

## FEATURED ARTICLE

### L-Carnitine Reduces Muscle Cramps in Patients Taking Vismodegib

Matthew S. Dinehart BA M.Ed<sup>a</sup>, Stacy McMurray MD<sup>b</sup>, Scott M. Dinehart MD<sup>c</sup>,  
Mark Lebwohl MD<sup>d</sup>

<sup>a</sup>University of Arkansas for Medical Sciences, College of Medicine, Little Rock, AR

<sup>b</sup>Department of Dermatology, University of Tennessee Health Science Center, Memphis, TN

<sup>c</sup>Arkansas Dermatology, Little Rock, AR

<sup>d</sup>Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY

#### ABSTRACT

Vismodegib is an oral, small-molecule hedgehog pathway inhibitor (HHI) approved for the treatment of locally advanced and metastatic basal cell carcinoma. While an effective treatment option for these conditions, HHI therapy is associated with muscle cramps in a significant number of patients. This adverse effect negatively impacts patient quality of life and patient adherence to the prescribed treatment regimen.

Levocarnitine (L-carnitine) is a trimethylated amino acid known to play a critical role in lipid metabolism. It has antioxidant properties, and several studies have illustrated its effectiveness in lessening the severity of muscle cramps in various disease processes.

We present three patients who developed muscle cramping associated with vismodegib treatment for basal cell carcinoma. Each was started on L-carnitine therapy, and all three reported a significant decrease in the severity of their muscle cramps to the point that they were able to continue HHI therapy without taking a drug holiday. These cases illustrate a promising treatment option for the most common side effect associated with HHI treatment.

#### INTRODUCTION

Vismodegib is a novel oral Smoothed (SMO) antagonist, approved by the Food and Drug Administration (FDA) for the treatment of locally advanced (laBCC) and metastatic (mBCC) basal cell carcinoma.<sup>1</sup> Significant therapeutic results are obtained with vismodegib; however, adverse events often limit use to less than the time needed for optimal therapy. The most common side effect of HHIs is muscle cramps, reported in about 60-70% of patients.<sup>2,3</sup> Muscle

cramps are a frequent source of patient dissatisfaction and often result in a significant negative impact on patient quality of life. We report 3 patients taking vismodegib who experienced a reduction in muscle cramps after starting L-carnitine, a dietary supplement.

## CASE #1

The patient is a 74-year-old male who has been followed by his dermatologist for the treatment of an advanced basal cell carcinoma located in his right axilla, first diagnosed when he was 40 years old. Shortly after initial presentation, the lesion was excised via Mohs surgery, but clear margins were unable to be obtained, and the patient was treated with adjuvant radiation therapy. At the age of 46 the patient developed a mass in the right axilla, which, upon biopsy and subsequent excision, showed atypical basaloid cells. At the age of 52, pulmonary nodules were noted on chest x-ray. The nodules were biopsied and the pathological diagnosis of metastatic basal cell carcinoma was confirmed. The patient had previously been treated with oral acitretin 25 mg daily for the suppression of numerous prior basal cell and squamous cell carcinomas. At the age of 54 he was placed on 150 mg/day of vismodegib as part of a clinical trial. Because of severe muscle cramps, the patient took numerous drug holidays, including periods off the drug for up to six months. These breaks from therapy resulted in pulmonary recurrences, which were then suppressed upon the resumption of vismodegib. On a 0 – 10 scale, the patient rated his muscle cramps as a 10, and CPK levels drawn during that time were as high as 1496 U/L (upper limit of normal 200 U/L).

Due to recurrence of his pulmonary metastases, the patient was restarted on vismodegib. He once again developed his typical 10/10 severe muscle cramping and requested to halt treatment. He was instead started L-carnitine 1000 mg twice daily and experienced a reduction in muscle cramps severity after several weeks on the supplement. He reported a decrease in cramp intensity from the earlier documented level of 10 to a level of 3.

## CASE #2

An 85-year-old Caucasian woman presented with a bleeding, growing and painful mass on her nose. The lesion had been present for more than 2 years and had recurred from a previous Mohs surgery performed 3 years ago at another institution. Examination showed a 4x3 cm ill-defined mass involving her entire nasal tip with extension to part of her nasal bridge. Biopsy revealed basal cell carcinoma, and the patient was given options of palliative radiation to the area or treatment with a HHI. The patient chose the latter and was started on vismodegib 150 mg once a day.

At her one-month clinic visit, the patient was experiencing numerous side effects, the worst of which were muscle cramps. They occurred several times a day in her extremities and would frequently awaken her at night. She rated the cramps as a 5 on a visual analog scale of 0-10. She considered discontinuing the vismodegib due to the discomfort, but was hesitant because of the dramatic improvement in her nose lesion, which had stopped bleeding and shrunk considerably. She decided to continue her vismodegib therapy at 150 mg per day, with the addition of L-Carnitine 1000 mg each night.

At her two-month visit her tumor had continued to shrink. She also reported a notable decrease in muscle cramp severity. She now rated them a 1 out of 10 on the analog scale. She continued to report other side effects such as minimal hair loss and dysgeusia. Over the next two months her tumor continued to improve and at the patient's 4 month visit there was no tumor that could be identified visually. Muscle cramps were not a significant problem, and she continued to rate them a 1 out of 10. At this visit the patient was offered the choice to take continue her current therapy or take vismodegib the first 10 days of each month for 6 months rather than have further

biopsies of her nose. She elected the latter treatment option and continued the L-carnitine with her intermittent vismodegib dosing with no return of her muscle cramps.

