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Thalidomide: An Overview on Teratogenicity and its Newer Therapeutic Effects

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HUMAN

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ABSTRACT

Thalidomide was first introduced to the market in Germany under the brand name of Contergan in 1956, as a "non-barbiturate hypnotic", advocated to ensure a good night's sleep and to prevent morning sickness in pregnancy. It has been banned from the market since 1963 after it caused the worldwide teratogenic disaster: babies exposed to thalidomide in utero during the first 34-50 days of pregnancy were born with severe life-threatening birth defects such as Phocomelia. In addition to limb reduction anomalies, other effects later attributed to thalidomide included congenital heart disease, malformations of the inner and outer ear, and ocular abnormalities. The thalidomide tragedy was averted in the United States because of the hold on its approval by Dr. Frances Kelsey of the U.S. Food and Drug Administration, who was recognized by President John F. Kennedy as a recipient of the Gold Medal Award for Distinguished Civilian Service. The thalidomide tragedy also brought into sharp focus the importance of rigorous and relevant testing of pharmaceuticals before their introduction into the market place. Despite its unfortunate history, thalidomide has attracted scientific interest again in the 1980s, as it was found to be a powerful anti-angiogenic drug, inhibiting the growth of blood vessels in tumors. It has come into wide use as a cancer drug, primarily in the treatment of multiple myeloma. Its broad range of biological activities stems from its ability to moderate cytokine action in cancer and inflammatory diseases. Thalidomide is found to be highly effective in managing the cutaneous manifestations of leprosy, being superior to Aspirin in controlling leprosy-associated fever. In this study, the structure, chemistry, synthesis, structure activity and relationship, the history of thalidomide, its teratogenic effects, mechanism of teratogenicity, its newer therapeutic applications and development of less toxic and more active analogs are discussed. This study also gives brief information related to S.T.E.P.S (System for Thalidomide Education and Prescribing Safety) designed by Celgene pharmaceuticals.

1. INTRODUCTION

1.1 Structure:

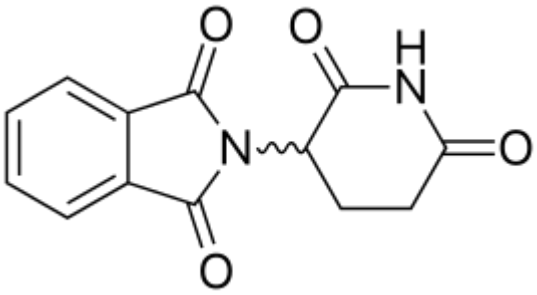


Figure No. 1: Structure of Thalidomide

IUPAC Name: (RS)-2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione

Molecular Formula: $C_{13}H_{10}N_2O_4$

Physical properties: [125]

State – Solid

Description – Thalidomide is off-white to white, odourless, crystalline powder.

Solubility – Slightly soluble in water, methanol, ethanol or acetone, highly soluble in dimethylformamide and DMSO, but insoluble in ether, chloroform or benzene.

1.2 Chemistry:

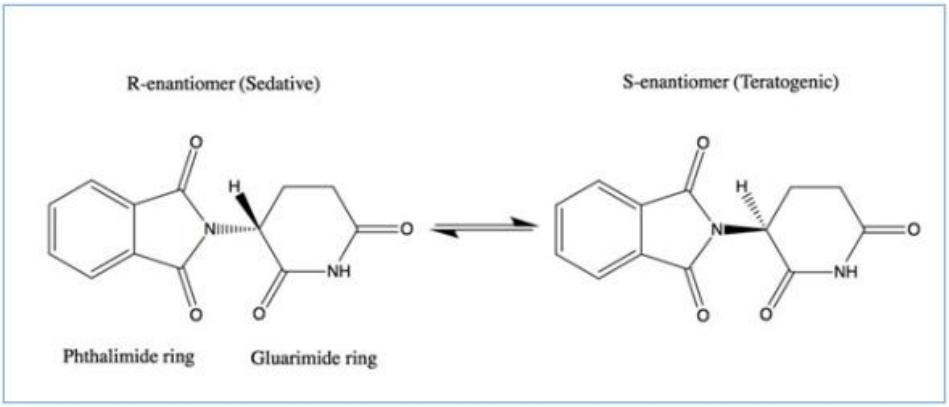


Figure No. 2: (+) – (R) and (-) – (S) Enantiomers of Thalidomide

Thalidomide (α-N- [phthalimido] glutarimide, $C_{13}H_{10}N_2O_4$), is a **glutamic acid derivative** initially introduced as a sedative hypnotic nearly forty years ago. It was withdrawn following numerous reports linking it to a characteristic pattern of congenital abnormalities in babies born to mothers who used the drug for morning sickness.[1]

Thalidomide is racemic; while the S-thalidomide is the bioactive form of the molecule, the individual enantiomers can racemize to each other due to the acidic hydrogen at the chiral centre, which is the carbon of the glutarimide ring bonded to the phthalimide substituent. [2]

R and S Enantiomers are the chemical compounds that are the mirror image to each other and may have different active properties. The racemic mixture is the one having both R and S enantiomers.

R or the Right enantiomer is identified as the isomer that rotates the polarized right to the right and the S to the left. Hence, they are called + and – isomers. [3]

The R-isomer of TD has sleep-inducing properties and is 55% plasma protein - bound while the S-isomer is teratogenic with 65% plasma binding [4]. R-isomer, with useful properties, was tried to isolate and purify it as a drug but TD turns into a racemic mixture as it enters into the human plasma [5]. Knoche et al. found that human serum albumin influences the racemization process. Therefore, even purified TD would be converted into both isomers in the human plasma and become teratogenic. [6]

1.3 Structure Activity Relationship (SAR):

Studies on the structure activity relationship (SAR) of the metabolites of thalidomide and its analogues have revealed that the phthalimide ring system is an essential pharmacophoric fragment.[7]

Substituted N-phenylphthalimides are of high interest because they have been found to inhibit TNFα [8,9] and COX [8], and have tubulin binding properties [10]. With these properties in mind, phthalimide has usually been employed in the design of potential anti-inflammatory [11], immunomodulatory [12- 14], antiangiogenic [15-17] and antitumour [18-21] drugs.

