Review Article

Thalidomide: Clinical Implications in Oral Mucosal Lesions - An Update

Shamimul Hasan[1]*, Shazina Saeed[2], Arpita Rai[1], Ansul Kumar[3], Priyadarshini Choudhary[4], Rajat Panigrahi[5] and Pradyumna Kuma Sahu[5]

[1]Department of Oral Medicine and Radiology, Faculty of dentistry, Jamia Millia Islamia, New Delhi, India; [2]Amity Institute of Public Health, Amity University, Noida (UP), India; [3]Department of CTVS, RIMS, Ranchi Jharkhand, India; [4]Department of Oral Medicine and Radiology, Kalinga Institute of Dental Sciences, KIIT University, Bhubaneswar, Odisha, India; [5]Department of Oral Medicine and Radiology, Institute of Dental Sciences, SOA University, Bhubaneswar, Odisha, India

Corresponding author:
Shamimul Hasan,
Department of Oral Medicine and Radiology, Faculty of dentistry, Jamia Millia Islamia, New Delhi, India,
Tel: 09953290676;
E-mail: shamimo571@gmail.com

Abstract

Thalidomide is perhaps one of the most notorious drugs ever to have been used in clinical practice. The distressing teratogenicity resulted in sudden withdrawl of the drug about 55 years back. Recently, thalidomide has revoked the interest of researchers due to demonstrable significant improvement in certain clearly defined disorders. Because of its salient anti-inflammatory, immunomodulatory and anti-angiogenic potential, the drug has become extensively significant even in dental clinical practice. Currently, thalidomide is being used as therapeutic entity in severe aphthous stomatitis, Behcet's syndrome, Erosive lichen planus, and oral features of HIV infection, Marshal Syndrome, orofacial granulomatosis and certain malignancies.

Keywords: Oral mucosal lesions; Peripheral neuropathy; Teratogenicity; Thalidomide

Introduction

A Swiss pharmaceutical firm, Chemische Industrie Basel (CIBA) first initiated the manufacture of thalidomide in early 1950's. Further researches were made by German pharmacy Chemie Grunethal and thalidomide was introduced in 1954 as Contegran. [1] The drug was considered as one of the safest sedatives because even small doses were effective and acute adverse effects such as motor impairment were not seen. [2,3] Life threatening adverse effects, such as teratogenicity and peripheral neuropathy were soon recognised and led to the drug's withdrawl in early 1960's. [4,5] An Israeli practitioner, Sheskin, prescribed previously stored thalidomide supplies to a patient with mania and leprosy, and resulted in remarkable and almost complete remission of the patient's skin symptoms. [6] These results were tested in other parts of the world and in 1998, U.S Food and Drug Administration (FDA), accepted the "orphan drug" status of thalidomide in the treatment of Erythema Nodusum Leprosum (ENL). Thalidomide should be prescribed under strict guidelines of System for thalidomide Education and Prescribing Safety (STEPS) program to minimize the risk of devastating teratogenic effects. [7] The drug's anti-tumor necrosis factor-alpha (TNF-α) action and investigational affirmation of anti-angiogenic potential revoked the attention of the researches in the clinical application of the drug. Currently, the drug is in use for many recalcitrant inflammatory conditions and possible malignancies. [8] This paper aim to highlight the implications and possible mechanism of action of thalidomide in various oral mucosal lesions.

Literature Review

Recurrent Apthous Stomatitis (RAS)

Apthous stomatitis, characterized by recurrent, localized painful ulcers is the most frequently observed disorder of the oral cavity. (Incidence rate of 5-25%). [9] The condition requires immense clinical consideration because of its multi-factorial etiopathogenesis and various therapeutic protocols with not much of a cure. [10]

Cell mediated immunity has a role to play in the immunopathogenesis of RAS. TNF-α, produced by T cells, macrophages and mast cells induces mucosal inflammation by causing adhesion of endothelial cells and chemotaxis of neutrophils. [11]

The immunomodulatory potential of thalidomide and its inhibitory action on TNF-α overproduction signifies the therapeutic role of thalidomide in aphthous stomatitis, although, still the precise mechanism of action of thalidomide in RAS cannot be clearly delineated. [12-14] Table 1 enumerates numerous trials demonstrating the use of thalidomide in RAS. [15-23]

As aphthous stomatitis is a self-healing entity, the use of thalidomide should be reserved for severely distressing or intractable orogenital ulcerations. [24]

Recurrent aphthous stomatitis in immunocompromised individuals (HIV Patient's)

Aphthous stomatitis is a potentially debilitating disorder in

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Table 1: Thalidomide in RAS.

