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Thalidomide - a chance for use in modern disease treatment?

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ABSTRACT

Thalidomide, despite its controversial history associated with teratogenic effects is currently used in the treatment of various conditions including oncological, immunological and dermatological diseases. The drug exhibits anti-inflammatory, immunomodulatory and anti-angiogenic effects, making it potentially effective in the treatment of various diseases. The mechanism of action is based on modulating the CRL4CRBN E3 ubiquitin ligase complex by binding to cereblon (CRBN), which leads to a change in the substrates recognized by this complex and the degradation of specific proteins. Thalidomide is used in the treatment of multiple myeloma, especially in cases resistant to other treatment methods. In addition, it can support the treatment of glioblastoma multiforme due to its anti-angiogenic and immunomodulatory effects. It is also used in the treatment of Crohn's disease, systemic lupus erythematosus, and idiopathic pulmonary fibrosis (IPF). In Crohn's disease it works by blocking TNF-α and modulating the immune response. In cutaneous lupus erythematosus it reduces inflammation, modulates the immune response and inhibits angiogenesis. In IPF, it inhibits the production of pro-inflammatory cytokines and reduces oxidative stress. The use of thalidomide is associated with a risk of teratogenicity, which requires strict control and the use of effective methods of contraception. In addition, thalidomide can cause side effects, mainly hematological and gastrointestinal disorders. Due to the side effect profile, the use of thalidomide requires caution and close monitoring of the patient by a physician.

RESULTS:

Thalidomide- despite its tragic history associated with teratogenic effects is currently used in the treatment of various oncological, immunological, and dermatological diseases. Its action is based on anti-inflammatory, immunomodulatory, and antiangiogenic properties. The mechanism of action of thalidomide involves the modulation of the CRL4CRBN E3 ubiquitin ligase complex by binding to cereblon protein (CRBN) leading to the degradation of specific proteins. The effectiveness of thalidomide has been demonstrated in conditions such as multiple myeloma, Crohn's disease, COVID-19, glioblastoma multiforme, lupus erythematosus, and dermatological disorders. It is important to remember the risk of thalidomide's teratogenicity, which requires strict control and the use of effective contraception methods. Additionally, thalidomide can cause adverse effects such as blood clots, hematological and gastrointestinal disorders, which necessitates caution and close patient monitoring by a physician.

CONCLUSION

Despite its teratogenic history, thalidomide is used to treat various oncological, immunological, and dermatological diseases. It works through anti-inflammatory, immunomodulatory and anti-angiogenic effects modulating the CRL4CRBN complex. It treats conditions like multiple myeloma, glioblastoma, Crohn's disease, lupus, and pulmonary fibrosis. However, due to teratogenic risks and side effects, it requires strict medical supervision.

Keywords: thalidomide, molecular mechanism, teratogenic effect, anti-inflammatory effect, immunomodulation, anti-angiogenesis, treatment

INTRODUCTION

Thalidomide is a drug with many applications but also a controversial history marked by both therapeutic promise and tragedy associated with its teratogenic effects and serious birth defects. Initially, thalidomide was synthesized in 1954 by the German pharmaceutical company Chemie-Grunenthal. [1] In 1957, it was introduced to the market under the name "Contergan." [1] It was advertised as a safe, multifunctional drug that can treat symptoms from anxiety to hyperthyroidism. [1] Thalidomide was available without a prescription in many countries and was widely used as a sedative, hypnotic, and as a remedy for morning sickness in pregnant women. [1]

Shortly after its introduction, a link was observed between the use of thalidomide by pregnant women and the occurrence of severe birth defects in newborns, such as phocomelia (limb reduction), heart and ear defects. [1] The early 1960s brought reports from McBride and Lenz, which independently showed that thalidomide is highly teratogenic. [2] It is estimated

that approximately 10,000 children worldwide were born with birth defects caused by thalidomide. [1] As a result, thalidomide was withdrawn from the market in 1961. [1]

Currently, thalidomide is used in the treatment of various conditions including:

- β-thalassemia, where it exhibits the ability to increase the level of fetal hemoglobin (HbF) [3], [4]
- multiple myeloma [2]
- inflammatory conditions [5]
- cancers [1]
- tuberculosis of the central nervous system [6]