In this promising scenario, the strategy of molecular hybridization using phthalimide as a pharmacophoric fragment has figured prominently and led to many successful cases. [9]

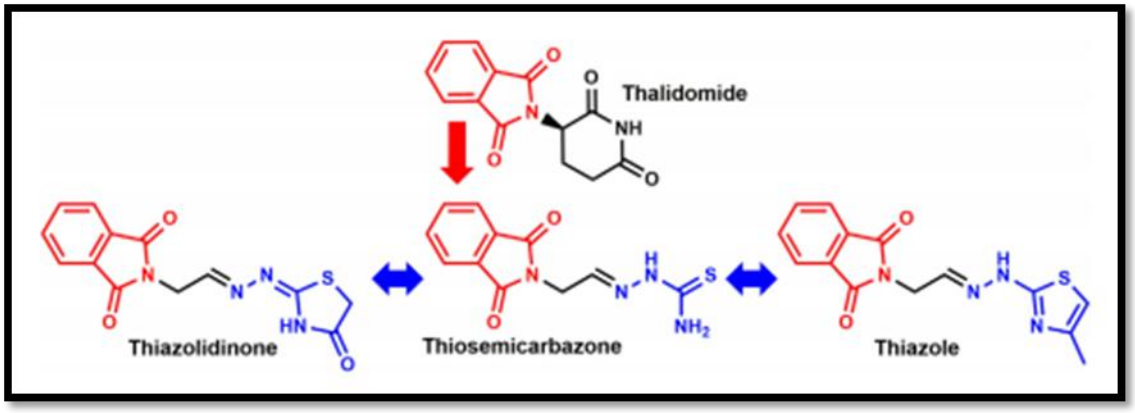


Figure No. 3: Bioisosteric relationship between thalidomide and the proposed thiosemicarbazones, thiazolidinones and thiazoles

On the other hand, thiosemicarbazones are compounds of considerable interest because of their important chemical properties and potentially beneficial biological activities [22-25].

4-N-substituted thiosemicarbazones show remarkable activity in comparison with their unsubstituted counterparts. An enhanced inhibitory effect may be attributed to the increased lipophilicity that allows the molecules to easily cross the cell membrane.[26]

The 4- N nitrogen of the thiosemicarbazone skeleton may contain:

a) Two hydrogen atoms (unsubstituted thiosemicarbazones);

b) One hydrogen atom and one alkyl or aryl group and

c) Two alkyl or aryl groups or may be a part of a cyclic ring.

The 2-N and 4-N nitrogen of the thiosemicarbazone skeleton were then substituted by alkyl groups to improve the lipophilicity. [26]

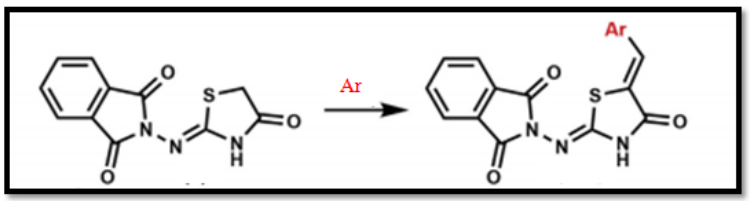


Figure No 4: Substitution of thiosemicarbazone skeleton with an alkyl group to improve lipophilicity

1.4 Synthesis:

Celgene Corporation originally synthesized thalidomide using a three-step sequence starting with L-glutamic acid treatment, but this has since been reformed by the use of L-glutamine.

N-carbethoxyphtalimide reacts with L-glutamine to yield N-phthaloyl-L-glutamine. Cyclization of N-phthaloyl-L-glutamine occurs using carbonyldiimidazole, which then yields thalidomide.

Celgene Corporation's original method resulted in a 31% yield of S-thalidomide, whereas the two-step synthesis yields 85–93% product that is 99% pure. [27]

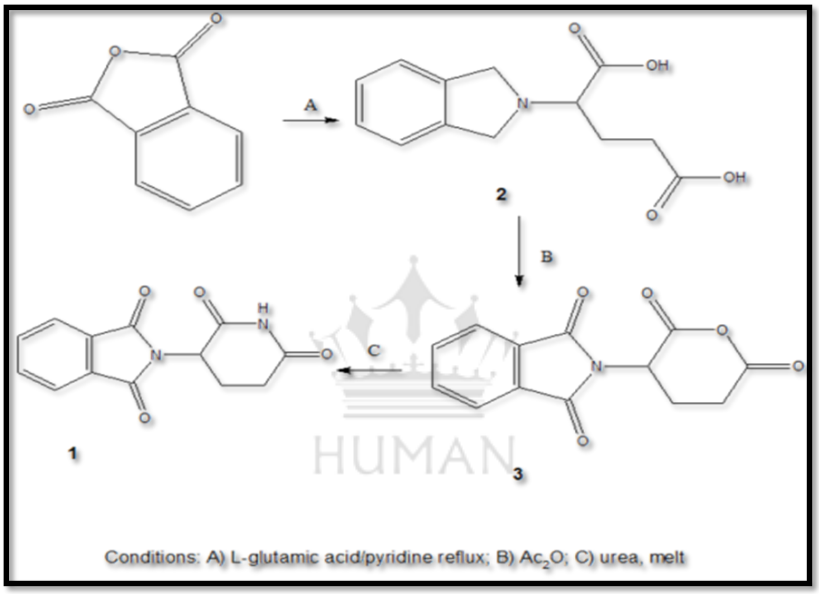
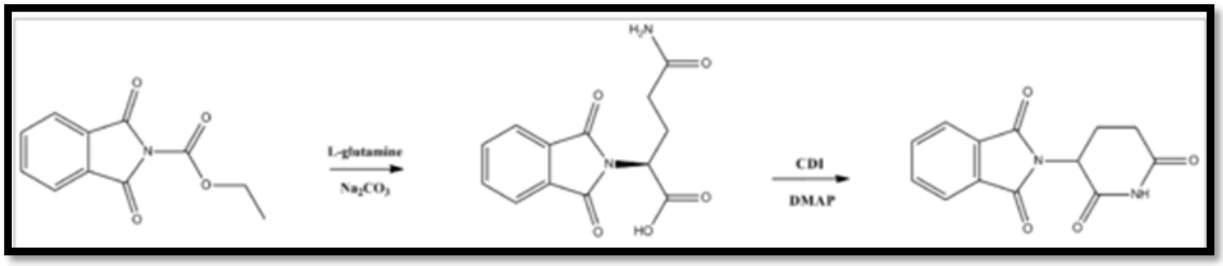


Figure No. 5: Three step synthesis (Older Method)



N-Carbethoxypthalimide N- phthaloyl-L-glutamine Thalidomide

Figure No. 6: Muller et al. Two-step Thalidomide Synthesis

2. TERATOGENICITY:

Teratogens are substances that may cause birth defects via a toxic effect on an embryo or foetus. [28]

Teratogenicity is a manifestation of developmental toxicity, representing a particular case of embryo/fetotoxicity, by the induction or the increase of the frequency of structural disorders in the progeny.[29]