Author	Year	No. of Patients (n)	Study Details	Clinical Outcome	Remarks
Mascaro et al. [15]	1979	06	100 mg thalidomide/day was given to patients with genital and oral ulcers	Ulcers were painless after 2-3 days, and complete remission was observed in 7-10 days.	
Torras et al. [16]	1982	09	100 mg thalidomide/day was given to patients for 10 days	8 patients reported complete resolution from ulcers, minimal pain and diminished recurrence rate.	
Jenkins et al. [17]	1984	15	400 mg OD (once a day) thalidomide was prescribed to patients for 5 days, followed by 200 mg for 4 weeks.	14 patients showed complete remission and 1 patient had marked improvement in the lesions within 5-21 days.	Recurrences were seen within a month of therapy cessation.
Grinspan et al. [18]	1985	40	300 mg thalidomide was given to patients with severe aphthae and 100 mg thalidomide was given for patients with less severe aphthae.	Regardless of the thalidomide dose, 75% remission in the symptoms was observed by the patients.	Patients with recurrences were managed with 100 mg thalidomide daily for 12 days.
Ramsellar et al. [19]	1986	67	In this randomized, placebo controlled clinical trial, patients were given 100 mg thalidomide daily or placebo for 2 months each and then switched therapy without a wash out period.	Complete resolution was seen in 48% thalidomide treated group, while only 9% resolution was observed in the placebo group.	
Revus et al. [20]	1990	73	In this randomized placebo controlled clinical trial, patients were given 100 mg thalidomide daily or placebo for 2 months	Complete resolution was seen in 44% (32 out of 73) thalidomide treated group, while only 8% resolution was observed in the placebo group.	Therapy cessation was followed by recurrences (within 20 days)
Bonnetblanc JM et al. [21]	1996	25	This retrospective study focussed at assessing how many individuals could undergo therapy cessation or decrease the dose of therapy.	Only a few patients showed a good response and could undergo therapy cessation. A low dose of thalidomide maintenance regimen was aimed to minimize serious side effects.	
Mimura et al. [22]	2009	21	Efficacy of the 4 systemic drugs-thalidomide, dapsone, colchicine, and pentoxifylline was assessed. Initially, patients were given a 2-week course of (0.5 mg/kg/day) prednisone to bring them to a baseline status. Following this, one of the four trial drug was assigned to each patient for a 6 month interval. If adverse effects or unsatisfactory results were seen, the patients were switched to one of the other three drugs and the 6-month limit of the treatment was then reset.	Thalidomide was the most efficient and best-tolerated drug; 7 out of 8 patients showed complete remission (87.5%). Out of 9 dapsone treated patients, complete resolution occurred in 5 patients, and considerable improvement was noted in 8 patients (89%). Colchicine was prescribed to ten patients. 4 patients showed complete resolution and 9 showed significant improvements (90%). Out of 5 patients treated with Pentoxyfilline, one patient showed complete remission with benefits observed in three (60%)	Least recurrences were seen in dapsone treated group. (Remained ulcer free for 9 months) Thalidomide treated patients showed no relapse for a period of 2-week to 4-month. This study strengthened the efficacy of thalidomide for RAS treatment, as 5 of 6 major aphthae patients showed major clinical improvements with thalidomide.
Muriel H et al. [23]	2010	92 (76 had oral or bipolar aphthosis, and 16 had Behcet disease)	A multicenter retrospective descriptive cohort study was carried at 14 different centres between Jan 2003 to May 2006. 15 patients were subjected to short term thalidomide therapy, because of adverse effects and poor outcome. (less than 3 months) 77 patients were subjected to maintainence therapy more than 3 months (60 patients for continuous therapy and 17 patients for intermittent therapy in cases of episodes of ulcerations)	Thalidomide was rapidly effective: 85% (78/92) entered complete remission (CR) within a median of 14 days. The median maintenance dose was 100 mg/week, and did not reflect the initial dose (r = 0.18). The intermittent-treatment group's median dose was significantly lower and its median duration of thalidomide intake significantly longer than for patients on continuous therapy. After 40 months of follow-up, 60% of patients were receiving maintenance therapy, according to a continuous or intermittent regimen, with favorable efficacy/safety ratio, and at low thalidomide doses (e3 capsules/wk) for most of them	Mild adverse events occurred in 78% (72/92) of patients. The most frequent were somnolence (36%), paresthesia (19%), constipation (19%), and weight gain. Adverse events were severe for 21% (19/92) of patients. No teratogenicity was reported. Peripheral neuropathies

