New Medical Indications for Thalidomide and its Derivatives

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Abstract

Thalidomide is an anti-inflammatory and an anti-angiogenesis drug that is being used around the world for a variety of malignant and inflammatory diseases. Is it justified to continue prescribing and developing thalidomide given the discovery of many well-known side effects including catastrophic birth defects? To answer this question, this paper will discuss the pharmacology and history of thalidomide, as well as many of its proposed mechanisms of action. The medical indications for the current use of thalidomide as well as for several newer and more potent derivatives are mentioned for their therapeutic results, as well as their adverse side effects.

Introduction to Thalidomide

"Thalidomide remains, arguably, the greatest disaster in medical history" (Greener, 2011). Thalidomide was introduced in 1957 by a German pharmaceutical company as a sedative and hypnotic drug. It was also widely used in several countries to alleviate morning sickness in early pregnancy. It was sold in more than forty-six countries without any testing for teratogenicity, as was common practice for new drugs at that time. More than 10,000 children around the world developed severe birth defects, especially shortening or absence of limbs. There was also an increase in miscarriages and infant mortality. Remarkably, the United States Food and Drug Administration did not approve sale of thalidomide despite five requests from manufacturers. As a result, only seventeen babies were affected in the United States, probably from thalidomide purchased in Canada (Huang, et. al. 2008).

By 1961 production and distribution of thalidomide were banned worldwide. Due to the risk of teratogenicity, almost no research into the use of thalidomide took place for the next decade. The first new indication for thalidomide was in treating a complication of leprosy known as erythema nodosum leprosum (ENL) (Sharma, et. al. 2007). Beginning in 1967, anecdotal reports of the use of thalidomide in cancer treatment began to be published. Some of the diseases treated were astrocytoma, multiple-myeloma, chronic lymphocytic leukemia, and malignant melanoma. New research is being done to investigate the mechanism of action of this class of immunomodulatory drugs in various malignancies and in non-malignant conditions such as Alzheimer's Disease and persistent erythema multiforme (He, et. al. 2013).

Methods

Articles and studies researched in this paper were obtained through the EBSCO and ProQuest databases with access provided by the Touro College Library. Additional research articles were obtained through the National Center for Biotechnology Information (NCBI) website and the Jackson Laboratory website. Images and diagrams that are used throughout the paper were obtained from the research articles cited.

Chemical Analysis

Thalidomide is a racemic glutamic acid analogue also known as [+] alpha-[N-phthalidimo]-glutarimide. It consists of two linked rings: a glutamic ring and a phthalic ring. Because it contains a chiral carbon the molecule is unstable and can switch back and forth between two enantiomers which are mirror images of each other. This reaction takes place rapidly in water or body fluids. While only one state, the S-enantiomer is thought to be teratogenic, the safer state, the R-enantiomer, is not stable and cannot be preserved in the body. (Bartlett, et. al. 2004)

Thalidomide has traditionally been synthesized by a multistep process which uses expensive ingredients and produces a very low yield. A recent research study by chemists at Stockton University in New Jersey reports on a new rapid synthesis of thalidomide and its analogs using easily obtained reagents which rapidly interact with the assistance of a microwave. It produces relatively high yields. The reaction of the corresponding anhydrides using DMAP (4-N, N- dimethylaminopyridine) as a base catalyst takes place in ten minutes at 150 degrees Celsius. The chemists developing this new method of production describe their innovation as a, "novel green one-pot synthetic technique." (Benjamin, et. al. 2017)

Pharmacology

Thalidomide has an active half-life of 8 to 12 hours. It is broken down by hydrolysis in tissue fluids and metabolized by the liver using the cytochrome p450 system. Although it is absorbed slowly, it has a high oral bioavailability. The plasma concentration peaks after at least two hours. Little drug is bound to protein in the plasma. The average elimination half-life of both enantiomers is five hours. (Vargesson, et. al. 2015)

According the British Columbia Cancer Drug Manual accessed online, high fat meals increase the time to peak concentration. Thalidomide is distributed mostly in the internal organs such as the gastro-intestinal tract, liver and kidneys. It is found to cross the blood brain barrier and is also found in the ejaculate.