METHODS

This study is a narrative literature review on the new opportunities for thalidomide use in selected disease entities. The authors used the PubMed database employing the terms 'thalidomide'/'thalidomide new treatment' resulting in over two thousand articles. Inclusion criteria such as years 2015-2025, English language text, full-text access and specific article types like reviews and randomized studies were applied, thereby minimizing the literature review to 210 articles. The authors conducted a personal review of the articles and due to inconsistency with the content of this work and thematic redundancy, content inappropriate for the article was removed. In the methodology, articles manually selected by the authors, expanding on the topics of selected diseases like multiple myeolma, beta-thalassemia, crohn's disease, Systemic Lupus Erythematosus, Selected Dermatological Conditions, COVID-19, glioblastoma multiforme were added including one article from 2001.

THALIDOMIDE CHEMICAL STRUCTURE

Thalidomide is a synthetic derivative of glutamic acid characterized by a specific chemical structure, which consists of a glutarimide ring and a phthalimide ring. [24] The chemical structure features one chiral center. [24] The phthalimide ring in combination with the glutarimide ring forms the characteristic skeleton of thalidomide and its derivatives. The

glutarimide ring is a common structural element for thalidomide, lenalidomide and pomalidomide, compounds classified as immunomodulatory imide drugs (IMiDs). Thalidomide exists in the form of R (+) and S (-) enantiomers, which can interconvert in vivo forming an optically inactive racemic mixture. The R (+) enantiomer has a sedative effect. [24]

MECHANISM OF THALIDOMIDE

Thalidomide exhibits anti-inflammatory, immunomodulatory and anti-angiogenic effects. It functions by inhibiting angiogenesis, stimulating the immune system, and suppressing the adhesion of neoplastic cells to stromal cells thereby impeding tumor development.

In recent years, thalidomide has found application in the treatment of advanced malignancies and autoimmune disorders. Specifically, in the context of colorectal cancer thalidomide can suppress the expression of VEGF-A and HIF-1α, influencing the growth and proliferation of neoplastic cells. Research indicates that thalidomide may be the sole medication capable of assisting patients with cancer-related anorexia-cachexia syndrome (CACS) in mitigating weight loss and promoting the accrual of lean body mass. Due to the inherent risk of teratogenicity the administration of thalidomide is strictly regulated by programs such as the System for Thalidomide Education and Prescribing Safety (STEPS) in the United States and the Thalidomide Education and Risk Management System (TERMS) in Japan.

The molecular mechanism of action of thalidomide and its derivatives is predicated on the interaction with the cereblon (CRBN) protein, a component of the Cullin-RING ligase 4 (CRL4CRBN) E3 ubiquitin ligase complex. [2]

Key aspects of thalidomide's mechanism of action based on the referenced literature are delineated below:

- Cereblon (CRBN) as previously described constitutes the molecular target of thalidomide, which binds directly to CRBN serving as a substrate receptor dependent on the ligand within the CRL4CRBN E3 ubiquitin ligase complex. Upon thalidomide binding to CRBN the CRL4CRBN complex recognizes various "neosubstrates,"

contingent upon the ligand's configuration. CRL4CRBN binds to multiple neosubstrates in the presence of diverse ligands. [2]

