THALIDOMIDE : 21st Century Challenge

Dr. A. Raouf Al Suwaid, MD. *
Dr. Hani Gamil Arafa, MBBS, DDV **

ABSTRACT

Thalidomide (? N-phthalimido-glutarimide) is a derivative of glutamic acid produced in West Germany in1954 . However,it was rapidly withdrawn from the international market leaving thousands of children born with terrible sequels.

Recently, the drugs is used as an immuno-modulator and anti-inflammatory agent in many dermatological and medical conditions with promising results. It should be very cautiously used in women in childbearing age and neurologic examination should be done before and during therapy.

This article reviews the history of this notorious drug and gives a profound perception as to how to be practically implemented in medicine.

BACKGROUND

Thalidomide (? N-phthalimido-glutramide) is a derivative of glutamic acid first produced in West Germany in 1954. Preliminary studies in laboratory mice showed a very safe drug with no teratogenic properties. It was used in the 1st trimester of pregnancy as antiemetic, sedative and hypnotic . Soon many countries started to use the drug in Europe , Asia, Australia, Americas and Africa. Unfortunately, that was followed by an epidemic of congenital malformations of limbs and internal organs[1]. An Australian gynecologist , Dr. McBride of Sydney suspected that thalidomide was the cause of limbs and bowel malformations in 3 children he had seen at Crown Street Women's hospital, four and a half years after the wide use of the drug during early pregnancy. The 1st Accusation against Chemie Grunenthal reached the public prosecutors office at the country of Aachen by the end of 1961[2]. 10,000-12.000 babies were born with defect around the world in the fifties and sixties as a consequence of the drug thalidomide and no one will ever know how many were stillborn or miscarried due the effects of this powerful drug. The defect most associated with thalidomide is phocomelia (seal flipper like limbs). Thalidomide induced phocomelia is bilateral (both arms, both legs or all four limbs)1. The drug was consequently withdrawn from the market. In 1964 a physician in Jerusalem was confronted with severe Erythema Nodosum Leprosum patient that was resistant to all available treatment options. He tried thalidomide and the results was something of legend, within a few days the nodules vanished. Moreover, the nodules did not come back so long as the drug was continued over the next few years, thousands of patients with Erythema Nodosum Leprosum (ENL) were treated with thalidomide and most of them responded very well[3].

Thalidomide the most notorious drug of the fifties and sixties recently licensed for use in the USA on July 16,1998, following studies of its immunomodulatory and anti-inflammatory effects[4]. In this article, thalidomide action, its recent uses and side effects , will be reviewed.

METABOLISM

The route of thalidomide breakdown in human and animals is through spontaneous hydrolysis with subsequent elimination in the urine. Thalidomide did not inhibit metabolism of cytochrome P-450 specific substrate and therefore any interaction with other drugs that are metabolized by the same enzyme system is unlikely[5].

WITH THE RETURN OF THALIDOMIDE CAN BIRTH DEFECTS BE PREVENTED ?

Thalidomide, the drug that caused a worldwide epidemic of serious birth defects in the late fifties and early sixties has been recently approved by US FDA for use in treating ENL. The drug is also promising in treating other serious diseases .

Hundreds of thousands of women with childbearing ability could be treated with thalidomide. In an effort to prevent fetal exposure to thalidomide, FDA mandated a comprehensive programme to regulate prescribing, dispensing and use of the drug .

The programme is designed to register all drug pre-

* *Sr. Consultant & Superintendent*
Department of Dermatology & Genito Urinary Medicine Al Nahdha Hospital
** *Medical Officer*
Department of Dermatology & Genito Urinary Medicine Bausher Polyclinic
Address for Correspondence:
Dr. Hani Gamil Arafa, Dermatologist
Department of Dermatology & Genito Urinary Medicine
Bausher Polyclinic
P.O. Box 77, Postal Code 118, Muscat
Sultanate of Oman.
Tel:594860(968), GSM 9013307(968)
Email: hania333@omantel.net.om.

scribers, pharmacies and patients.

