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Authors

Zhang, Lisa
Au, Sonoa
Aronson, Iris K

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Letter

Successful long-term thalidomide therapy for discoid lupus erythematosus-lichen planus overlap syndrome

Lisa Zhang BS, Sonoa Au MD, Iris K Aronson MD

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University of Illinois at Chicago, Department of Dermatology (MC 624), 808 South Wood Street, Room 376 CME, Chicago, IL 60612

Correspondence:

Iris K. Aronson
University of Illinois at Chicago, Department of Dermatology (MC 624)
808 South Wood Street, Room 376 CME, Chicago, IL 60612
Phone: (312) 996-6966 Fax: (312) 996-1188
iaronson@uic.edu

Abstract

Although thalidomide is a U.S. Food and Drug Administration (FDA) approved medication for erythema nodosum leprosum and multiple myeloma, it has many off-label uses, including for discoid lupus erythematosus (DLE), Behçet's disease, aphthous ulcers in HIV patients, and prurigo nodularis. Herein, we present a patient with an overlap of discoid lupus erythematosus and lichen planus who was successfully treated with thalidomide for over 19 years without significant side effects. We propose that some of the most common side effects, including peripheral neuropathy, numbness, paresthesias, sedation, and constipation, can be avoided at lower doses, typically less than 100mg/day.

Key words: Thalidomide, discoid lupus erythematosus, lichen planus, peripheral neuropathy, side effects

Introduction

Since the devastating connection between thalidomide and phocomelia was recognized in the 1960s, thalidomide's use has been severely limited. Although many off-label uses include discoid lupus erythematosus (DLE), Behçet's disease, aphthous ulcers in HIV patients, and prurigo nodularis [1], currently, the only FDA approved indications for thalidomide are erythema nodosum leprosum (ENL) and multiple myeloma in conjunction with dexamethasone [2]. In our patient, thalidomide was used for a period of 19 years to treat a rare overlap syndrome of DLE and lichen planus (LP) exhibiting erosions of palms and soles refractory to any other treatment apart from high dose systemic corticosteroids. To the authors' knowledge, this patient marks the longest documented course of thalidomide usage for DLE and LP overlap without significant side effects.

Case synopsis

A 27-year-old woman presented to our dermatology clinic for treatment of a rare overlap syndrome of DLE and LP, originally diagnosed at age 17 after clinical evaluation and histopathologic confirmation. She had extensive atrophic, erythematous, and hyperpigmented plaques involving her scalp, face, and extremities. She had multiple flares throughout the years with extensive ulceration of both hands and feet that hindered ambulation and required several hospitalizations.

Numerous treatments were tried unsuccessfully including topical corticosteroids, griseofulvin, dapsone, azathioprine, hydroxychloroquine, cyclophosphamide, cyclosporine, isotretinoin, erythromycin, beta-carotene, methotrexate, and

photochemotherapy with psoralen and ultraviolet A. The only treatment that had been effective was oral prednisone, which she took for a period of 15 years. However, the patient developed diabetes, cataracts, and bilateral femoral head necrosis for which she had bilateral hip replacements at the age of 37. Owing to these complications and her refractory disease, thalidomide was obtained from the FDA after filing an Investigational New Drug application. She was started on a dose of 100 mg alternating with 50 mg daily; her ulcers and facial rash cleared within one month. Eight years into treatment, she was tried on mycophenolate mofetil briefly owing to concern about the unknown side effects of long-term thalidomide use. After the change, her disease flared and she had to be restarted on thalidomide.

She has had annual neurological evaluations and electromyograms (EMG) throughout her treatment course. Ten years after starting thalidomide, a mild multifocal neuropathy with primarily axonal features was seen, although the patient was asymptomatic. Her thalidomide was reduced to her current dose of 50 mg four times a week. Subsequent EMGs repeated over the next 9 years showed right hand carpal tunnel syndrome but no polyneuropathy.

Over 19 years on thalidomide, she has not had any significant new eruptions and does not report any serious side effects apart from drowsiness at higher doses (100 mg daily) and occasional fatigue and dizziness. The patient is enrolled in the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S) program, has been on contraceptives throughout the length of her use of thalidomide, and has monthly pregnancy tests. Out of all of her treatments, thalidomide has been the most effective with the least side effects.