2.1 History of Thalidomide and Related Teratogenicity:

Thalidomide was originally released in the *Federal Republic of Germany* (West Germany) under the label of *Contergan* on October 1, 1957, by *Chemie Grünenthal*. The drug was primarily prescribed as a sedative or hypnotic, but it was also used as an antiemetic (morning sickness in pregnant women), and sedative. The drug was banned in 1961 after its teratogenic properties were observed. The problems with thalidomide were, aside from the teratogenic side effects, both high incidence of other adverse reactions along with poor solubility in water and absorption from the intestines.[30] Adverse reactions include peripheral neuropathy in majority of patients, constipation, thromboembolism along with dermatological complications.[31]

Four years after thalidomide was withdrawn from the market for its ability to induce severe birth defects, its anti-inflammatory properties were discovered when patients suffering from erythema nodosum leprosum (ENL) used thalidomide as a sedative and it reduced both the clinical signs and symptoms of the disease. Thalidomide was discovered to inhibit tumour necrosis factor-alpha (TNF-α) in 1991. TNF-α is a cytokine produced by macrophages of the immune system, and also a mediator of inflammatory response. Thus the drug is effective against some inflammatory diseases such as ENL.

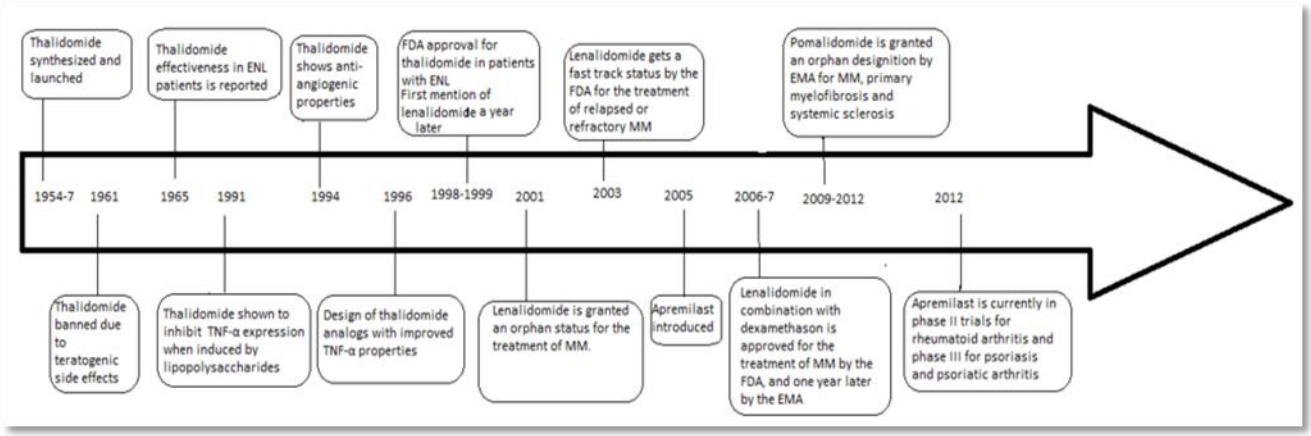


Figure No. 7: History of Thalidomide and its Analogs

In 1994 Thalidomide was found to have anti-angiogenic activity[32] and anti-tumor activity[33] which propelled the initiation of clinical trials for cancer including multiple myeloma. The discovery of the anti-inflammatory, anti-angiogenic and anti-tumor activities of thalidomide increased the interest of further research and synthesis of safer analogs.[34] [35]

2.2 Phocomelia:

In the late 1950s and early 1960s, more than 10,000 children in 46 countries were born with deformities, such as phocomelia, as a consequence of thalidomide use.[36]

Phocomelia is the most serious adverse effect of Thalidomide.

The word “phocomelia” means seal limbs and the term was first used by a French anatomist Etienne Geoffroy Saint-Hilaire for the flipper-like limbs [37]. Limbs and bone defects are the most striking component of Thalidomide Embryopathy. The condition involving malformations of arms and legs is known as phocomelia. Phocomelia is characterized by the severe shortening of the limbs where long bones are reduced or missing and distal elements or hand-plates remain with further anomalies. [38][39]

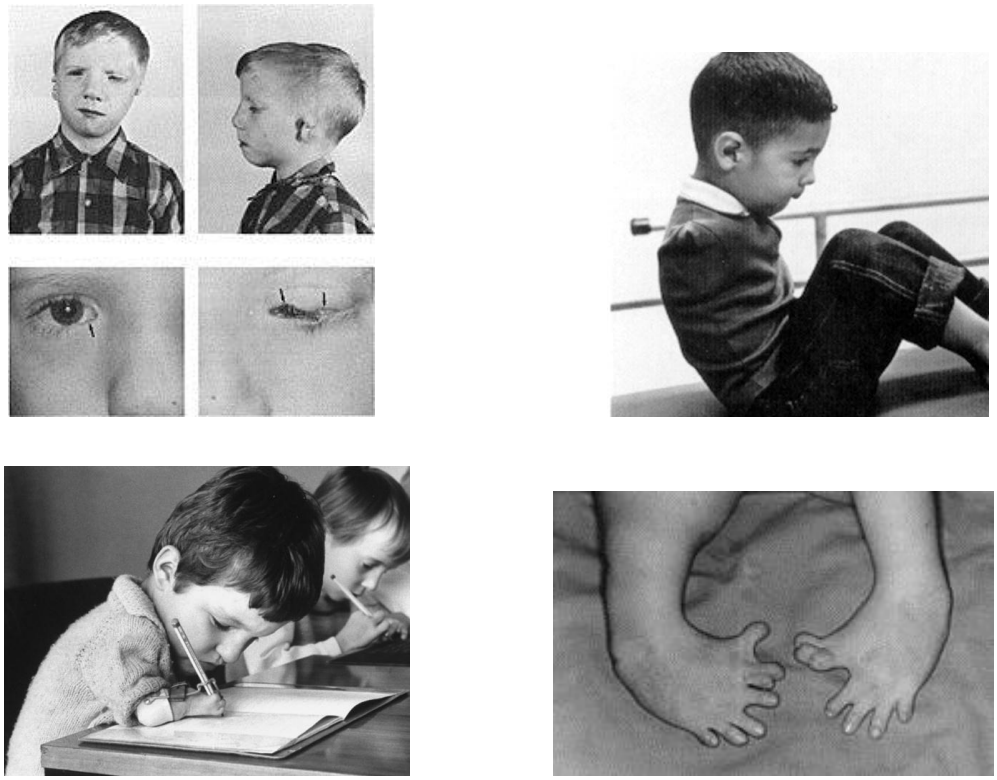


Figure No. 8: Children affected with Thalidomide

The severity and location of the deformities depended on how many days into the pregnancy the mother was before beginning treatment; thalidomide taken on the 20th day of pregnancy caused central brain damage, day 21 would damage the eyes, day 22 the ears and face, day 24 the arms, and leg damage would occur if taken up to day 28. Thalidomide did not damage the foetus if taken after 42 days of gestation.[40]