- Thalidomide and its derivatives such as lenalidomide, induce the degradation of specific proteins culminating in therapeutic effects. For instance lenalidomide selectively degrades IKZF1 and IKZF3 in multiple myeloma cells. [1]
- CRBN is utilized in PROTACs technology, enabling the specific targeting of proteins for degradation. Heterobifunctional molecules, such as dBET1 are being developed to specifically degrade target proteins. [2]
- Thalidomide and its analogs exhibit immunomodulatory effects influencing the immune system, as well as exerting antineoplastic effects by inhibiting angiogenesis and impacting neoplastic cell growth. [2] Thalidomide diminishes the level of tumor necrosis factor-alpha (TNF-α) by impairing the stability of its mRNA thereby accelerating its degradation and reducing inflammation. [27] It induces the production of T helper type 2 (Th2) lymphocytes while concurrently inhibiting the production of T helper type 1 (Th1) lymphocytes, shifting the immune response toward the suppression of inflammatory reactions. [27] Thalidomide blocks the translation of interleukin-12 (IL-12) by inhibiting the activity of nuclear factor kappaB (NF-κB). Additionally, it reduces the levels of IL-2, interferon-γ, and integrins, while augmenting the production of IL-4 and IL-5, thereby attenuating the migratory capacity of white blood cells. [27] Thalidomide decreases the expression of intercellular adhesion molecule-1 (ICAM-1), which inhibits the regeneration of microvascular endothelial cells in the small intestine. [27]
- Thalidomide inhibits angiogenesis a critical factor in the context of cancer treatment. [6] The precise mechanism of thalidomide's anti-angiogenic action remains incompletely understood, but studies suggest several potential pathways. It enhances the expression of integrin genes and reduces VEGF levels. [25] Thalidomide targets epidermal growth factor-like domain 6 (EGFL6) and inhibits angiogenesis via the EGFL6/PAX6 axis. [26] Thalidomide and other immunomodulatory drugs (IMiDs) decrease cell migration and adhesion by inhibiting the VEGF receptor thereby reducing capillary density in fibrotic lesions. [26]
- Thalidomide may play a role in facilitating the safe reduction of steroids while preventing immunological reconstitution. [6]

In summary the mechanism of action of thalidomide is based on its capacity to modulate the CRL4CRBN E3 ubiquitin ligase complex through binding to cereblon (CRBN), leading to alterations in the substrates recognized by this complex and the degradation of specific proteins, thereby influencing immunomodulatory, antineoplastic, and anti-inflammatory processes. [2]

SIDE EFFECTS OF THALIDOMIDE

Thalidomide despites current applications in the treatment of certain conditions, is associated with the risk of serious side effects. [21] The most significant side effect of thalidomide is teratogenic effect, which is the most well-known and tragic side effect of thalidomide causing severe birth defects in children whose mothers took this drug during pregnancy. A characteristic symptom is phocomelia, which is the shortening or absence of the long bones of the limbs. The arm bones may be shortened or absent, and the fingers may connect directly to the shoulder or the end of the shortened humerus and ulna. [21] The period of sensitivity to the teratogenic effects of thalidomide is between the 20th and 36th day after fertilization. [22] Earlier exposure during this window causes more severe damage. A single 50 mg tablet may be sufficient to damage the developing embryo or fetus. [22]

Thalidomide affects many other tissues and organs, including the eyes, ears, face, heart and circulatory system, gastrointestinal tract, reproductive system, urinary system, and spine. [21] Ear damage is usually symmetrical and includes the absence of the external ear (anotia) or its reduction (microtia). [23] Deafness or hearing impairment, as well as cranial nerve palsy, may also occur. Facial defects associated with thalidomide include an enlarged birthmark or hemangioma on the forehead, facial asymmetry, dental abnormalities, micrognathia, cleft lip and palate and a small nose. Other defects include kidney defects abnormalities of the genitals (including hypospadias in males and uterine defects in women), anal atresia, intestinal atresia, pyloric stenosis and inguinal hernia. [23] Long-term use of thalidomide in adults can lead to peripheral neuropathy, as well as constipation, skin ras, or drowsiness and fatigue. [21], [22]

APPLICATION OF THALIDOMIDE IN SELECTED DISEASE ENTITIES

Multiple Myeloma

Thalidomide is a valuable tool in the therapy of multiple myeloma demonstrating anti-cancer activity especially in cases resistant to other treatment methods. However, potential risks associated with its use must be remembered [7]. In the past melphalan-based regimens were standard, but they are now being phased out due to the risk of stem cell damage and the development of secondary blood cancers. In patients who do not qualify for bone marrow transplantation, thalidomide therapy often in combination with other drugs, aims to control symptoms and slow disease progression [6], [7]. Lenalidomide, bortezomib and daratumumab are often used as adjuncts to dexamethasone therapy. Thalidomide exhibits anti-cancer activity in treatment-resistant multiple myeloma [7]. However, the use of thalidomide increases the risk of blood clots so antithrombotic prophylaxis, such as aspirin, warfarin, or enoxaparin, is necessary [9].