## CASE #3

A 56-year-old woman was seen in consultation for biopsy proven basal cell carcinomas on her back, chest and left leg. She reported a previous surgery by a general surgeon to treat the tumor on her back. This tumor had recurred and had been steadily growing until it reached 22x20 cm in size. It had also recently begun to bleed. The tumors on her chest and left leg were smaller, both less than 2 cm in size. The patient was given options of surgery, radiation, or treatment with a HHI. She preferred a medical treatment course and was started on vismodegib 150 mg each day.

After two months of treatment the smaller skin cancers were no longer clinically apparent and the larger tumor on her back, while still present, was significantly reduced in size. She also noted severe muscle cramps, occurring daily, that were beginning to hamper her employment. The patient rated these cramps as a 6 on a scale of 0 - 10. She was started on L-carnitine 1500 mg per day in hopes of reducing the muscle cramps.

At her 4 month visit the patient noted a decrease in muscle cramps and rated their severity as a 2 on a scale of 0 - 10. Her most significant complaint on this visit was a relative ageusia. She reported a 10-pound weight loss since beginning therapy.—The tumor on her back had continued to shrink, with only 25 x 20 mm of basal cell carcinoma remaining. At this time, the patient was given the option of a reduced dosage schedule for the vismodegib or a

drug holiday but she decided to continue the HHI with concurrent L-carnitine supplementation. Imiquimod cream was added to her regimen in an attempt to hasten clearance of the lesion. She continues to be followed.

## DISCUSSION

Vismodegib has a relatively benign safety profile, yet its use is often marked by multiple adverse events (AEs) including muscle cramps, alopecia, dysgeusia, gastrointestinal complaints, and weight loss. Between 95-100% of users experience at least one adverse event during the course of their HHI treatment.<sup>4</sup> Muscle cramping is the most commonly reported AE with individual studies estimating that between 60-70% of users experience cramping.<sup>2,3</sup> These cramps often begin early during therapy, worsen with length of therapy and are a reason frequently cited by patients when requesting a drug holiday or discontinuation of treatment. While the mechanism is not fully understood, the spasms are believed to be related to the paradoxical activation of the noncanonical SMO/Ca<sup>2+</sup>/AMPK axis and inhibition of the canonical SMO signaling pathway by vismodegib, which results in Ca<sup>2+</sup> influx into muscle cells and consequent muscle contraction.<sup>5</sup>

A variety of options have been employed in an attempt to lessen or eliminate the cramps associated with HHI therapy. Good hydration, gentle exercise, stretching, and massage have been suggested for mild cases of cramping.<sup>4</sup> In more severe cases different pharmacologic treatments have been used with variable effectiveness. Ally et al found modest decreases in cramping within two weeks of starting treatment with calcium channel blockers.<sup>6</sup> Case reports detailing medical marijuana and magnesium

supplementation have been published.<sup>7,8</sup> Other studies have suggested use of muscle relaxants such as low-dose cyclobenzaprine, baclofen, or quinine, though the latter is discouraged by the FDA due to severe cardiac risks.<sup>9,10</sup> Outside of pharmacologic approaches, some practitioners have found intermittent dosing of vismodegib to lessen cramps, and several trials are underway examining the clinical effectiveness of intermittent dosing.<sup>11,12,13</sup>

Levocarnitine (L-carnitine) is a non-essential amino acid that is found in almost all cells, but is concentrated in tissues like skeletal and cardiac muscle that utilize fatty acids as energy. It is naturally produced in the liver and kidneys and can be found in several dietary sources, mainly animal products such as red meat and dairy.<sup>14</sup> It has been found to be an effective treatment for muscle cramps that occur in end-stage renal disease patients on hemodialysis and those with liver cirrhosis.<sup>15,16</sup> L-Carnitine can be obtained without a prescription because it is sold as a dietary supplement.

L-carnitine produces energy in cells by transporting long chain fatty acids from the cytosol into mitochondria where they are oxidized to form adenosine triphosphate (ATP). It is thought that this beta-oxidation of fatty acids in skeletal tissue produces energy that stabilizes the sarcolemma, thus allowing the muscle to rest.<sup>17</sup>

Optimal dosage for vismodegib-related cramps has yet to be determined, but 1000-2000 mg per day was sufficient to help our patients. Adverse events from L-carnitine are uncommon, and its use appears to be reasonably safe. In one study, patients given 3000mg of L-carnitine each day for 21 days did not see any negative effects as assessed by a comprehensive blood panel which was conducted at the beginning and

end of the study.<sup>18</sup> Other studies have confirmed L-carnitine's safety at dosages of 2000mg per day.<sup>19</sup> In these investigations mild adverse events, including nausea and stomach discomfort were noted. Uncommon side effects included muscle weakness in uremic patients and seizures in those with known seizure disorders.<sup>20</sup>

We are now routinely placing patients with advanced BCC on L-carnitine at the time they begin or before they begin vismodegib to prevent development of muscle cramps. Future studies that help identify optimal dosage of L-carnitine for vismodegib associated muscle cramps would be beneficial. In addition, larger trials are needed to confirm the observations that we have documented in our 3 patients.

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**Corresponding Author:**

Matthew S. Dinehart, BA, M.Ed  
University of Arkansas for Medical Sciences  
Little Rock, AR  
501-650-2879 (Office)  
501-221-0214 (Fax)  
msdinehart@gmail.com

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