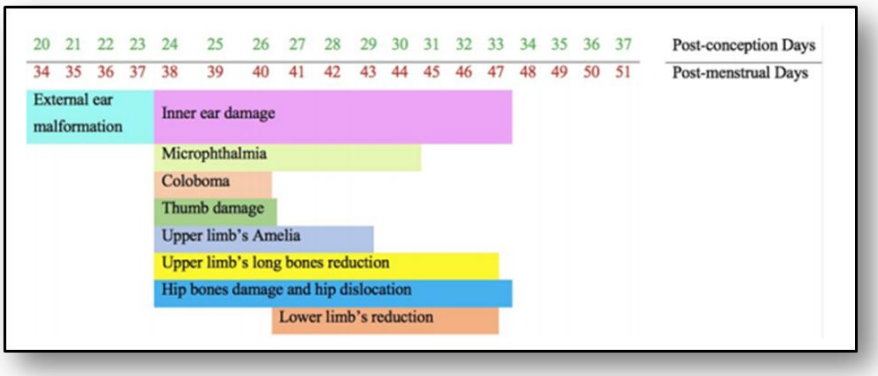


Figure No. 9: Thalidomide Embryopathy hallmarks indicated with a time- sensitive period

2.3 Mechanism of Action of Thalidomide resulting in Teratogenicity:

The proposed mechanisms of Thalidomide teratogenicity include:

- Apoptosis or cell death through Reactive Oxygen Species (ROS) [41]
- Inhibition of Nitrous Oxide (NO) in endothelial cells [42] and
- Degradation of SALL4 transcription factor by binding to the Cullin 4 (CUL4)-CRBN E3 ubiquitin ligase complex. [43]

SALL4 degradation via CRBN binding and species specificity:

This is the most recently proposed mechanism for Thalidomide induced teratogenicity which is explained as follows:

SALL4 (Spalt-like transcription factor 4) is a transcription factor essential for limb development and its heterozygous loss during human development results in phenocopies of TD-like features such as phocomelia, thumbs, ear, eye, and heart defects. Recently, Donoven et al. have shown that TD degrades SALL4 in humans, primates, and rabbits indicating a possible mechanism of action for TD. On the other hand, TD did not effect SALL4 in rodents or fish demonstrating the species-specific and possibly the mechanism of TD teratogenicity. [44]

CRBN is a protein encoded by the CRBN gene and plays an important role in embryo development as it forms a ligase complex with other proteins and targets developmentally important transcription factors [45]. TD makes a complex with CRBN which is the component of CUL4-CRBN complex.

TDCRBN-CUL4 complex degrades the SALL4 transcription factor in human cells and rabbits but not in resistant species as mice. [41, 42]

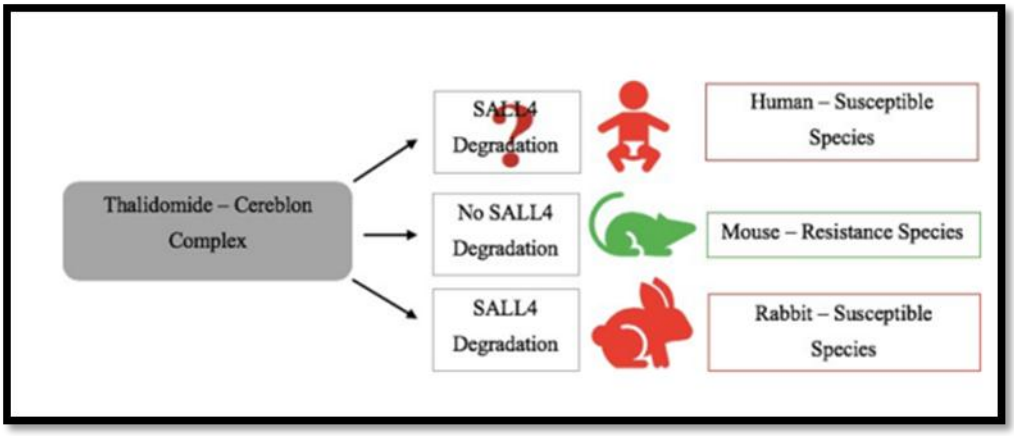


Figure No. 10: Mechanism of Species-Specific thalidomide teratogenicity

It is proposed that the sequence differences in SALL4 between susceptible species, human and rabbit and, resistant species i.e., the mouse is responsible for the degradation of SALL4 by TD-CRBN-CUL4 complex. [46]

The currently proposed mechanism of TD teratogenicity is supported by the striking resemblance between Thalidomide Embryopathy and the congenital syndromes, Duane Radial Ray and Holt-Oram, which result from the mutation of the SALL4 gene. [47]

The investigation into the species-specific differences dates back when Fratta et al. investigated the teratogenic effect of oral administration of TD on rabbits, rats, hamsters, and mice and found that the rabbits were the only species that showed the dose-dependent foetal anomalies in the tissues of mesodermal origin such as pes valgus, syndactyly and polydactyly. [48]

A new study published in the March 12 issue of *Science* has identified one primary target of thalidomide's teratogenicity (potential to cause fetal malformations) - a protein called cereblon. Using zebrafish and chick embryos, Takumi Ito and colleagues from the Tokyo Institute of Technology showed that thalidomide binds to cereblon, causing pectoral fin malformations in zebrafish and the complete absence of forelimbs in chicks. The researchers concluded that thalidomide exerts these effects by inhibiting cereblon function because genetically induced overproduction of cereblon prevented the malformations. Cereblon's normal function is unknown, but mutations in the gene encoding it are implicated in mild mental retardation. [49]

3. OTHER ADVERSE EFFECTS OF THALIDOMIDE:

There is a high risk that thalidomide can cause excessive **blood clots**. [50][51]

Thalidomide can also interfere with the formation of various kinds of new blood cells, creating a risk of **infection via neutropenia, leukopenia, and lymphopenia**.[50][51]