It also requires the use of effective methods of contraception and periodic pregnancy testing of all female patients with childbearing ability during treatment.

The patient should sign an informed consent before the beginning of treatment.

This mandatory programme promises to be effective in preventing fetal exposure to thalidomide[4].

MECHANISM OF ACTION

1. Inhibitor of phagocytosis in PMNL and inhibitor chemotaxis in monocytes[6].
2. Potent inhibitor of Tumor Necrosis Factor alpha(TNF-alpha) in human monocytes in vitro[7] and in vivo[8] by accelerating its m-RNA degradation9 and by reduction of TNF?m-RNA levels[10].
3. Inhibitor of lymphocytes proliferation in response to allogenic and mitogenic stimuli[11].
4. Thalidomide decreases the ratio of CD4 to CD8 lymphocytes in ENL patients[12].
5. Thalidomide has the capacity to inhibit the replication of human immunodeficiency virus type 1 (HIV-1) in monocytic cells of infected patients through reduction of TNF alpha[13]

   TNF alpha has an important role in HIV-1 replication , viral gene expression and the propagation of infection[14].
6. Inhibitor of angiogenesis: It inhibits the growth of new vessels by inhibiting the movement and migration of cells that are necessary for the formation and extension of new vessels[15]. Inhibition of angiogenesis could literally starves cancer and stunts its growth.
7. Thalidomide increases human keratinocytes migration and proliferation[16].

So, thalidomide is classified as : immunomodulator having no toxic effects on cells of immune system , but does alter the ratio of various types of immune cells and changes the expression of molecular markers on their surfaces , and an anti-inflammatory drug that is a potent inhibitor of cell that are normally attracted to sites of tissue damage . It also has the ability to inhibit TNF which is a potent stimulator of inflammation.

INDICATIONS

A. Dermatosis :

1. ENL [17,18].
2. Pyoderma Gangrenosum [19,20]
3. Erythema Multiformis [21].
4. Scleroderma[22]
5. Porphyria Cutanea Tarda[23].
6. Jessner's Lymphocytic Infiltration[24].
7. Prurigo Nodularis [18].
8. Lichen Planus [25,26].
9. Actinic Prurigo[27].
10. Pruritus [28].
11. Refractory Non-healing Ulceration[29].
12. Lupus Pernio[30].
13. Behcet's Disease [31,32].
14. Discoid Lupus Erythematosus (DLE) and Subacute Cutaneous Lupus Erythematosus (SCLE)[33,34,35]
15. Melkersson Rosenthal syndrome [36].

B. HIV Related Conditions:

1. Oral aphthous ulcers and oesophageal ulcers.[37,38,39].
2. HIV wasting[40].
3. HIV-TB[41].
4. HIV diarrhea[30,42]
5. HIV - Mycobacterium Avium Complex (MAC)[30,42]
6. Kaposi's sarcoma [30,42].

C. Other indications:

Graft Versus Host Diseases (GVHD)[30], Systemic Lupus Erythematosus (SLE) [30], Multiple Sclerosis[43], Crohn's disease[44], Rheumatoid Arthritis[44], multiple myeloma [45,46,47,48], glioma[49] and Malignancies [50,51]

.

SIDE EFFECTS

1. Teratogenicity:

It may cause quite different malformations in different children . It does not produce malformations if only taken before the 34th day of last menstruation (35-49 days of pregnancy is the sensitive period). Malformations include limbs, ears and internal organs[2].

2. Peripheral neuropathy [29,52,53].
3. Dizziness and drowziness [53].
4. Constipation [53].
5. Decreased libido [54].
6. Xerosis [54].
7. Skin rash [52,54].
8. Gastric pain [54].
9. Neutropenia [52].
10. Hypersensitivity reactions [54].
11. Erythroderma [55].

THALIDOMIDE CAUSE BIRTH DEFECTS (TERATOGENICITY) ?