In the treatment of multiple myeloma drugs from the CELMoD (cereblon E3 ligase modulators) group are used, a new class of drugs derived from IMiDs (immunomodulatory drugs), which include thalidomide [7]. Both CELMoDs and IMiDs bind to the cereblon E3 ubiquitin ligase complex, but CELMoDs show a higher affinity for this complex. This stronger binding in CELMoDs leads to increased degradation of IKZF1 and IKZF3 transcription factors essential for the survival of multiple myeloma cells. The main side effects of CELMoDs include hematological disorders such as myelosuppression, neutropenia, anemia, and thrombocytopenia, as well as gastrointestinal disturbances, fatigue, and rash. Due to the side effect profile, the use of thalidomide requires caution and close monitoring of the patient by a physician [7].

Beta-thalassemia

Thalidomide is a promising drug in the treatment of beta-thalassemia [4]. A meta-analysis of the efficacy and safety of thalidomide in the treatment of patients with beta-thalassemia erythroblasts were observed [3]. Parameters reflecting hemolysis, including LDH and bilirubin were significantly reduced. In response to treatment an overall response rate (ORR) of 85% was achieved, while the complete remission rate (CRR) was 54% [4]. Approximately 30% of patients taking thalidomide experienced mild side effects such as constipation, drowsiness, high levels of alanine aminotransferase (ALT) and rash [4]. In summary, thalidomide may be an effective treatment option for patients with beta-thalassemia,

but further large-scale studies are needed showed that thalidomide may be a relatively safe and effective therapy in reducing the need for blood transfusions and raising hemoglobin levels in patients with beta-thalassemia [4]. In a clinical trial on the effect of thalidomide on hemoglobin synthesis in patients with moderate thalassemia intermedia (TI). Thalidomide was administered orally at a dose of 50 mg at night for 3 months. After treatment with thalidomide a statistically significant increase in mean Hb levels and a decrease in the number of

Crohn's Disease

Thalidomide although burdened with history finds application in the treatment of Crohn's disease (CD), especially in cases where other methods fail [10]. Its action is based on blocking TNF-α, a key mediator of inflammation in CD and modulating the immune response [5]. In clinical practice thalidomide is often combined with azathioprine (AZA) creating induction and maintenance therapy for patients resistant to AZA alone [10]. Dosing starts at 25 mg per day, gradually increasing the dose every two weeks until reaching 50-100 mg per day [5]. Studies indicate effectiveness in inducing clinical remission and maintaining long-term remission without the need for steroids. In one study a clinical response was obtained in 80.3% of patients within approximately 6.5 weeks. Endoscopic studies show a decrease in CDEIS and Rutgeerts scores indicating improvement in the intestinal mucosa [5]. Thalidomide may be an option for patients who have failed biological drugs or cannot use them for economic reasons [10]. Research on thalidomide in CD has some limitations such as small sample sizes and relatively short observation periods [5]. Nevertheless, it appears to be a promising therapeutic option for patients with treatment-resistant Crohn's disease, but its use requires careful consideration of benefits and risks and close monitoring for side effects [3].

Systemic Lupus Erythematosus

Thalidomide, while burdened with serious side effects remains a valuable tool in the treatment of cutaneous lupus erythematosus (CLE), particularly in cases resistant to standard therapies [11]. Its versatile actions, including reducing inflammation, modulating immune responses and inhibiting angiogenesis, provide benefits to patients struggling with difficult-to-treat skin lesions. The recommended starting dose is typically 100 mg per day with the option to gradually increase it based on clinical response [11]. In some instances, a low maintenance dose may suffice to maintain remission and minimize the risk of side effects. Analogs like lenalidomide and iberdomide are also employed in lupus treatment to mitigate side effects, demonstrating promising efficacy and a potentially improved safety profile. Lenalidomide

possesses stronger immunomodulatory properties than thalidomide and may be effective in thalidomide-resistant cases. Iberdomide improves skin symptoms in moderate to severe lupus. Future research should prioritize the development of new, safer thalidomide analogs that could be utilized in earlier CLE treatment stages, preventing irreversible skin damage [11].