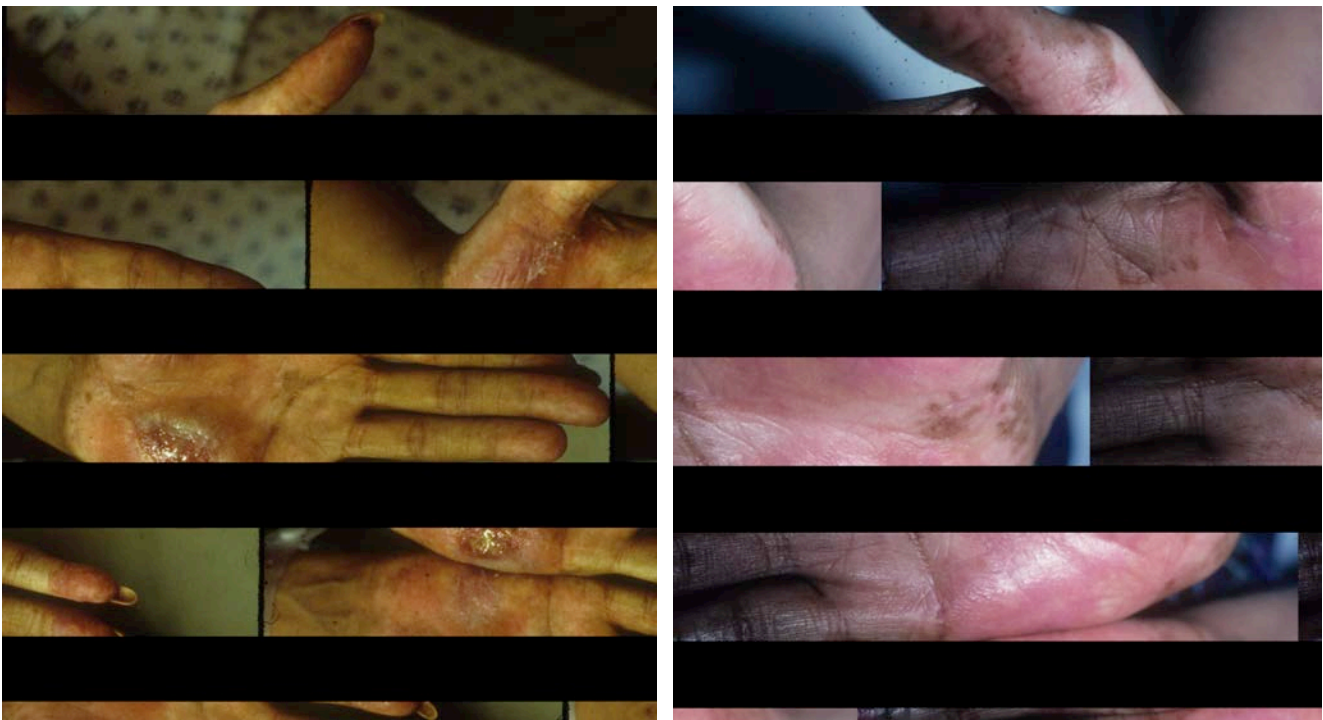


Figure 1. Severe involvement of the bilateral palms with erythema and erosions after the thalidomide was discontinued for a short time

Figure 2. Bilateral palms are shown after the patient was on thalidomide for 19 years. There is post-inflammatory hyperpigmentation, but no active lesions.

Discussion

There have been several case series in the literature in which thalidomide has been effectively used for the treatment of DLE and/or LP [3-5]. However, an extended course of thalidomide without many adverse side effects has not been reported. The most common side effects that cause patients to stop taking thalidomide are peripheral neuropathy, including numbness and paresthesias, sedation, and constipation [3]. More rarely, thalidomide can cause drug eruption, leukopenia, headache, joint pain, dizziness, lower extremity swelling, and deep venous thrombosis [5, 6]. Our patient tolerated thalidomide treatment for 19 years and did not develop any significant side effects that would require discontinuation.

After an extensive literature search, the longest study that followed patients on thalidomide was in Israel in 1980. This report described a group of 26 patients being treated for leprosy for 13 years. Motor conduction velocity in the ulnar nerve was measured at various times and the results indicated that no significant neurotoxic side effects were experienced. However, the patients

experienced other side effects including constipation, increased appetite, unilateral edema of the extremities or face, sleepiness, and urticarial and vesicular lesions [7].

Another more recent study completed in 2012 followed a cohort of 60 patients with varying types of cutaneous lupus erythematosus for up to 8 years. Of these patients, 85% had a complete response on thalidomide, but there was a 70% relapse rate after cessation. The most common side effects noted in this study were drowsiness, polyneuropathy, constipation, and weight gain [6].

At low doses, thalidomide can still be effective at clearing cutaneous disease with a lower chance of peripheral neuropathy. In a case series of 7 patients taking thalidomide to treat cutaneous lupus erythematosus, 6 experienced significant improvement or resolution of cutaneous lesions. Even at a dose of 100mg/day, with some patients being treated up to 9 years, none of the patients had evidence of peripheral neuropathy on nerve conduction studies [13]. In another case series of 10 patients with DLE, patients were treated with thalidomide at doses ranging from 50-200mg/day. Thalidomide quickly cleared their cutaneous disease and peripheral neuropathy developed in only 2 of the patients; this resolved upon discontinuation of the drug [14]. The incidence of peripheral neuropathy varies widely and in one study of thalidomide being used for dermatological conditions, it ranged from 21-50% [11]. Thalidomide neuropathy tends to be sensory, although muscle weakness may also occur [12].

It has also been observed that the severity of the peripheral neuropathy increases as the cumulative dose of thalidomide increases. Another series described 7 patients taking thalidomide for a host of reasons with doses ranging from 100 to 1,200 mg/day and resulting in cumulative dosages of 24 to 384 g [15]. Of the 7 patients, 6 had some evidence of sensory polyneuropathy presenting with paresthesias or numbness. The patients at higher cumulative doses developed more severe disease [15]. Also of note, patients with underlying neuropathy, such as those with prurigo nodularis, may be more prone to developing neuropathy [12].

Other side effects noted on the FDA label include neutropenia, increased HIV viral load, bradycardia, Stevens-Johnson syndrome, toxic epidermal necrolysis, seizures, tumor lysis syndrome, and hypersensitivity. The more common side effects include headaches, dizziness, drowsiness, mood changes, and xerostomia [1]. The most common laboratory abnormality is hypocalcemia, found in 96% of patients in a Phase 1 safety study of the drug [16].

Our patient did not experience any of these serious side effects despite taking thalidomide almost continuously for 19 years. Her most notable side effects include fatigue and occasional dizziness. We propose that some of the most treatment-limiting side-effects can be avoided at lower doses, typically less than 100mg/day. This is a rare case in which thalidomide has been successfully used, with minimal side effects for an extended time to control DLE/LP overlap disease.

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