In 2004, a new derivative of thalidomide was introduced for treatment of multiple myeloma. Lenalidomide, under the trade name Revlimid is considerably more potent than thalidomide. It has an added amino group at position 4 of the phthaloyl ring and removal of a carbonyl group from the phthaloyl ring. Pomalidomide (3-aminothalidomide) was the second thalidomide analog to be used in treating multiple myeloma. It is even more potent than the analogs before it. A third thalidomide analog, Apremilast is now showing effectiveness as an oral treatment for psoriasis and psoriatic arthritis. (Bartlett, et. al. 2004)

Mechanism of Action: Innate immunity: Effects on Epidermal Regeneration, Soluble Mediators, and Natural Killer Cells

Studies of epidermal regeneration have shown that thalidomide increases human keratinocytes migration and propagation. Testing was done with a motility assay and thymidine incorporation assays to better understand how thalidomide promotes this proliferation. In addition, the chemokine IL-8 that promotes migration of neutrophils and keratinocytes significantly increases with thalidomide treatment. Because of this, researchers have theorized that the mechanism with which thalidomide aids in wound healing is by promoting keratinocyte production and movement. This may be useful in explaining its ability to treat ulcerative diseases, such as Behcet's (a rare disorder causing inflammation in blood vessels with symptoms that include mouth and genital sores, inflamed eyes, and rashes) and aphthous stomatitis (shallow sores inside the mouth or at the base of the gums that make it hard to eat or talk) (Paravar & Lee, 2008).

The exact mechanism of thalidomide's anti-inflammatory action via soluble immune mediators is still being investigated. However, researchers have linked thalidomide's anti-inflammatory action to its ability to speed up the degradation of messenger RNA in blood cells. These effects have been analyzed in both human monocytes and mouse macrophages (Paravar, Lee, 2008).

By reducing the half-life of the messenger RNA coding for TNF-alpha, (Tumor Necrosis Factor) it in turn reduces the blood serum level of TNF-alpha. TNF-alpha is a cell signaling protein (cytokine) involved in systemic inflammation. By reducing TNF-alpha, thalidomide is an effective treatment for inflammatory diseases such as erythema nodosum leprosum (ENL) and lupus erythematosus (LE). Many studies have been performed that confirm this reduction of TNF-alpha. For example, 48-68% of patients with ENL have a reduction of TNF-alpha in the serum from their pretreatment levels. Tuberculosis patients also show reduced levels in in-vitro and in-vivo studies and patients gained a significant amount of weight while on the medication. HIV-1 patients also had reduced TNF-alpha levels while under treatment with thalidomide. A further confirmation comes from studies using rodent models of pancreatitis in which thalidomide was seen to have similar effects (He, et. al. 2013).

Another proposed mechanism of action involves thalidomide's effects on Natural Killer (NK) cells which are vital in destroying tumor cells, intracellular pathogens, and cells infected by viruses. Using in-vitro studies, thalidomide has been observed to enhance NK-cell-mediated lysis of cancerous cells. This was demonstrated in a study that co-cultured NK cells with the same patient's cancerous cells. Additionally, thalidomide increases the secretion of NK cell activators such as IL-12 and specifically induces NK cell antitumor responses. In an in vivo study, the number of NK cells in a multiple myeloma patient were increased with thalidomide therapy. The results of these studies indicate that thalidomide's ability to enhance NK-cells is the mechanism by which it aids in the treatment of multiple myeloma (Paravar, Lee, 2008).

Adaptive immunity: B Cell Antibody Suppression, T Cell Stimulation

Thalidomide suppresses B cell antibody formation in studies primarily using New Zealand Black (NZB) and Murphy Roths Large (MRL) mice. These strains were chosen because they have a genetic predisposition to autoimmune disorders (The Jackson Laboratory Website, updated 2018). Thalidomide inhibits the usually increased production of splenic IgM in NZB mice and splenic and lymph node IgG1 in MRL mice. In clinical studies, leprosy patients receiving thalidomide and dapsone treatment had lower serum IgM levels than patients receiving dapsone alone. The combination of these studies suggests that thalidomide's action may be based on its downregulatory effects on antibody production (Paravar & Lee, 2008).