1. Thalidomide is a teratogen with anti-angiogenic properties and causes stunted limb growth (dysmelia) during human embryogenesis. Thalidomide exerts its anti-angiogenic properties via the generation of toxic hydroxyl radicals which impair vasculgenesis and angiogenesis during embryoid body development[56]
2. Thalidomide affects the following pathway during development:Insulin like growth factor and fibroblast growth factor 2 (IGF1 and FGF2) stimulate transcription of alpha v and beta 3 integrin subunit gene, the resulting alpha V beta 3 integrin dimer stimulates angiogenesis in the developing limb bud ,which promotes outgrowth of the bud . The promoters of these genes contain GC boxes. Thalidomide or its breakdown product specifically binds to these GC promoter sites decreasing transcription efficiency of the associated genes . A cumulative decrease interferes with normal angiogenesis which results in truncation of the limb.

CONCLUSION

Thalidomide has 40 years of controversial life .From the above review it is clear that thalidomide has come back in modern medicine and is used on a much wider scale.

We have to learn more about its mode of action, teratogenicity and neurotoxicity.

Its use should be restricted for conditions unresponsive to other medications.

From the above review it is clear that thalidomide has come back in modern medicine and is used on a much wider scale . The current situation is that the medicine is not easily available and the formalities for getting it is so complicated to the physician and for the patient remain the question of thalidomide tragedy whether preventable or not.

REFERENCES:

1. Calderon P, Anzilotti M, Phelps R. Thalidomide in dermatology. New indicationsfor an old drug. Int J Dermatol 1997 Dec; 36(12): 881-887

2. Lenz W . Apersonal perspective on the thalidomide tragedy. Teratology 1992 Nov ; 46(5) : 415-8

3. Shaskin J . Thalidomide in the treatment of lepra reaction Clin Pharmacol Ther 1965 ;6:303

4. Lary JM , Daniel KL, Erickson JD, Roberts HE, Moore CA . The return of thalidomide : Can birth defects be prevented ? Drug Saf 1999 Sep ;21 (3):161-9

5. Teo SK ,Sabourin PJ ,O'Brien, et al . Metabolism of thalidomide in human microsome J Biochem Mol Toxicol 2000 ; 14 (3) : 140-7

6. Barnhill RL, Doll NJ, Millikan LE, et al . Studies on the anti-inflammatory properties of thalidomide Arch Dermatol Res 1980 ;269 : 275-280

7. Samaio EP, Sarno EN ,Galilly R et al. Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated monocytes. J Exp Med 1991; 173:699-703

8. Tramontana JM, Utaipat U, Molloy A et al . Thalidomide treatment reduces tumor necrosis factor alpha production and enhances weight gain in patients with pulmonary tuberculosis Mol Med 1995; 1:384-397

9. Moreira AL, Sampaio EP , Zmurdinas A , et al Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing m-RNA degradation. J Exp Med 1993; 177:1675-1680

10. Makonkawkeyoon S, Limson-Pobre RNR, Moreira AL, et al Thalidomide inhibits the replication of human immunodeficiency virus type 1 Proc Natl Acad Sci USA 1993; 40:5974-5978

11. Keenan RJ, Eiras,Burckart GJ, et al Immunosuppressive properties of thalidomide. Inhibition of in vitro lymphocytes proliferation alone and in combination with cyclosporine or FK506 Transplantation 1991; 52 :908-910

12. Shannon EJ, Ejigau M, Haile-Mariam HS, et al Thalidomide effectivness in erythema nodosum leprosum is associated with a decrease in CD4 in the peripheral blood Lepr Rev 1992; 63 : 5-11

13. Poli G, Kinter A , Justment JS , et al Tumor necrosis factor alpha functions in an autocrine manner in the induction of human immunodeficiency virus expression. Proc Natl Acad Sci USA 1990; 87:782-785

14. Kaplan G, Moreira AL. TNF alpha regulation o HIV1 : Biology and therapy . Res Immunol 1994;145:685-689

15. JAMA HIV/AIDS Information center (Posted January 29, 1998)

16. Nasca MR, O'Toole EA, Palicharla P, et al . Thalidomide increases human keratinocyte migration and proliferation . J Invest Dematol 1999 Nov;113(5):720-4