HIV- positive patients, with an incidence rate of approximately 5-15%. Typically, the oral ulcers in HIV patients are larger in size, extremely painful, heal more slowly, and have a higher recurrence rate as compared to those seen in immunocompetent individuals. [25-27] A wide range of therapies including corticosteroids, pentoxyfylline, levimazole, colchicines, and granulocyte-colony stimulating factor (G-CSF) has shown variable responses, and no single drug has shown complete remission from the ulcers. [8]

Table 2 depicts numerous clinical trials [12,28-32] and few case reports [33,34] demonstrating the therapeutic potential of thalidomide in the management of aphthous ulcers in AIDS individuals.

HIV infection of mucosal cells induces a cascade of an immune mediated mechanism, and results in mucosal inflammation. Thalidomide, by virtue of its anti-inflammatory potential, causes inhibition of mucosal inflammation. [35]

Behcet's syndrome

In 1937, Hulusi Behcet, a Turkish dermatologist, first described Behcet's disease. It is characterized by recurrent oral and genital ulcers, uveitis and cutaneous lesions. Uncommon multi-systemic manifestations, such as gastrointestinal, central nervous system, vascular and joint infections may also be seen. [36] Behcet's syndrome is usually treated symptomatically and empirically, usually with systemic anti-inflammatory or immunomodulatory drugs. [37-39]

An increase in neutrophil chemotactic and migratory activity, along with immune complexes mediated vascular damage may play a role in the etio-pathogenesis of behcet's syndrome. [40] The precise mechanism of action of thalidomide in behcet's syndrome is not clearly delineated. Thalidomide may have an inhibitory action on the formation of superoxide and hydroxyl radicals causing tissue destruction at inflammatory sites. [40] Due to its anti-inflammotory and immunomodulatory properties, thalidomide decreases neutrophil chemotaxtic action and cell mediated immunity. [41]

Table 3 depicts numerous trials [12,42-44] and few published case reports [45,46] demonstrating the use of thalidomide in behcet's syndrome.

Lichen planus

Lichen planus (LP) is a chronic muco-cutaneous disease of the stratified squamous epithelium, frequently involving mucous membranes of the oral and genital region, skin, scalp, and nails. [47]

Lichen planus, an auto-immune disorder, is mediated by T CD 8 + cells, macrophages and Langerhan's cells. Immune mechanisms trigger apoptosis resulting in cell destruction and the appearance of characteristic histological changes. [48]

At present, the therapeutic regimen is aimed to reduce mucosal inflammation, ulcerations and minimize the symptoms during disease activity and possibly increase the disease remission period. [49] However, no single therapy has proven beneficial in the management of oral lichen planus.

Table 2: Thalidomide in RAS (HIV patients).