Thalidomide was shown to be able to co-stimulate T cells once they were already partially activated by the T cell receptor. Co-stimulation is an important mechanism for immune defense. A second signal is sent to naïve T cells which facilitates their initiation and further generation of an antigen-specific effector response. The co-stimulatory effect of thalidomide can be used as an immunological adjuvant, that is, it can enhance the response to tumor antigens in cancer patients (Bartlett, et. al. 2004).

Reduction of Tumorigenesis: Apoptosis and Restriction of Tumor Growth, and Antiangiogenic Activity

Tumors grow and expand due to their ability to evade apoptosis. In studies, thalidomide has induced apoptosis (G1 growth arrest) in human cancerous cells. It has also been shown to decrease the expression of the apoptosis-suppressing protein Bcl-2 in blood and bone marrow of patients with multiple myeloma. Another mechanism proposed is thalidomide's ability to induce monocyte apoptosis by involving the cytochrome c-dependent pathway. (Cytochrome c is known for its role in the mitochondria as a key contributor in ATP synthesis. In our case, we are more interested in thalidomide's stimulation of cytochrome c's other effect which is triggered when a cell receives an apoptotic stimulus. The cytochrome c is then released into the cytosol and triggers programmed cell death through apoptosis) (Paravar & Lee, 2008).

In 1971, Dr. Judah Folkman of Harvard Medical School formulated his hypothesis that tumor growth depends on angiogenesis, the formation of new blood cells in the malignant tissue. Thalidomide, as mentioned above, inhibits limb bud formation in the embryo. This led to the idea that the teratogenic and antiangiogenic actions may be related.

Dr. Folkman made the groundbreaking discovery that tumor

growth and angiogenesis were related when he was working on testing the efficacy of hemoglobin solutions as a substitute for blood transfusions. As a part of this study he injected isolated organs with mouse melanoma cells. He found that the tumors could not grow and spread in the isolated perfused organs, but when they transplanted these same tumor cells into mice, they were quickly vascularized and grew larger. After conducting more research trials to prove his hypothesis, Dr. Folkman published an article in the New England Journal of Medicine that stated that tumor growth depends on angiogenesis and that inhibiting angiogenesis can be used to treat certain cancers. From 1980 to 2005 Dr. Folkman's lab worked on testing twelve angiogenic inhibitors including interferon alpha, fumagillin, endostatin and, notably, thalidomide (Ribatti, 2008).

Angiogenesis, the development of new blood vessels, is vital to the growth and spreading of cancerous tumors. The cancer degrades basement membranes and extracellular matrix and brings endothelial cells towards an angiogenic stimulus. It also involves pericytes and smooth muscles cells as well. Various growth factors are also needed to form new blood vessels from preexisting micro vessels. These growth factors include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) (Fialho, et. al. 2013).

One proposed mechanism for thalidomide's antiangiogenic effect is its ability to inhibit VEGF and bFGF production, which thereby inhibits vessel growth. Studies using human endothelial cells showed that thalidomide inhibits VEFG secretion and cell migration and lowers the total number of capillaries. In studies using chicken embryonic chorioallantoic membrane (CAM) thalidomide inhibited VEGF and bFGF induced vessel growth. In one trial done by the Department of Cellular and Molecular Biology and Pathogenic Agents of the University of Sao Paulo, twelve CAMs from chicken eggs were incubated with thalidomide implants and analyzed after two days to review the percentage of vessel deterioration. The results showed significant regression of vessels in CAM that had thalidomide or thalidomide-loaded implants as compared to the negative control (NC) group and an implant not containing any drug (Fialho, et. al. 2013).

Another study proposed that thalidomide inhibits endothelial cell proliferation by inhibiting the binding of the SP-1 transcription factor, which has many binding sites on the VEGF promoter. This protein usually binds to the VEGF promoter to initiate and activate the transcription of the gene directly. When its binding is inhibited, it causes less VEGF to be produced and therefore limits the cells' growth (Yabu, et. al. 2005).

A third mechanism of action being researched is thalidomide's ability to suppress the VEGF gene by downregulating the VEGF receptors Flk-1 and neuropilin-1. By reducing the productivity of the VEGF receptors, thalidomide lessens the effects of the vascular endothelial growth factor in general. This causes less signals for angiogenesis to be sent, so the body forms less vasculature. With a smaller supply of blood, the growing limbs do not receive enough oxygen and nutrients, and they subsequently do not grow properly and result in under developed or malformed limbs (Yabu, et. al. 2005).