17. Moraes MO,Sarno EN, Teles RM, et al. Antinflammatory drugs block cytokine m-RNA accumulation in skin and improve the clinical condition of reactional leprosy patients J Invest Dermatol 2000 Dec;115(6):935-941

18. Stirling DI . Thalidomide and its impact in dermatology Semin Cutan Med Surg 1998 Dec; 17(4): 231-42

19. Hecker MS, Lebwohl MG. Recalcitrant Pyoderma Gangrenosum: treatment with thalidomide J Am Acad Dermatol 1998 Mar; 38(3): 490-1

20. Federman GL, Federman DG, Recalcitrant Pyoderma Gangrenosum treated with thalidomide Mayo Clin Proc 2000 Aug ; 75(8):842-4

21. Cherouati K, Claudy A, Souteyrand P, et al. Treatment by thalidomide of Chronic Erythema Multiformis , its recurrent and continuous variants . Ann Dermatol Venereol 1996; 123(6-7):375-7.

22. Oliver SJ, Moreira A ,Kaplan G .
Immune stimulation in scleroderma patients with thalidomide Clin Immunol 2000 Nov; 97(2):109-20

23. Monastirli A, Georgiou S, Bolsen K, et al .
Treatment of porphyria cutanea tarda with oral thalidomide .
Skin Pharmacol Appl Skin Physiol 1999 Nov-Dec ;12(6):305-11

24. Thalidomide : new preparation for well defined indications
Prescrire Int 1998 Oct ; 7 (37) : 131-4

25. Scully C, Beyli M, Ferreiro G, et al. Update on oral lichen planus Crit Rev Oral Biol Med 1998;9(1) : 86-122

26. Camisa C, Popovsky JL . Effective treatment of oral erosive lichen planus with thalidomide Arch Dermatol 2000 Dec ; 136 (12)1442-3

27. Lestarini D, Khoo LS, Goh CL ,
The clinical features and management of actinic prurigo :a retrospective study.
Photodermatol Photoimmunol Photomed 1999 Oct;15 (5) :183-7

28. Daly BM, Shuster S. Antipruritic action of thalidomide Acta Derm Venereol 2000 Jan-Feb ; 80(1)24-5

29. de Wazieres B, Gil H ,Magy N, et al
Treatment of recurrent ulceration with low doses of thalidomide . Pilot study in 17 patients Rev Med Intern 1999 Jul; 20 (7) : 567-70

30. Calabrase L, Fleischer AB,Thalidomide :current and potential clinical applications Am J Med 2000 Apr 15 ; 108 (6) : 487-95

31. Yaziu H, Yurdakul S , Hamuryudan V. Behcet's disease. Curr Opin Rheumatol 1999 Jan ; 11(1) 53-7

32. Hamuryudan V, Mat C, Saip S, et al , Thalidomide in the mucocutanous lesions of the Behcet's syndrome.
Ann Intern Med 1998 Mar 15;128(6):443-50

33. Duong DJ, Spigel GT, Maxley 3rd,et al,
American experience with low dose thalidomide therapy for sever cutanous lupus erythematosis. Arch Dermatol 1999 Sep; 135(9):1079-87.

34. Ordi-Ros J, Cortes F, Cucurull E, et al
Thalidomide in the treatment of cutaneous lupus refractory to conventional therapy. J Rheumatol 2000 Jun ; 27(6):1429-33

35. Kyriakis KP, Koutochristopoulos GJ, Panteleos DN.
Experience with low dose thalidomide therapy in discoid lupus erythematosus
Int J Dermatol 2000 Mar; 39(3):218-22

36. Safa G, Joly P, Boullie ME, et al .
Melkersson Rosenthal syndrome treated by thalidomide.
Ann Dermatol Venereol 1995 ; 122(9) 609-11

37. Diz Dios P, Sopena B, Camesella J, et al,
Thalidomide for the treatment of acquired immunodeficiency syndrome associated refractory oral ulcers Arch Otolaryngol Head Neck Surgery 2000 Jan;126(1)89-90

38. Ramiraz-Amador VA, Esquivel-Pedraza L, et al,
Thalidomide as therapy for human immunodeficiency virus related oral ulcers: a double blind placebo-controlled trial .Clin Infect Dis 1999 Apr; 28(4):892-4.