Selected Dermatological Conditions

Thalidomide is used in the treatment of various dermatological conditions particularly those resistant to standard therapies [12]. Examples of such diseases include:

- Erythema Nodosum Leprosum (ENL) - ENL is a complication of leprosy characterized by painful inflammatory nodules on the skin. Thalidomide is the drug of choice for the treatment of ENL. Typically 100–400 mg/day is used adjusting the dose depending on the severity of the disease and then gradually reducing it [12].
- Behcet's Disease (BD) - BD is a chronic recurrent multisystem disorder. Thalidomide is used in cases of Behcet's disease resistant to other treatments in which 400 mg/day is used for the first 5 days, followed by 200 mg/day for the next 15–60 days. A lower dose of 100 mg/day is effective in treating oral and genital ulcers [12].
- Cutaneous Sarcoidosis - in cutaneous sarcoidosis, thalidomide can be considered as a therapeutic alternative in cases of steroid resistance or contraindications to their use. The treatment involves 200 mg/day for the first 2 weeks, then 100 mg/day for the next 11 weeks and then 100 mg every other day for the next weeks. Studies have shown improvement in patients' skin condition and a reduction in the size of granulomas and epidermal thickness in biopsies [12].

COVID- 19

In cases of severe lung damage caused by COVID-19, thalidomide in combination with a low dose of glucocorticoids may reduce inflammation and improve respiratory parameters [15]. Endothelial inflammation is a common symptom of COVID-19 and because thalidomide has well-documented vascular and anti-inflammatory effects, an attempt was made to examine the effect of thalidomide and its derivatives on the endothelium [20]. Chen et al. (2020) described the case of a 45-year-old woman with severe lung damage caused by COVID-19, where thalidomide administered as adjunctive therapy with short-term glucocorticoids reduced inflammation without side effects [13].The biggest challenge remains the teratogenic effect of

thalidomide, which requires special caution in its use, especially in women of childbearing age. The use of effective contraception and patient monitoring is necessary [13]. There is a need for further clinical trials to fully assess the efficacy and safety of thalidomide in the treatment of lung diseases. These studies should consider specific patient populations, dosing, and potential interactions with other drugs [13].

Glioblastoma Multiforme

Thalidomide may potentially support the treatment of glioblastoma due to its anti-angiogenic and immunomodulatory effects [16], [17]. As an inhibitor of vascular endothelial growth factor (VEGF). Thalidomide can inhibit the formation of new blood vessels in the tumor, limiting its growth and spread [16], [18]. Thalidomide has been studied in the context of recurrent glioblastoma treatment. It has been shown that when administered at doses of 100–1200 mg daily, it was generally well tolerated and may lead to disease stabilization. In one study, the median overall survival (OS) was 36 weeks. In another study, 35% of patients achieved one-year survival. Thalidomide in combination with irinotecan showed limited efficacy in the treatment of newly diagnosed or recurrent glioblastoma [16]. A meta-analysis showed that bevacizumab (another angiogenesis inhibitor) had a higher objective response rate (ORR) than thalidomide but both drugs gave comparable results in terms of progression-free survival and one-year overall survival. The use of cediranib and thalidomide also effectively reduced tumor size over time [17]. Thalidomide may be used as palliative treatment in advanced secondary glioblastoma improving patients' quality of life. A dose of 100 mg of thalidomide taken at bedtime may improve sleep and prolong survival in some patients. Thalidomide has also been studied in combination with temozolomide and celecoxib in the treatment of newly diagnosed glioblastoma, but the results did not show a significant increase in survival [16]. In summary, thalidomide can be a valuable tool in the treatment of glioblastoma especially in combination with other therapies.

NEW CHANCE AND RISKS OF THALIDOMIDE TREATMENT FOR PATIENTS

Thalidomide- like a double-edged sword carries both promising therapeutic possibilities and a dark history of tragic side effects. Its return to medicine is a story of rediscovering a drug with complex effects. It has proven to be a valuable weapon in the fight against certain cancers, especially multiple myeloma and its derivatives expand this potential. Its immunomodulatory

and anti-inflammatory abilities have restored its place in the treatment of erythema nodosum leprosum. [22] Studies shed light on its potential benefits in the therapy of refractory Crohn's disease in synergy with other drugs. [10] There are also hopes for its use in the treatment of idiopathic pulmonary fibrosis by inhibiting key inflammatory and fibrotic factors. [13] The intriguing mechanism of action of thalidomide related to the cereblon (CRBN) protein opens new doors in targeted therapies, such as PROTAC. [2] However, alongside new opportunities the risks of using thalidomide cannot be forgotten. It constantly reminds us of its terrible teratogenicity which causes severe birth defects. Long-term use carries the risk of peripheral neuropathy and other troublesome side effects. Due to its history and potential for harmful effects, its use is subject to rigorous controls and safety programs. [22]

A full understanding of all the mechanisms of action of thalidomide remains a challenge for scientists. Thalidomide remains a drug with enormous potential but also significant risks, requiring caution and awareness of its complex nature.