A study done using zebrafish embryos and Human Umbilical Vein Cells (HUVEC) showed promising results in this area. The thalidomide treated embryo was shorter in length than the control. In addition, the lumens of the dorsal artery and posterior cardinal vein were clearly seen (with hematoxylin and eosin staining) in the control but were so reduced in the embryo treated with thalidomide that they were barely visible (Yabu, et. al. 2005).

Teratogenesis

Over the past fifty years, many separate models for thalidomide embryopathy have been proposed, however a full understanding of its mechanism of action is still incomplete. The proposed theories are not necessarily mutually exclusive. And it is possible that multiple mechanisms of action are each involved to some extent. Additional theories include nerve toxicity, inhibition of cell adhesion molecules and effects on chondrogenesis.

One breakthrough discovery revealed that Cereblon (CRBN), a protein encoded by the CRBN gene, may be the primary target for binding by thalidomide. The authors found that thalidomide binds directly to CRBN, a substrate receptor for the CUL4A-DDB1 E3 ubiquitin ligase, a protein that employs an E2 ubiquitin-conjugating enzyme that carries ubiquitin, recognizes a protein substrate, and assists the transfer of ubiquitin from the E2 to the protein substrate. The ubiquitin is used to tag specific proteins to be broken down by proteasomes. This binding inhibits the activity of the assembled E3 ubiquitin ligase complex so that it does not tag the specific proteins, and an unknown substrate is allowed to accumulate. This in turn effects the expression of the fibroblast growth factor eight (FGF8) and causes growth defects. Thus, the action of the E3 ubiquitin ligase complex is necessary for limb outgrowth (particularly in zebrafish) and by disrupting this complex, thalidomide induces teratogenic effects. Consequently, they demonstrated that the deformities caused by thalidomide were directly mediated through stopping its inhibition of CRBN. In zebrafish and chickens, when they used an overexpression of a CRBN mutant that does not bind thalidomide, they did not notice the defects usually caused by this drug, proving that it is the binding of the drug to CRBN that is responsible for the embryopathy effect (Ito. et. al. 2010).

Following this discovery, CRBN was also shown to be crucial for the mechanism of action of thalidomide's anti-myeloma properties, as well as other immune-modulatory drugs (IMiDs). One of the downstream targets of CRBN was shown to be interferon regulatory factor 4 (IRF4). This protein which regulates the transcription of interferons is essential for myeloma cell survival and is downregulated by IMiD therapy (Zhu, et. al. 2013).

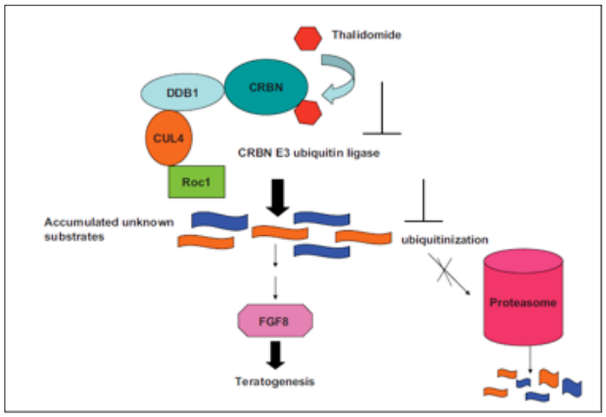

Figure 1. Depiction of the downstream targets of thalidomide that may lead to its teratogenic properties (Zhu, et. al. 2013).

A recent series of experiments supported in part by the National Cancer Institute further confirmed the hypothesis that antiangiogenesis and teratogenesis are related. The researches tested a variety of angiogenesis inhibitors, including thalidomide and its analog CPS49, using zebrafish and chicken embryo models. They focused on assessing the developmental defects and teratogenic effects that the drugs caused. They concluded that different classes of angiogenesis inhibitors, regardless of the molecular target or specific mechanism of action, are teratogenic to chicken embryos. This study also proved that using chicken embryos and zebrafish embryos is a valid way to screen new drugs for teratogenic effects before they are used in clinical trials on women of childbearing age (Beedie, et. al. 2016).