39. Jacobson JM, Greenspan JS, Spritzler J, et al.
Thalidomide for treatment of oral aphthus ulcers in patients with human immunodeficiency virus infection N England J Med 1997 May 22; 336(21):1487-93

40 Kaplan G, Thomas S, Fierer DS, et al, Thalidomide for the treatment of AIDS-associated wasting AIDS Res Hum Retrovirus 2000 Sep 20 ; 16 (14):1345-55

41. Bekker LG, Haslett P, Maartens G, et al ,
Thalidomide induced antigen specific immune stimulation in patients with human immunodeficiency virus type1 and tuberculosis. Infect Dis 2000
Mar ;181(3):954-65

42. Ravot E, Lisziewiez J, Lori F .
New uses for an old drugs in HIV infection :the role of hydroxyurea, cyclosporine and thalidomide Drugs 1999 Dec ; 58 (6) :953-63

43. Sastry PS et al ,
Inhibition of TNF alpha synthesis with thalidomide for prevention of acute exacerbations and alter the natural history of multiple sclerosis .
Med Hypotheses 1999 Jul;53(1)76-7

44. Neiger BL et al ,
The re-emergence of thalidomide :results of a scientific conference
Teratology 2000 Dec; 62 (6):432-5

45. Rajkumar SV, Witzig TE ,.
A review of angiogenesis and antiangiogenetic therapy with thalidomide in multiple myeloma Cancer Treat Rev 2000 Oct; 26(5): 351-62 Review

46. Hideshima T, Chauhan D, Shima Y, et al,
Thalidomide and its analogous overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood 2000 Nov 1; 96(9):2943-50

47. Newton HB, . Novel chemotherapeutic agents for the treatment of brain cancer Expert Opin Invesig Drugs 2000 Dec ; 9(12)2815-29 Review

48. Rajkumar SV, Fonseca R, Dispenzieri A, et al, Thalidomide in the treatment of relapsed multiple myeloma Mayo Clin Proc 2000 Sep ;75(9):897-901

49. Cohen MH. Thalidomide in the treatment of high grade glioma
J Clin Oncol 2000 Oct 1;18(19):3453

50. Thomas DA, Kanturjian HM. Current role of thalidomide in cancer treatment . Curr Opin Oncol 2000 Nov; 12 (6)564-73

51. Thalidomide shows promise as cancer treatment Health News 2000 Jan ; 6(1):8

52. Jacobson JM, Greenspan JS, Spritzler J, et al
Thalidomide in low intermittent doses does not prevent recurrence of human immunodeficiency virus associated aphthous ulcers.
J Infect Dis 2001 Jan;183(2):343-346

53. Sato EI, Assis LS, Lourenzi VP, et a, l Long term thalidomide in refractory cutaneous lesions of systemic lupus erythematosus Rev Assoc Med Bras 1998 Oct-Dec ;44(4):289-93

54. Gunzler V., Thalidomide in human immunodeficiency patients. A review of safety considerations . Drug Safety 1992;7:117-133

55. Bielsa I, Teixido J, Ribera M, et al, .
Erytheroderma due to thalidomide: report of two cases Dermatology 1994; 189(2): 179-181

56 Sauer H, Gunther J, Hescheler J, et al ,
Thalidomide inhibits angiogenesis in embryoid bodies by the generation of hydroxyl radicals. Am J Path 2000 Jan;156(1):151-8

57. Stephens TD, Bunde CJ, Fillmore BJ., Mechanism of action in thalidomide angiogenesis.
Biochem Pharmacol 2000 Jun 15; 59(12):1489-99