Author	Year	No. of Patients (n)	Study Details	Clinical Outcome	Remarks
Youle et al. [28]	1989	7	Thalidomide 100 mg/day for 2 weeks was prescribed to HIV patients with refractory aphthous ulcers.	Patients reported with speedy resolution in the lesions.	
Paterson et al. [12]	1995	20	A retrospective review was conducted for a 4 year period (1989 to 1993) Thalidomide (200mg /day for 2 weeks) was given to patients with recalcitrant oropharyngeal, esophageal and genital ulcers.	Complete resolution was seen in 14 patients and 6 others had marked clinical improvement.	No changes in CD4 + cells were observed during or after therapy.
Weidle et al. [29]	1996	14	Thalidomide therapy (300mg or 600 mg daily) for 7 days was compared with placebo.	75% patients in the thalidomide group responded to therapy, while none responded to placebo treatment.	
Jacobson et al. [30]	1997	57	Thalidomide therapy (200mg daily) for 4 weeks was compared with placebo.	16 out of 29 patients (55%) treated with thalidomide showed complete remission, whereas only 2 out of 28 patients (7%) showed complete remission in the placebo group.	Adverse effects of thalidomide were observed. 7 patients reported somnolence and skin rash and 6 patients stopped treatment because of toxic effects.
Ramirez-Amador et al. [31]	1999	16	Thalidomide therapy in 10 patients was compared with placebo therapy in 6 patients. 400 mg oral thalidomide was given initially for 7 days, followed by 200 mg daily for 7 weeks.	9 out of 10 patients (90%) treated with thalidomide showed complete remission, whereas only 2 out of 6 patients (33%) showed complete remission in the placebo group.	Skin rash was reported by 80% patients treated with thalidomide.
Jacobson et al. [32]	2001	49	A multicenter randomized study of thalidomide versus placebo for oral and oesophageal ulcers was conducted. 100 mg thalidomide or placebo 3 times per week for 6 months was prescribed.	14 of 23 patients (61%) treated with thalidomide had recurrence as compared to 11 of 26 patients (42%) in the placebo group.	No difference in plasma levels of HIV RNA, TNF-ALPHA and soluble TNF receptor II at the time of ulcer recurrence.

Table 3: Thalidomide in Behcets syndrome.

Authors	Year	No. of Patients (n)	Study Details	Clinical Outcome
Saylan T. [50]	1982	22	Initial 5 days: 400 mg/ day thalidomide was given, followed by 200 mg/day for the next 15-60 days.	Spontaneous healing was observed in oral and genital lesions, with uncommon and milder recurrence rates. However, ocular lesions and arthritis remained non responsive.
Gardner et al. [26]	1994	59	Patients with recalcitrant orogenital ulcerations (OGU) were treated with 400 mg/ day thalidomide for the initial 5 days, followed by tapered thalidomide dose (200 mg/day) for the next 28 days.	81% patients showed complete resolution within one month of treatment with 200 mg thalidomide. Thalidomide therapy was not required in 20% responding patients, and in the remaining patients improvement was maintained at smaller doses (7-200mg).
Hamuryudan et al. [51]	1998	96	In this randomized, placebo controlled trial, patients were given either thalidomide (100 mg/ day or 300 mg/day) or placebo for a period of 24 weeks.	complete remission occurred in- 1) 2 out of 32 patients (6%) receiving thalidomide 100 mg/day. 2) 5 out of 31 patients (16%) receiving thalidomide 300 mg/day. Unsatisfactory outcome was observed in all the placebo treated patients
Wazieres et al. [52]	1999	17	Thalidomide was prescribed to seventeen patients with OGU. Thalidomide 1 tablet (50mg/ day) was initially given for 1 month. Dose tapering was done after improvement in the lesions (one tablet on alternate days) for 1 month and one tablet every 3 days thereafter. Nerve conduction studies (EMG) were conducted at inclusion in the study and every 6 months thereafter	***At 1 month therapy***-complete remission in 10 patients and improved condition in rest 7 patients. ***At 2 month therapy-***Complete remission was observed in six patients. ***At 4 month therapy-*** one patient showed complete remission the study showed that a initial dose of 50-mg/day is an effective therapy in OGU. Prescribing one tablet every 2 or 3 days is successful in more than 60% of the patients to maintain remission.

Table 4: Thalidomide in lichen planus.