New Research in Treatments Using Thalidomide and Its Derivatives: Multiple Myeloma (MM)

Multiple Myeloma is a type of blood cancer that affects plasma cells. In multiple myeloma, malignant plasma cells amass in the bone marrow crowding out the normal plasma cells that help fight infection. This disease can damage the bones, immune system, kidneys, and cause anemia. A randomized trial compared the costs and benefits of using a melphalan (chemotherapy) and prednisone (steroid) treatment in conjunction with thalidomide (MPT) as opposed to melphalan and prednisone (MP) alone. The testing was done on 135 elderly patients over the age of 65 with MM who were ineligible for stem-cell transplants. The results showed a significant increase in the median progression-free survival (PFS) of patients using a combination of drugs that included thalidomide. PFS is the length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse. Also, the overall survival (OS) rate was 52 months as opposed to only 32 months for patients using only melphalan and prednisone. The following graph compares the progression-free survival rate of patients using MPT versus MP treatment. The MPT group has a significantly higher PFS rate. The Y axis is the fraction of living patients who began in the study. Both the MPT and MP groups start at 1.00, meaning that 100% of participants are alive. The X axis is the months of the treatment. The MPT group has a higher PFS rate during the forty months of the trial. The P value is 0.02, meaning the results are statistically significant (Sacchi, et. al. 2011).

One downside of adding thalidomide to the treatment regiment is the adverse side-effects that were more frequent in patients using thalidomide, which will be discussed in more detail in the "Adverse Effects of Thalidomide" section of this paper. Researchers observed a significant increase in neutropenia, deep venous thrombosis, infection, and peripheral neuropathy. The incidence of toxicity correlates with the drug dosage. The study concluded that while including thalidomide in the therapy showed an increase in activity against MM, it came with a substantial cost, which will be discussed later.

Trials have also been conducted using the second-generation thalidomide derivate, lenalidomide. In a randomized, controlled clinical trial, lenalidomide therapy (in combination with dexamethasone, a corticosteroid, or with melphalan and prednisone) significantly improved PFS in patients with newly diagnosed MM who were not eligible for stem-cell transplants as compared to MP treatment alone. These improvements in progression-free survival were also reflected in patients' health-related quality of life (McCormack, 2015).

In general, the analog was found to have improved efficacy and increased tolerability as compared to thalidomide. Although the treatment regiments had similar efficacy results, lenalidomide was observed to have fewer toxic side-effects than its parent drug. The continuous use of lenalidomide did not have a negative impact on the drug's tolerability. It also did not increase the cases of neutropenia as compared with shorter-term use of the drug. With new analogs, melphalan and prednisone plus a thalidomide-type drug could be considered the new standard of care for the treatment of patients with MM over age 65 years and for younger patients who are transplant-ineligible (McCormack, 2015).

Recent studies are working on understanding lenalidomide's mechanism of action. They propose that it affects signal transduction, also known as cell signaling, which leads to the suppression of COX-2 but not COX-1. This can partly explain its selective efficacy on cells. Meaning, it is able to be more selective in the cells it targets so it can have a greater potency with less side effects. Even though the exact molecular targets of lenalidomide are not well known, its activity across a spectrum of conditions highlights the possibility of multiple target sites of action (Kotla, et. al. 2009).

Malignant Melanoma

Malignant melanoma is the most aggressive and life-threatening skin cancer. It develops in the melanocytes and has a very high

tendency to spread to other parts of the body. Symptoms can include a new, unusual growth or a change in an existing mole. Brain metastases will develop in almost half of the patients with advanced melanoma and in 15-20% of these patients, the central nervous system is the first site of relapse. The overall survival rate is very short, only two to four months (Vestermark, et. al. 2008).

In one study, the antitumor activity and toxicity of thalidomide was evaluated in patients with phase II brain metastases related to metastatic melanoma. Thalidomide was administered orally to patients, with the dose increasing over a one-month period from 100 mg per day to 400 mg per day. Twenty-five men and eleven women with a median age of forty-eight years were enrolled in the study. The average survival rate for the study group was unchanged from historical data. Median PFS was 1.7 months and OS was 3.1 months. Although thalidomide showed limited activity against the metastatic melanoma in the central nervous system, minor effects on peripheral tumor manifestation were noted. This led researchers to conclude that thalidomide may one day be part of the treatment plan for patients with that form of metastasis in the future. Researchers also concluded that more investigation should be done using thalidomide in combination with Temozolomide, a cytotoxic chemotherapy drug (Vestermark, et. al. 2008).