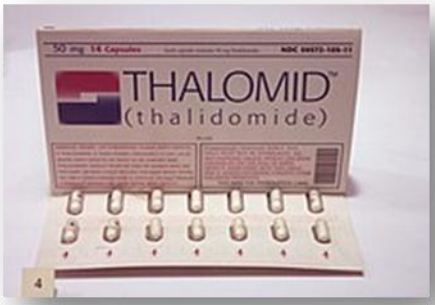


Figure No. 11: Marketed drugs of Thalidomide

There is also a risk of **anaemia** via lack of red blood cells. The drug can also damage nerves, causing **peripheral neuropathy** that may be irreversible.[50][51]

Thalidomide has several **cardiovascular adverse effects**, including the risk of heart attacks, pulmonary hypertension, and changes in heart rhythm including syncope, bradycardia, and atrioventricular block. [50][51]

It can cause **liver damage** and severe **skin reactions** like Stevens-Johnson Syndrome. [50][51]

It tends to make people sleepy, which create risk when driving and operating other machinery. [50][51]

As it kills cancer cells, it can cause **tumor lysis syndrome**. Thalidomide can prevent menstruation.[50][51]

Other than the above, **very common** (reported in more than 10% of people) adverse effects include tremor, dizziness, tingling, numbness, constipation, and peripheral edema. [50][51]

Common (reported by 1–10% of people) adverse effects include confusion, depressed mood, reduced coordination, heart failure, difficulty breathing, interstitial lung disease, lung

inflammation, vomiting, dry mouth, rashes, dry skin, fever, weakness, and a sense of unwellness. [50][51]

4. INTERACTIONS

There are no expected pharmacokinetic interactions between thalidomide and other medicines due to its neutral effects on P-glycoprotein and the cytochrome P450 family. It may interact with sedatives due to its sedative action and bradycardic agents, like beta-blockers, due to its bradycardia-inducing effects.[52]

The risk of peripheral neuropathy may be increased by concomitant treatment with other agents known to cause peripheral neuropathy.[52] The risk of venous thromboembolisms with thalidomide seems to be increased when patients are treated with oral contraceptives or other cytotoxic agents (including doxorubicin and melphalan) concurrently.[50][51][52]

Thalidomide may interfere with various contraceptives, and hence it is advised that women of reproductive age use at least two different means of contraception to ensure that no child will be conceived while they are taking thalidomide. [50][51][52]

5. NEWER THERAPEUTIC EFFECTS OF THALIDOMIDE:

[A REMARKABLE COMEBACK]

Early studies done in 1953 established the anxiolytic, hypnotic, antiemetic, and adjuvant analgesic properties of thalidomide [53,54]. Subsequently, thalidomide was found to be highly effective in suppressing erythema nodosum leprosum (cutaneous manifestation of leprosy). [55,56]

Based on its beneficial effects in the treatment of inflammatory dermatoses associated with this specific condition, the drug has been used for the treatment of other inflammatory, autoimmune, and/or dermatological disorders, such as rheumatoid arthritis, inflammatory bowel diseases, lupus erythematosus, pyoderma gangrenosum, tuberculosis, sarcoidosis, Behcet's disease, chronic GVHD, and Sjögren's syndrome. [57]

Recent studies have demonstrated consistent responses in graft-versus-host disease (GVHD) and cancer, including multiple myeloma, myelodysplasia, Kaposi's sarcoma, and several other solid tumors. It also possesses an anti-angiogenic activity. [58]

Thalidomide acts as an agent in palliative care.[59]

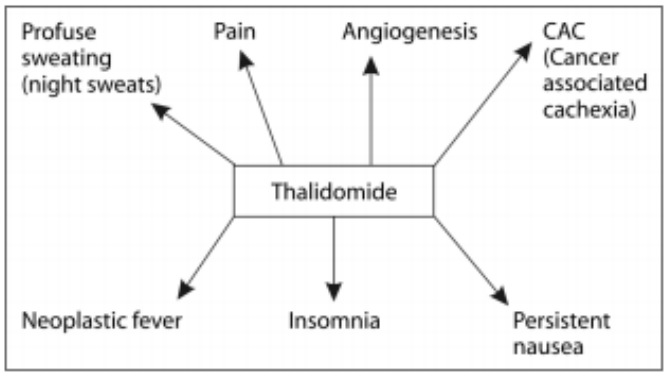


Figure No. 12: Thalidomide as an agent in Palliative care

The Anti-neoplastic, Anti-angiogenic activity and the role of Thalidomide in the treatment of Leprosy are explained in detail:

5.1 Anti- Neoplastic Activity:

Malignant tumours are angiogenesis dependent. Several experimental studies suggest that primary tumour growth, invasiveness, and metastasis require neovascularisation.[60] Experimental research suggests that modulation of angiogenic activity is associated with tumour regression in animals. Thalidomide has been shown to block the activity of angiogenic substances like bFGF (basic fibroblast growth factor), VEGF (vascular endothelial growth factor), and interleukin-6 apart from decreasing TNF-α. [61][62] It has shown anti-tumour activity, as a single agent; and phase II clinical trials are in progress for its use in AIDS-relateded Kaposi's sarcoma, glioma, multiple myeloma refractory to chemotherapy, and androgen independent carcinoma of the prostate. In contrast, poor response has been seen in breast and lung cancers. [61][62]

Mechanism of action:

The precise biologic mechanism whereby thalidomide exerts its antineoplastic effect remains to be determined. Perhaps its most interesting property is the ability to block the growth of blood vessels. Angiogenesis is a central property of tumors and a prognostic factor for survival in carcinomas of the breast [63][64], esophagus [65], lung [66], and prostate. [67]

The density of tumor vasculature also correlates with increased metastases, recurrences, and overall worse prognosis for carcinomas of the bladder [68,69], colon [70], stomach [71], and melanoma. [72]