Authors	Year	No. of Patients (n)	Study Details	Clinical Outcome	Remarks
Yun Wu et al. [52]	2010	69	The randomized clinical trial was conducted to evaluate the short term efficiency and safety of topical thalidomide for erosive lichen planus. 1% thalidomide paste was given to 37 patients and dexamethasone paste was prescribed to 32 patients for a week. After 7 days of treatment, recurrences were looked for in patients free from erosions, whereas patients with ongoing erosions were prescribed same therapy for 3 more weeks. Erosion size, visual analogue scale (VAS), 3 months recurrence rate and adverse effects at 1 year were the parameters.	***After a week of therapy*** A noteworthy decrease in erosive areas and VAS scores was reported by patients in both groups. 18 patients out of 33 (54.5%) in thalidomide group showed complete remission, whereas 17 patients out of 30 (56.7%) in the dexamethasone group showed complete remission. Erosive area size and VAS score were similar in the two groups. ***After 1 month therapy*** Complete remission was seen in 24 patients out of 33 (66.7%) in Thalidomide group, and in 22 patients out of 30 (73.3) in the dexamethasone group. ***At 3 month follow up*** The two groups did not show any major difference in recurrence rate. ***At 1 year follow up*** Side effects were not reported.	Topical thalidomide was considered as efficient as dexamethasone in the management of erosive oral lichen planus.

Thalidomide applicability in lichen planus can be justified based on its re-epitheliazation tendency and immunomodulatory potential. Keratinocyte proliferation and their movement are the two significant and crucial stages in the re-epithelialization of skin wounds. A 2-3 fold enhancement in both the proliferative activity and migratory activity of keratinocytic cells has been observed at therapeutic concentration of thalidomide. [50]

Naafs and Faber were the first to utilize the salient properties of thalidomide in managing lichen planus lesions. [51]

Currently, a single clinical trial [52] [Table 4] and few case reports [53-57] have supported the role of thalidomide as a treatment modality in erosive oral lichen planus.

Marshal's syndrome

Marshall Syndrome is also known as PFAPA syndrome (periodic fever, adenitis, pharyngitis, aphthae). It is characterized by recurrent febrile episodes, accompanied by aphthous ulcers, pharyngitis and cervical adenitis. [58,59]

Numerous controlled studies have recommended different therapeutic regimens. However, the mainstay of treatment of PFAPA syndrome still remains controversial. [60] The disease usually shows self-remission after several years, although some adults have also reported with persistent attacks. [61] Utilizing the proven anti-inflammatory and immunomodulatory potential, Marque et al. were the first to report successful management of a refractory case of PFAPA syndrome with thalidomide. [62]

Discussion

Thalidomide as an anti-cancer agent

The pioneer observation of thalidomide's anti-angiogenic properties by D-Amato and colleagues revoked the interest of clinicians to use it as an anticancer agent. [63] The anti-angiogenic potential of thalidomide was further highlighted by studies in rabbit cornea model and isolated rat aorta model. [64-66] Angiogenesis is a complex mechanism that involves various growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF). [67] An *in vitro* study on chicken embryonic chorioallantoic membrane (CAM) was conducted and it was observed that thalidomide has an inhibitory action on VEGF plus bFGF-mediated vessel formation. This anti-angiogenic outcome was amplified by preincubation with human microsomes. [68]

Thalidomide's anti-angiogenic potential and also the fact that anti-angiogenesis was a suitable target for cancer therapy, justifies the role of thalidomide in the treatment of multiple myeloma (MM) and Kaposi's sarcoma. [8]

Thalidomide showed significant efficacy in cases where human herpes virus-8 (HHV-8) was demonstrable both in skin and serum of patients. [69] A study by Jin X et al. detailed the remedial benefits of thalidomide in OLP and chronic discoid lupus erythematosus (CDLE) and recommended the application of thalidomide as a potential therapeutic regimen for potentially malignant lesions of the oral cavity. [70]

Orofacial granulomatosis

Orofacial granulomatosis (OFG) is a general terminology that encompasses a variety of disorders, including Melkersson-Rosenthal syndrome, granulomatosis cheilitis, Crohn's disease, sarcoidosis, and infectious entities such as tuberculosis. It is characterized by non-necrotizing granulomatous inflammation of the oral and maxillofacial region. The condition clinically manifests as perioral and/or mucosal swelling, labial enlargement, oral mucosal ulcerations, and gingivitis. [71] Few published case reports have shown the role of thalidomide as a successful therapeutic regimen for severe orofacial granulomatosis. [72-74]

Table 5 depicts the role of thalidomide in Orofacial granulomatosis.