Persistent Erythema Multiforme

Erythema multiforme is a common, usually self-limited disease which predominantly affects patients in their 20s and 30s. Its symptoms include target shaped lesions (circular red patches with central clearing) on the skin and mucous membranes. There are three clinical subgroups of erythema multiforme: classical, recurrent, and persistent erythema multiforme. The most severe form is the persistent erythema multiforme which can leave a patient stricken with continuous lesions. No potential cause has been found yet, so this subgroup is defined as idiopathic.

Thalidomide can be effectively used as a treatment for this skin condition. It was initially introduced as a treatment for persistent erythema multiforme as early as the 1980's because of its immunomodulatory and anti-inflammatory effects. The following case report in the recent literature illustrates its effectiveness. A fifteen-year-old boy in the Republic of China experienced a sudden onset of target-like lesions on his trunk and limbs. Although the wounds healed within two weeks, new eruptions continued to appear. After unsuccessful treatment attempts with oral corticosteroids and topical agents as well as the antiviral drug valaciclovir, thalidomide was prescribed to the patient. After two weeks of administering 100 mg per day, the lesions gradually healed, and no new ones developed. After two months of slowly reducing the dosage, there was no recurrence of disorder. The researchers noted that because of the risk of neuropathy associated with taking daily doses of this medication, clinical vigilance and regular neurological exams are advised (Chia-Wei, et. al. 2008).

Cutaneous Lupus Erythematosus (CLE)

Cutaneous Lupus Erythematosus is an autoimmune disease, which affects multiple organ systems in the body. In this disease an individual's own immune system attacks various cells causing a wide variety of symptoms. Typically, it causes extensive, disfiguring lesions. Although these lesions are not life threatening, they can be very itchy or painful. Many patients respond to standard treatment methods such as sunscreen, topical corticosteroids, or oral antimalarial drugs. However, for cases in which these treatments did not prove useful, or if the CLE was severe, thalidomide can be an important therapeutic option (Sharma, et. al. 2007).

In a study done by the Department of Dermatology at the University Hospital of Leuven, Belgium, thirty patients received thalidomide treatment for refractory CLE over fifteen years (from February 1998 to August 2013.) Each of these patients had previously tried at least two different drug treatments with no success. All of them were required to follow vigorous contraceptive methods because of thalidomide's known teratogenic properties. Patients received an initial dose of 50 mg per day, which was increased to 100 mg if the CLE was extensive. Although six patients prematurely stopped treatment due to the negative side-effects, all patients who continued in the study experienced improvements within 1-9 weeks after beginning treatment. A high rate of relapse (73%) was observed in patients who stopped thalidomide treatment. In addition, five patients were not able to be weaned off the drug due to flare-ups of CLE when they attempted to taper off the doses. The researchers concluded that while thalidomide treatment for CLE does have strong efficacy, because of its considerable risk of polyneuropathy, it should only be considered as a possible therapy for severe cases of CLE or for patients who have exhausted other treatment options without significant relief (Baret, et. al. 2015).

In another study done on twenty-five patients in India suffering from various inflammatory skin diseases, including discoid lupus erythematosus, thalidomide was found to be an effective treatment. Of the seven patients with LE, four had excellent response, two had partial response and one discontinued treatment due to deep vein thrombosis (DVT). The authors recommended thalidomide as an effective treatment but advised physicians to be watchful of thrombo-embolic events (Sharma, et. al. 2007).

Erythema Nodosum Leprosum (ENL)

When the author's father, Stanley Newfield MD, was a young dermatology resident training at the United States Public Health Service Hospital in Staten Island, New York he was involved in diagnosing and treating many cases of leprosy, also known as Hansen's disease. This research interest was perhaps especially appropriate since he is a kohen, the traditional caretaker for

people suffering from *tzoras* (leprosy) in the Torah.

