypermetabolic activity along with reduction of the size and number of the lung lesions was also noted. However, a new osteolytic LCH lesion (SUVmax 9.5) at the left iliac bone was also revealed (Fig. 1) that responded completely to a single intralesional steroid injection. No adverse events from treatment with denosumab were recorded and the patient has no active disease 6 months after the last denosumab administration.

2.2. *Patient 2*

A 38-year-old female, presented with a sharp right hip pain radiating to the right thigh and calf. The pain was relieved only with NSAIDs, and gradually became intense affecting significantly her mobility, rendering the use of a wheelchair mandatory for any long distance movements. Subsequent CT and MRI scans revealed a 2.5 cm osteolytic cystic lesion at her right iliac bone exhibiting a weak signal in T1 and high intensity signal in T2 weighted sequences with substantial surrounding edema. A CT-guided biopsy confirmed the diagnosis of LCH [2] and subsequent systemic evaluation revealed multiple micronodular lesions in the middle and upper lung fields of both lungs but unaffected lung function tests although the patient was a current smoker (11 pack-years at baseline). An 18-FDG PET CT scan showed that the osteolytic lesion exhibited a heterogeneous peripheral uptake (SUVmax of 3.7) while the lung lesions had a mild hypermetabolic activity of up to 2.7 (Fig. 2). Similarly to patient 1, she gave her consent to be treated with denosumab and the treatment plan was approved accordingly. She also received 4 doses of denosumab 120 mg s.c. every 2 months along with calcium and vitamin D supplementation and experienced a complete pain relief within the first two weeks of treatment. The intermediate evaluation one month after the 2nd dose of denosumab revealed a slight reduction in the size of the

osteolytic lesion and unchanged lung lesions. A repeat 18-FDG PET CT scan, one month after the last denosumab injection, showed a complete regression of the hypermetabolic activity of both the osteolytic and the lung lesions, while the latter were also significantly reduced in number (Fig. 2). Against our advice the patient continued smoking throughout the treatment period. No adverse events from treatment with denosumab were recorded, and the patient remained in complete remission 6 months following the last denosumab dose.

3. Discussion

We have previously reported high osteoprotegerin (OPG) and low receptor activator of RANKL levels in the serum of patients with and without bone involvement [6] suggesting of a potential role of this system in the initiation or perpetuation of the disease process in LCH. More recently we have found that RANKL is abundantly expressed in cells of adult LCH lesions from different tissues, especially within inflammatory infiltrates [7] further supporting this hypothesis. Furthermore, concomitant nuclear staining of p65 NFκB, the main downstream effector of RANKL signaling, was associated with increased RANKL expression, suggesting that RANKL could be directly involved in an ongoing local lesional cell activation [7]. We have therefore speculated that high OPG levels could present a countervailing process against lesional RANKL activation in LCH. Denosumab, a RANKL inhibitor, is currently approved for the prevention of skeletal related events in patients with bone metastases from solid tumors in a dose of 120 mg administered every four weeks, while it is also widely used in osteoporosis treatment in a dose of 60 mg every 6 months [8]. Denosumab administration seems a rational treatment strategy in LCH in order to enhance further endogenous OPG action and interrupt the lesional immunological process if RANKL related. Although currently there is no phase I or II studies evaluating the safety and optimal denosumab dose in patients with LCH, a bimonthly treatment schedule (Q8W) with 120 mg administered s.c. in adult patients, appears appropriate based on previous experience with empirical i.v. bisphosphonate administration [2]. In addition, following s.c. denosumab administration the peak serum concentrations (Cmax) of the drug are reached within 4 weeks following the initial dose [9,10], and then decline over 4–5 months with an approximate mean half life of 25–30 days [9–11]. We considered that a Q8W administration scheme could sustain high concentrations of the drug, at which the RANKL-mediated clearance pathway would be adequately if not fully saturated, at least in patients with low risk LCH.

In our patients the administration of denosumab resulted in a significant remission of disease activity at both osseous and non-osseous lesions. Although this could be anticipated after treatment of osteolytic lesions with an antiresorptive agent such as denosumab, it is rather unexpected in pulmonary lesions unless a systemic effect is apparent. This is further reinforced as it was observed in patients with lung involvement who continued to smoke perpetuating further the pathogenetic process. One could argue that a single bone lesion could be also treated locally either with intralesional steroids or even irradiation and may not require systemic therapy even in patients with treatment naïve lung disease. However, as both patients did not consider smoking cessation as the appropriate therapeutic intervention they agreed to a therapeutic trial with denosumab considering the favorable side effect profile of the drug. Indeed, following this therapeutic trial a significant improvement in both lesions was obtained. Given that no treatment provides complete response and the risk of relapse is approximately 30% in patients with multisystem LCH [2,12], the new bone lesion observed in Patient 1 may indicate that a more intense schedule, such as the one used for the prevention of skeletal related events in patients with bone metastases from solid tumors may be also investigated.

It is prudent to suggest that denosumab could be considered as another treatment option among adults with multisystem LCH exerting a significant analgesic effect in bone lesions. In contrast to chemotherapy and/or long-term immunosuppressive treatment, denosumab is probably a more convenient and patient-friendly treatment modality with minimal adverse events, at least in low risk patients, although we cannot provide any long-term follow-up results at the moment.

The major limitation of our preliminary study is the small number of cases and the short period of follow-up. However, the strength of this report is the accurate evaluation of LCH activity through the repeated 18-FDG PET CT scans and the lack of interference of any other treatments. Finally, we believe that the potential benefit of denosumab, even in extraosseous disease, is an important and new message provided by this report.

In conclusion, a clinical study is urgently needed in order to prove the efficacy of denosumab in LCH as well as to define the optimal treatment dose, and appropriate handling following denosumab discontinuation.

Authors' Contributions

P.M. conceived, designed, and executed the treatment protocol. P.M., M.T., M. Th., G.K. contributed in patients' recruitment and treatment. P.M., A.D.A., G.K. wrote the manuscript.

Funding

This study was funded by investigators' own resources.

Acknowledgments

We are indebted to "Artemis" Association for Histiocytosis, Greece, for offering to cover the publication fees of this article.

Conflicts of Interest

P. Makras has received lecture fees and research grants from Amgen and lecture fees from ELPEN, UniPharma, Vianex; A.D. Anastasilakis has received lecture fees and research grants from Amgen and lecture fees from Vianex, and ITF; M. Tsoli, M. Thanou and G. Kaltsas have no conflict in relation to the study.

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