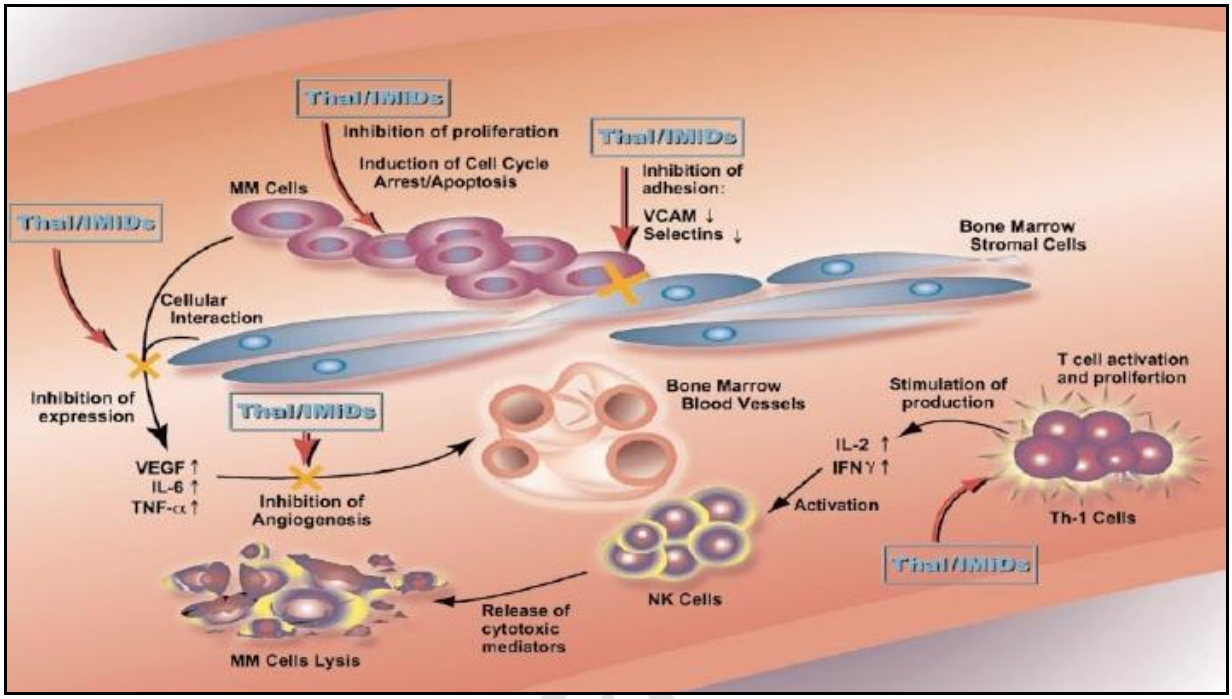


Figure No. 13: Mechanism of action of Antineoplastic activity of Thalidomide

One experiment in which the drug was incubated with microsomes suggested that the anti-angiogenic effect of thalidomide might be a result of its metabolic activation by cytochrome P450. [73] Since most malignant tumors depend on angiogenesis to proliferate and metastasize, this could be the major mechanism of its beneficial action in patients with myeloma and solid tumors. [74]

The effects of thalidomide on myeloma may result from the inhibition of cytokine pathways that control myeloma cell growth and viability. IL-6 is secreted by bone marrow stroma and macrophages, as well as by some myeloma cells. It supports myeloma growth in vitro and facilitates CD-44 mediated contact through beta-integrins and fibronectins to bone marrow stroma. Attachment to stroma by myeloma cells stimulates the production of VEGF and bFGF, both potent angiogenic factors, as well as many other cytokines (TNF-, IL-1, and IL-10), which further promote the proliferation of myeloma cells. Thalidomide blocks IL-6 secretion by myeloma cells, thus interrupting the cascade of cytokine secretion and proliferation. [74]

5.2 Anti-Angiogenic Activity:

It has been suggested that the teratogenic effects of thalidomide on foetal limbs may be due to inhibition of angiogenesis in foetal limb bud. Thalidomide inhibited basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) induced angiogenesis in rabbit corneal tissue. However, a similar effect was not observed in solid tumours in mice, suggesting that the anti-angiogenic effect of thalidomide is 'species-specific'. [75]

The mechanism of thalidomide's anti-angiogenic effect is unknown. It has been suggested that inhibition of cytokine synthesis (especially that of TNFα) may contribute to thalidomide's anti-angiogenic effect. However, some evidences suggest a direct inhibitory effect on some component of angiogenesis by thalidomide. [75]

Mechanism of action:

It suppresses TNF- and interferon (IFN-) secretion, both of which upregulate endothelial cell integrin expression, a process crucial for a new vessel formation.[76]

It inhibits the secretion of basic fibroblast growth factor (bFGF), an angiogenic factor secreted by human tumors. [77][78][79] Whether any or all of these effects account for its antitumor activity is unknown.

5.3 Treatment of Leprosy:

Leprosy is a chronic skin disease caused by a gram positive acid-fast bacillus Mycobacterium leprae. Clinically, leprosy has two main presentations, tuberculoid and lepromatous. Tuberculoid leprosy is presented with skin erythroid plaques and sensory or motor nerve dysfunction while lepromatous leprosy is characterized by macrophage skin glomerulata containing bacilli, sensory nerve damage and hands and feet deformities. [80]

Clinical trials have demonstrated that TD is effective in the treatment of ENL. ENL is the Type-2 leprosy immune reaction and the systemic disorder associated with fever, malaise, anorexia, leukocytosis, and anemia along with erythematous painful nodules in the skin and subcutaneous tissue anywhere in the body [81]. Thalidomide has been approved by the Food and Drug Administration (FDA), USA, in 1998 for the treatment of ENL. The World Health Organisation has also recommended thalidomide for use in ENL. [82]

Various studies have shown a 92% response rate with thalidomide. Most patients feel the benefit within 24-48 hrs., starting at a dose of 25-200 mg/ d. Its antipyretic effect and steroid sparing effect (61 to 100%) is an added advantage for its use in ENL. The effectiveness of thalidomide is due to its inhibition of TNF-α.[82]

Mechanism of action:

TD's Beneficial action in treating ENL comes from its Anti-inflammatory action by selective degradation of mRNA of Tumor Necrosis Factor-alpha (TNF-α) produced by the monocytes. [83] Physiologically, TNF-α controls the inflammatory response by regulating the interleukins therefore, ENL responds very quickly and effectively to TD. [84]

Clinically, TD decreases TNF-α levels in ENL patients while reducing the ENL toxic and systemic symptoms including fever, arthralgia, and the painful subcutaneous nodules.[83]

5.4 Immune Modulation:

Thalidomide has a broad range of inhibitory and stimulatory effects on the immune system. It inhibits the migration of both immune and phagocytic cells in experimental systems. For example, it blocks leukocyte chemotaxis and phagocytosis, an effect associated with decreasing integrin beta-chain production. [76][85][86][87]

It reduces tumor-associated macrophage infiltration possibly through suppressing the expression of endothelial cell adhesion molecules.[88] In experimental animals, it promotes the switch to a TH-2 immune response, enhances the production of interleukins (IL) 4 and 5, and decreases helper T-cell production. [89][90]

Mechanism of action:

In humans, thalidomide treatment is associated with multiple changes in cytokine levels and cellular cytokine secretion. It stimulates IL-2 and IL-12 production in HIV-infected patients, [89][90] suppresses IFN- production in macrophages [91] but stimulates IFN- production in lipopolisacharide stimulated polymorphonuclear cells in healthy individuals [92] and blocks TNF- production in patients with erythema nodosum leprosum.[93] Also, two indirect anti-tumor effects of thalidomide have been recognized: inhibition of secretion of IL-6, a cytokine secreted by the bone marrow stroma essential for survival and proliferation of myeloma cells, and stimulation of secretion of IL-12, a potent inhibitor of angiogenesis and stimulator of

IFN- synthesis. The broad nature of its action raises the possibility that at least part of its anti-tumor effects could be dependent on these or other as yet unrecognized effects on cytokines or specific immune cell subpopulations. [94]

5.5 Activity of Thalidomide against Myelodysplasia:

There is evidence for the involvement of cytokines in the development of myelodysplastic syndrome. [95-97] Some of the immunomodulatory properties of thalidomide can be attributed to the inhibition of monocyte/macrophage cytokine secretion, which provides the rationale for its use in cytokine-driven disease. Data from clinical trials using thalidomide in myelodysplastic syndrome are limited, but positive outcomes have been noticed among certain populations of these patients.[98-100]

Patients with refractory anemia or refractory anemia with ringed sideroblasts in the early phase of disease demonstrated a better response than those with more advanced disease. Responses included the correction of anemia and/or increased platelet and neutrophil counts. [101]

Patients with low cytokine and apoptosis levels seemed to have benefited from the treatment with thalidomide. [74]

5.6 Activity of Thalidomide against Graft-Versus-Host Disease:

Because of its immunosuppressive properties thalidomide has been studied in bone marrow allotransplant patients for the suppression of chronic GVHD (Graft-Versus-Host Disease) unresponsive to other therapies. There have been 150 patients reported, and the dose of thalidomide ranged from 100 mg to 600 mg. A complete response was obtained in 32% and a partial response in 27% of patients. Most studies included patients who previously failed treatment with cyclosporine, azathioprine, and/or corticosteroids. [102-105]

5.7 Activity of Thalidomide against Kaposi's Sarcoma:

Preliminary laboratory studies have suggested that thalidomide may have a potential in the treatment of AIDS patients.[106,107] It significantly reduced human immunodeficiency virus (HIV-1) replication both in mononuclear cells from the human peripheral blood and in laboratory cell lines,[106] and it inhibited the proliferation of endothelial cells in vitro. [107]

Since Kaposi's sarcoma is a tumor derived from endothelial cells, several phase I or phase I/II trials have been performed in patients with AIDS–related Kaposi's sarcoma. Altogether 62 patients have been treated and their median age was 39 years. The dose of thalidomide ranged from 100-1000 mg/day, given mostly before sleep. There were 34% partial responses, and the disease was stable in an additional 38% of patients.[108-111]

6. ANALOGS / DERIVATIVES OF THALIDOMIDE:

The development of analogs of thalidomide was precipitated by the discovery of the anti-angiogenic and anti-inflammatory properties of the drug yielding a new way of fighting cancer as well as some inflammatory diseases after it had been banned in 1961. The problems with thalidomide included; teratogenic side effects, high incidence of other adverse reactions, poor solubility in water and poor absorption from the intestines.

In 1998 thalidomide was approved by the U.S. Food and Drug Administration (FDA) for use in newly diagnosed multiple myeloma (MM) under strict regulations.[112]

This has led to the development of a number of analogs with fewer side effects and increased potency which include lenalidomide, pomalidomide and apremilast, all of which are currently marketed and manufactured by Celgene. [112]

6.1 Development of Lenalidomide and Pomalidomide:

One of the analogs of interest was made by isoindolinone replacement of the phthaloyl ring. It was given the name EM-12. This replacement was thought to increase the bioavailability of the substance because of increased stability. The molecule had been reported to be an even more potent teratogenic agent than thalidomide in rats, rabbits, and monkeys. Additionally, these analogs are more potent inhibitors of angiogenesis than thalidomide.[113]

As well, the amino-thalidomide and amino-EM-12 were potent inhibitors of TNF-α.[114] These two analogs later got the name lenalidomide, which is the EM-12 amino analog, and pomalidomide, the thalidomide amino analog.[115]

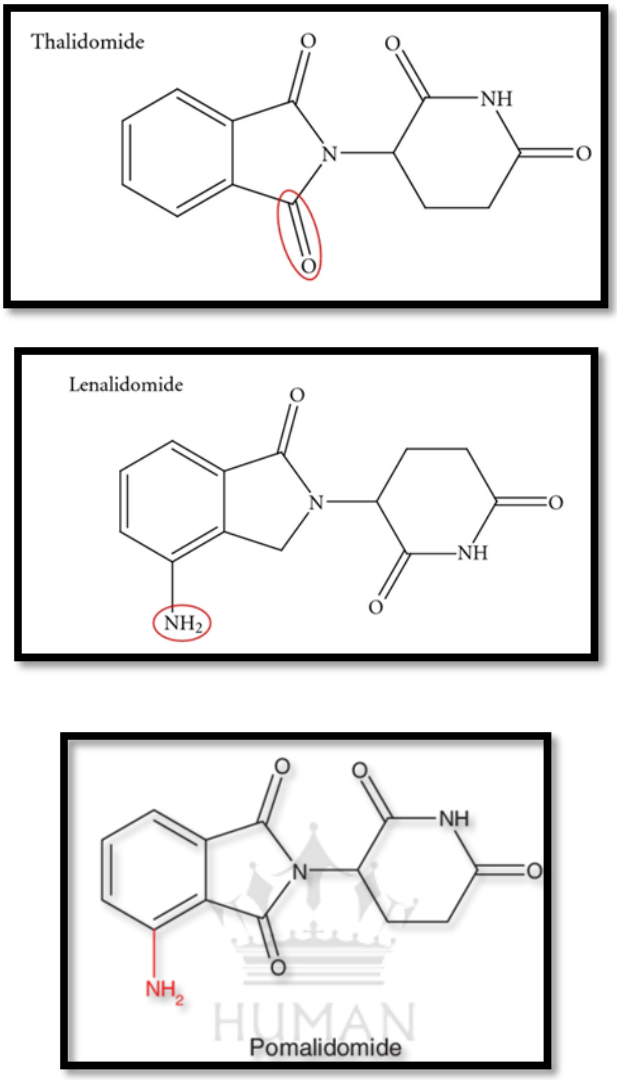


Figure No. 14: Analogs of Thalidomide

Uses of Lenalidomide:

Lenalidomide is approved in nearly 70 countries, in combination with dexamethasone for the treatment of patients with MM who have received at least one prior therapy. Orphan indications include diffuse large B-cell lymphoma, chronic lymphocytic leukemia and mantle cell lymphoma. Lenalidomide is also approved for transfusion-dependent anemia due to low or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities in the U.S., Canada, Switzerland, Australia, New Zealand, Malaysia, Israel, and several Latin American countries, while marketing authorization application is currently being evaluated in several other countries. [116]

Uses of Pomalidomide:

European Medicine Agency has already granted pomalidomide an orphan designation for primary myelofibrosis, MM, systemic sclerosis, post-polycythemia, and post-essential thrombocythaemia myelofibrosis.[117]

6.2 Development of Apremilast:

After finding a novel set of analogs of thalidomide, namely 3-(1,3-dioxo-1,3 dihydroisoindol-2-yl)-3-(3,4-dimethoxyphenyl) propionic acid, which had PDE4 inhibition activity the work began to optimize the activity. For that purpose the researchers used a known structure moiety, 3,4-dialkoxyphenyl, that is a recognized pharmacophore in PDE4 inhibitors such as rolipram shown in figure and roflumilast and added it onto the structure of the previously mentioned analog series.

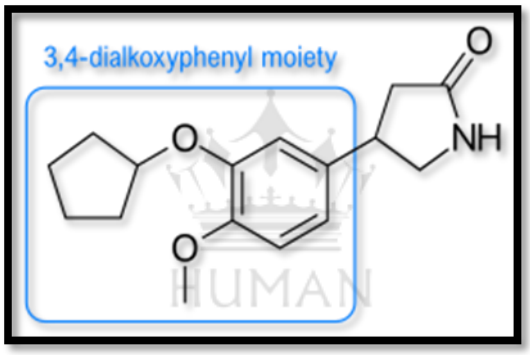


Figure No. 15: Rolipram

After tweaking the structure and testing different substitutions at the 4-position of the phthaloyl ring and the carboxyl acid the researchers finally landed at a molecule that potently inhibits PDE4 and TNF-α, which they later named **apremilast**. The S-enantiomer of apremilast was chosen since it was the more active enantiomer.[118] Since the structure of apremilast lacks the acidic chiral hydrogen it should not racemize in vivo, unlike thalidomide, lenalidomide, and pomalidomide.[119][120]

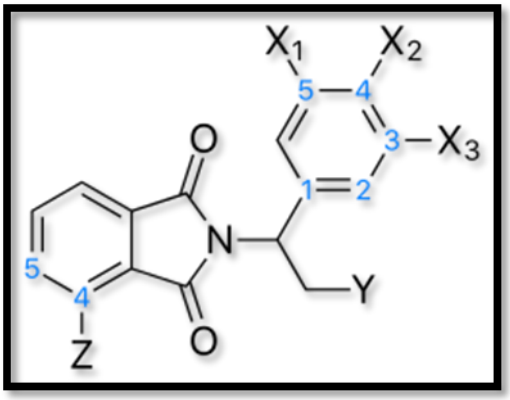


Figure No. 16: Common structure

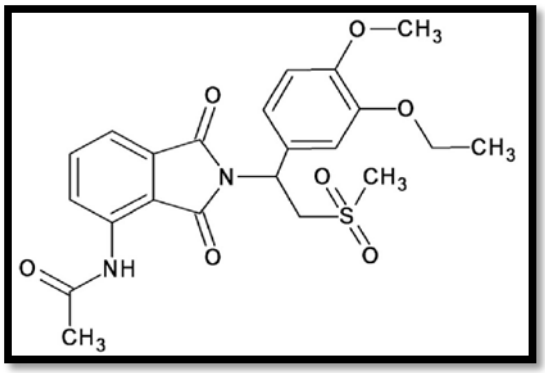


Figure No.17: Apremilast

PDE4 – Inhibiting Thalidomide Analogs

Uses of Apremilast:

As of September 2012 apremilast is in phase III trials for psoriasis and phase II trials for rheumatoid arthritis. [121]

In March 2014 apremilast has been approved for psoriatic arthritis. In September 2014, the U.S. FDA approved apremilast for the treatment of moderate-to-severe plaque psoriasis.[122]

7. THE SYSTEM FOR THALIDOMIDE EDUCATION AND PRESCRIBING SAFETY (S.T.E.P.S):

Despite its harmful side effects, thalidomide is FDA-approved for two uses today—the treatment of inflammation associated with Hansen's disease (leprosy) and as a chemotherapeutic agent for patients with multiple myeloma, purposes for which it was originally prescribed off-label. [123]

Because of its known adverse effects on fetal development, the dispensing of thalidomide is regulated by the **System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program**. [123]

The S.T.E.P.S. program, designed by Celgene pharmaceuticals and carried out in pharmacies where thalidomide prescriptions are filled, educates all patients who receive thalidomide about potential risks associated with the drug. [123]

To prevent the serious side associated with Thalidomide, the S.T.E.P.S program tightly regulates its distribution. The examples listed below are just a sampling of the measures in place: [123]

- Product labelling that indicates the risk of thalidomide.
- Required registration of all prescribers, patients, and pharmacists who prescribe, receive or dispense thalidomide.
- A patient acknowledgement/ Informed consent form.
- A required telephonic survey that patients and prescriber must complete.
- Required pregnancy testing in females of childbearing potential.
- Compliance with measures to prevent pregnancy and thereby prevent fetal exposure to thalidomide.
- Educational materials providing the patients information regarding the potential benefits and side effects of Thalidomide.
- Patient counselling.
- Limiting prescription to a 28 day supply.
- Prohibition of telephone prescriptions and automatic refills.

CONCLUSION

This study focusses on Thalidomide, a drug first introduced into the market in Germany under the brand name of Contergan in 1956, as a “non-barbiturate hypnotic”, which was banned due to its teratogenic effects when taken by pregnant women to treat morning sickness but was reintroduced into the market as it made its way by the development of more active and less toxic analogs i.e., Lenalidomide, pomalidomide, and Apremilast.

The remarkable comeback of Thalidomide is due to its newer applications ranging from its use in the treatment of leprosy, other inflammatory, autoimmune, and/or dermatological disorders, such as rheumatoid arthritis, inflammatory bowel diseases, lupus erythematosus, tuberculosis, also due to its anti-angiogenic property and antineoplastic activity, etc.

Since the research is not yet completed regarding the adverse effects of these thalidomide derivatives, the use of Thalidomide must be restricted in Pregnant women. In order to prevent the teratogenic effects of Thalidomide a system called **System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program** was developed by Celgene Pharmaceuticals which must be practiced in all the pharmacies during the distribution/ dispensing of this drug.

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