As a federal institution, his hospital was responsible for caring for patients with transmissible infectious diseases. Leprosy patients were referred from a large area of the north-eastern United States for treatment. One of the complications of leprosy is the immune-system reaction known as Erythema Nodosum Leprosum. ENL is characterized by the presence of many inflammatory skin nodules and symptoms such as fever, arthritis, eye inflammation, neuritis, and swollen lymph nodes. It was observed that many patients suffered from ENL, which was even more distressing to them than some of the other leprosy symptoms such as loss of sensation in the extremities and/or exaggerated skin folds on the face.

Dr. Newfield explained that he was surprised, back in 1979, to find that the infamous drug, thalidomide, was the miraculously effective treatment for ENL. He was well-aware of the teratogenic effects of the drug which he learned about in detail in medical school. Now this same drug was resurrected for a new use, albeit with strong precautions to avoid administration to pregnant women. Due to his involvement in leprosy treatment, he was coauthor of a research report on the epidemiology of leprosy in New York City, which was published in the prestigious Journal of the American Medical Association.

Many people have a fear of leprosy since it is transmissible through contact with an infected patient. However, this seems to require prolonged exposure, usually in a household setting. The research verified that very few leprosy patients acquire the disease in the continental United States, rather they brought the disease with them when they immigrated to this country. The average latent period from entering the United States until onset of symptoms was 4.8 years, with a range of 0 to 38 years (Levis, et. al. 1982).

Almost forty years have passed since thalidomide was first used for ENL treatment, and it remains the drug of choice for this condition, as evidenced by two current research reports originating from India, a country with a large number of leprosy patients. The first paper reports on eleven patients with ENL. Six of those patients had excellent response to thalidomide and five had to stop treatment prematurely due to side-effects (most commonly DVT but also rashes and tremors.) (Sharma, et. al. 2007) In the second study following one hundred patients diagnosed with ENL, the group of fifty patients treated with thalidomide had a faster and longer lasting clinical response than the control group of fifty patients treated with prednisolone, a strong steroid medication. Patients on thalidomide also experienced fewer relapses of their cutaneous symptoms (Kaur, et. al. 2009).

Animal Models of Alzheimer's Disease (AD)

Alzheimer's Disease is a degenerative disease that destroys memory and other important mental functions. This is an incurable condition that afflicts an estimated 5.7 million people in the United States, mostly over the age of sixty-five. Research studies are currently being performed on a mouse model of AD. In one study, healthy mice were injected with streptozotocin (STZ), a chemical that causes AD-like cognitive deficits. In this study, one group of mice were pre-treated with thalidomide. Learning and memory behaviors were evaluated on the seventeenth, eighteenth and nineteenth days of the study using the Morris water maze test. In this test, a mouse is placed in the center of a circular pool and must find the hidden platform that allows it to escape. Mice that are not treated with the drug will improve their time to escape after doing the test multiple times. The SZT injections caused a significant decrease in the mice's improvement in their performance on the test. In comparison, the learning and memory behaviors of the thalidomide treated mice were significantly better preserved and they were able to complete the tests with improved timing, although they were not as improved as the mice who did not receive any drugs. This positive result appears to be due to the anti-inflammatory effect of TNF-alpha inhibition (Elçioğlu, et. al. 2013).

A second study used a strain of mice with the human APPswedish transgenic (APP23) mutation. This mutation is associated with Alzheimer's Disease. These mutated mice show deficits in spatial memory which become severe with age. (The Jackson Laboratory Website. 2018) This report showed that thalidomide treatment improved memory and learning ability in the mutated mice. The level of TNF-alpha in the thalidomide treated mice was decreased. This in turn reduced the amount of amyloid (A beta 1-42,) a harmful protein, which accumulated in their brain tissue. The control group mice treated with the inactive vehicle had 750 units of harmful amyloid, while the thalidomide group had only approximately 100 units (He, et. al. 2013).

In mice brain tissue, the control group (treated with the vehicle) developed a large number of harmful senile plaques but the thalidomide treated group showed very few.