Side effects

Thalidomide is categorized as pregnancy category X drug.

Table 5: Thalidomide in orofacial granulomatosis.

Authors	Year	No. of Patients (n)	Study Details	Clinical Outcome	Remarks
Odeka EB, Miller V (Case Report)	1997	01	oral thalidomide (100 mg daily, later reduced to 50 mg daily was given to a 8 year old male patient with oral Crohn's Disease Refractory to Conventional Medical Treatment (oral prednisolone (2-maximum 60 mg/kg daily and combination of azathioprine and prednisolone).	The pain eased within days, and the ulcers disappeared within 2 weeks.	The patient had longer ulcer-free intervals, and ulcers respond to ad hoc use of TLD 50 mg daily.
Hegarty A, Hodgson T, Porter S	2003	05	Low dose thalidomide was given to 5 orofacial granulomatosis patients recalcitrant to recognized immunosuppressant therapy.	All patients had clinical resolution of their symptoms and signs. Transient somnolence was the only reported adverse effect. Remission was maintained by extending the period between thalidomide doses.	Thalidomide should be considered an effective therapy for the short-term treatment of severe orofacial granulomatosis in appropriately counseled patients.
Eustace K, Clowry J, Kirby B, Lally A. (Case Report)	2014	01	100 mg OD (once a day) thalidomide was prescribed to refractory orofacial granulomatosis patient for 8 weeks	Remission was seen following thalidomide therapy.	

Table 6: Adverse effects of thalidomide

Severe	Common [79]	Uncommon [79]
• Teratogenicity • Peripheral neuropathy	• Somnolesence • Fatigue • Constipation • skin rash	• Xerostomia • Neutropenia • Toxic Epidermal Necrolysis/Stevens-Johnson Syndrome • Deep Venous Thrombosis • Hypothyroidism • Menstrual Irregularities • Loss of Libido • Impotence • Hyper- or Hypoglycemia • Asthenia, Tremors, Confusion • Peripheral Edema • Elevation of Liver Enzymes • Pruritus • Hair Loss • Fever

Teratogenicity is the most serious and devastating side effect. [75]

According to McBride, the teratogenic effects may be categorized as: [76]

• **Abnormalities of the extremity:** Amelia (absent limbs), flipper hands and feet (phocomelia), hypoplastic or even absent bones.

• **Anomalies of the eyes and ears:** absent ears, absent or small auditory canal, absence of one or both eyes (anophthalmia), abnormally small eyes with anatomical malformations (microphthalmia), with or without accompanied facial palsy.

• **Internal organ deformities:** congenital heart defects, malformed gastrointestinal and urinary tract.

Peripheral neuropathy

Peripheral neuropathy is another significant adverse effect which should be given a consideration in cases where thalidomide needs to be prescribed. [77] The most commonly observed neuropathic manifestations include senso-motor symptoms (lack of sensation, prickling, painful extremities, or fatigue), with or without hindrance in daily activities. The condition is usually managed either with dose reduction or cessation of therapy. However, in few individuals, even the treatment cessation could not reverse the condition. [78-80] Table 6 summarizes the various adverse effects of thalidomide.

Conclusion

Hence, a number of conducted trials and case studies have established the efficacy of thalidomide in a wide range of clinical entities, resistant to conventional treatment modalities. With its salient immunomodulatory, anti-inflammatory, and anti-angiogenic potential, the drug holds a promising future for the management of variety of medical and dental conditions.

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Conflict of Interest

All authors disclose that there was no conflict of interest.

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