CONCLUSION

Despite tragic history associated with teratogenic effects thalidomide has found its place in the treatment of various oncological, immunological, and dermatological conditions. Its return to medicine exemplifies the rediscovery of a drug with complex effects. The key mechanism of action of thalidomide is the ability to modulate the CRL4CRBN E3 ubiquitin ligase complex by binding to the cereblon (CRBN) protein. This binding leads to a change in the substrates recognized by this complex and the degradation of specific proteins which ultimately induces immunomodulatory, anticancer and anti-inflammatory effects. Thalidomide is a valuable tool in the therapy of multiple myeloma particularly in cases refractory to other treatment methods. It exhibits anticancer activity and is often used in combination with other drugs in patients ineligible for bone marrow transplantation. However, it is important to remember the increased risk of blood clots which requires antithrombotic prophylaxis. In the treatment of myeloma a new class of IMiD (immunomodulatory drugs) derivatives called CELMoD (cereblon E3 ligase modulators) is also used which exhibits stronger affinity for the cereblon complex, leading to increased degradation of IKZF1 and IKZF3 transcription factors. It may also be a promising drug in the treatment of beta-thalassemia contributing to a reduction in the need for blood transfusions and an increase in hemoglobin levels. Studies have shown a statistically significant increase in mean hemoglobin levels and a decrease in the number of erythroblasts in patients treated with thalidomide. In Crohn's disease it is used especially in

cases refractory to other therapies. It works by blocking TNF-α, a key mediator of inflammation in this disease and modulating the immune response. It is often combined with azathioprine in induction and maintenance therapy in patients refractory to azathioprine alone.

It is a valuable tool in the treatment of cutaneous lupus erythematosus particularly in cases refractory to standard therapies. Its action involves reducing inflammation modulating the immune response and inhibiting angiogenesis. Thalidomide analogs such as lenalidomide and iberdomide are also used in the treatment of lupus, showing promising efficacy and a potentially better safety profile. In cases of severe lung damage caused by COVID-19, thalidomide in combination with a low dose of glucocorticoids can reduce inflammation and improve respiratory parameters. Thalidomide may support the treatment of glioblastoma multiforme due to its antiangiogenic and immunomodulatory effects, inhibiting the formation of new blood vessels in the tumor. It shows potential in the treatment of recurrent glioma and in some studies, it improved patient survival. It can also be used palliatively in advanced secondary glioma improving patients' quality of life. There are hopes for the use of thalidomide in the treatment of IPF by inhibiting key inflammatory and fibrotic factors. However, it is absolutely essential to remember the risk of thalidomide teratogenicity and its most well-known tragic side effect causing severe birth defects in children whose mothers took this drug during pregnancy. The period of greatest sensitivity to teratogenic effects is between 20 and 36 days after fertilization and even a single dose can be harmful. For this reason, the use of thalidomide requires strict control and the use of effective contraception. In addition, thalidomide can cause other side effects mainly hematological and gastrointestinal disorders as well as peripheral neuropathy, drowsiness and fatigue. Therefore, its use requires caution and close monitoring of the patient by a doctor. Thalidomide, despite its controversial history, is now used in the treatment of many serious diseases due to its multidirectional effects. Its mechanism of action based on the modulation of the CRL4CRBN complex opens new possibilities in targeted therapies, such as PROTAC. Nevertheless, due to the risk of teratogenicity and other potential side effects, its use is associated with the need to exercise extreme caution and comply with rigorous control and safety programs. Further research is needed to fully understand all the mechanisms of action of thalidomide and to develop safer analogs that could be used in the earlier stages of treatment of various diseases.

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