Adverse Effects of Thalidomide

This section summarizes the adverse effects of thalidomide, some of which have also been mentioned previously. Thalidomide was withdrawn from widespread use shortly after the devastating effects on developing embryos was discovered. The drug came back into limited use for malignant and inflammatory diseases in non-pregnant women. It can still have serious harmful effects: peripheral neuropathy (pain and tingling in the hands and feet), venous thrombosis (blood clots in the veins), skin rashes, constipation, somnolence (excessive daytime sleepiness), weakness, and bradycardia (BC Cancer Drug Index. updated 2018).

Peripheral neuropathy is a common side effect that is associated with prolonged use of the drug, but there is no clear mechanism of action that explains its correlation with a cumulative dose. The risk for nerve damage is highest after 6 months or more of therapy. The symptoms are usually reversible when the

patient stops thalidomide treatment, although some patients do suffer long term nerve damage (Rajkumar, et. al. 2002).

Constipation caused by thalidomide can vary from mild to severe. As many as 90% of patients can develop mild constipation. This effect is thought to be secondary to thalidomide's action on the autonomic nerve endings in the gut. Severe constipation usually occurs in patients who are taking high doses of thalidomide. It is especially prevalent among patients who are already prone to developing constipation, such as those who lead an inactive lifestyle. Change of diet and exercise can help alleviate this side effect (Hall, 2003).

Deep vein thrombosis and pulmonary embolisms only occur in one to three percent of the patients receiving thalidomide as treatment for myeloma. There is not enough research done yet to determine whether the risk of DVT in these patients is higher than usual for patients receiving other types of treatment for this severe malignancy, due to the nature of the disease or the side effect of immobility that it can cause. Patients confined to bed rest tend to have higher rates of DVT. The risk is also elevated when patients receive thalidomide treatment in combination with dexamethasone or other chemotherapy drugs, have an inherited thrombotic predisposition, or are over the age of sixty-five (Hall, 2003).

A recent case report documents a thirty-eight-year-old female from Puerto Rico with a history of prenatal thalidomide exposure. She suffered from phocomelia, the dramatic birth defect in which the hands or feet are attached close to the trunk. An MRI scan revealed that the uterus and vagina were also absent. These internal anomalies have been less appreciated by physicians because they are not noticeable without special imaging, however they can cause serious symptoms such as pain and malignancy (Dotters-Katz, et. al. 2013).

The analog drug, lenalidomide, has not been found to be teratogenic in rabbits, a sensitive species used to detect birth defects. However, it may still have adverse effects such as morbilliform rashes (Huang, et. al. 2008). In a study done at Mount Sinai Medical Center in New York City, doctors found that 7.2% of the 806 patients receiving IMiD treatment developed rashes. In almost all cases, the rashes could be managed without having to discontinue treatment. Thus, it appears that lenalidomide may lack some of the adverse effects of thalidomide, while still having superior immunomodulatory and antiangiogenic efficacy than its parent drug (Barley, et. al. 2016).

An additional analog, Pomalidomide, is now an approved drug for MM. A research study conducted in Aberdeen, United Kingdom analyzed its effect on zebrafish and chicken embryos. The tests showed no detectable teratogenic, antiangiogenic or neurotoxic effects. Despite having less side effects, it has more anti-inflammatory properties than either thalidomide or lenalidomide (Mahony, et. al. 2013).

Conclusion

The psalmist wrote, "The stone that the builders rejected became a cornerstone." (Psalm 118:22) This report illustrates this concept as it pertains to the drug, thalidomide. This drug was universally banned due to its harmful side-effects. Years later it was found to have unique healing properties in several serious diseases.

It appears that the continued use and development of thalidomide treatments is justified. Although it can have many serious side effects, specifically crippling teratogenesis, it is often the last resort as treatment for patients suffering serious diseases. Care should be taken to prevent pregnant women from using this drug to avoid causing birth defects. Given the significance of these effects, the future of thalidomide is not in the drug itself but in the derivatives that are now being tested. Lenalidomide and pomalidomide are more effective and have less toxic effects. As scientists continue to discover their specific mechanisms of action they will be able to alter the drug to have even less adverse effects and help more patients worldwide. The prognosis for PFS and OS for patients with MM and other forms of cancer will decrease even more and give the people suffering with these diseases hope for their future. With this new and exciting research thalidomide and its analogs have justly become important medical treatments.

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