REVIEW ARTICLE

Potential Therapeutic Uses of Thalidomide for Pulmonary Fibrosis

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Received: 2023-04-24, Revised: 2023-06-09, Accepted: 2023-06-18, Published: 2023-06-30

Abstract

Thalidomide was widely used to avoid morning sickness in pregnant women, but was recalled due to its teratogenic effects and malformations in thousands of children. However, potential beneficial effects such as anti-inflammatory, system regulatory activities and the anti-angiogenic effect of thalidomide have been reported. As the studies about thalidomide continued, its new effects and applications made researchers more interested in it and became a promising agent in the treatment of a variety of clinical situations where standard treatments have failed. To make this purpose more achievable, Scopus, Science Direct, Google Scholar, and PubMed were searched. After obtaining and reviewing articles related to thalidomide and its indications, different therapeutic uses of thalidomide for pulmonary diseases are classified on mechanisms. In recent years, thalidomide has been an effective agent in treating cough associated with pulmonary fibrosis and the main suggested mechanism refers to regulation production of inflammatory mediators, including cytokines and chemokines, which trigger Epithelial-Mesenchymal Transition (EMT). The mechanism of EMT is related to the inhibition of Transforming growth factor-beta (TGF-β1)-mediated signaling pathways, Smad2 (Suppressor of Mothers against decapentaplegic homolog 2) / 3, Akt / Glycogen synthase kinase 3 beta (GSK-3β), and Mitogen-activated protein kinase (MAPK). Thalidomide is also involved in paraquat-induced and bleomycin-induced pulmonary fibrosis. Also, Thalidomide gained attention as a suitable agent for the treatment of cough associated with idiopathic pulmonary fibrosis (IPF) and for severe pulmonary damage cause by severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2), responsible for the global pandemic in 2020, due to its anti-inflammatory-anti-angiogenesis and pro-apoptotic properties.
J Pharm Care 2023; 11(2): 102-109.

Keywords: Thalidomide; Covid-19; Pulmonary Fibrosis; Bleomycin,

Introduction

Thalidomide was first synthesized in 1953 and introduced as a sedative/hypnotic in 1954 until scientists began to notice cases of congenital malformation involving shortened or absent limbs in neonates whose mothers consumed thalidomide during gestation. As a result, about 10,000 children worldwide, were born with a rare birth defect and, as a result, it was discontinued from the European and Canadian markets in 1961 and 1962, due to its teratogenic effects (1). In contrast, potential beneficial effects such as anti-inflammatory system regulatory properties, the safety, and the

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antiangiogenic effect of thalidomide have been reported (2, 3). Previous studies have shown the effectiveness of thalidomide or its analogs in treating nodosal erythema, rheumatoid arthritis, Crohn's disease, renal cell carcinoma, myelodysplastic, and multiple myeloma. It has been declared that the combination of thalidomide and dexamethasone in patients resistant to a sequence of dexamethasone-containing regimens and single-agent thalidomide (5). In recent years, low dose of thalidomide has been an effective agent in treating pulmonary fibrosis (6, 7). Moreover, IPF is a progressive pulmonary disorder with a high rate of mortality in the majority of patients within 3–5 years of diagnosis (8). One of the most notable features of IPF is a persistent dry cough. As chronic cough can be problematic in a patient's quality of life, amelioration of the IPF cough with thalidomide can be a way to compensate for the ominous fate of this highly potent drug to be a beneficial choice for patients.

In this regard, the present study was designed to evaluate all documents on the effectiveness of thalidomide on lung fibrosis to propose a new therapeutic drug for the treatment of respiratory disorders.

Methods

In this review, the keywords Thalidomide, pulmonary fibrosis, respiratory disorders, paraquat, anti-fibrotic, Bleomycin, exposure, SARS-CoV-2, and Anti-inflammatory were used to find relevant articles indexed in Scopus, Science Direct, Google Scholar, and PubMed databases, published until December 2021. The obtained articles were screened using the abstract and keywords. Then, the full texts of related articles were reviewed, and reports that addressed thalidomide use in pulmonary diseases were included in the narrative review.

Results and Discussion

Thalidomide and respiratory disorders, including cough and fibrosis

One of the symptoms of IPF is a persistent dry cough, which is present in 80% of patients. According to studies, thalidomide can improve cough and respiratory quality in these patients (9). It also can improve therapeutic functions for sarcoidosis, acute pneumonitis, and IPF (10).

IPF, characterized by epithelial injury and fibroblast proliferation in the lungs, is a chronic progressive lung disease with a prevalence of 16–18 in 10,000 and a five-year mortality rate of over 50% (11). Inflammatory cytokines and angiogenesis serve critical roles in the pathological progression of IPF. It has been reported that thalidomide exerts an inhibitory effect on the cytokine profile in patients with IPF (12, 13). Japanese researchers reported that thalidomide pretreatment prevented the development of bleomycin-induced pulmonary fibrosis (PF) in a mouse model (14). Choe et al., further confirmed that the TGF-β1 induced activation of the Extracellular signal-regulated Kinase 1/2 (ERK1/2) signaling pathway accounted for the anti-fibrotic effect of thalidomide in a bleomycin-induced PF model (15). Moreover, in a clinical trial conducted in 2012, thalidomide treatment was demonstrated to improve coughing and respiratory symptoms and quality of life in patients with IPF (9). Recent studies have shown that thalidomide has anti-fibrotic effects in animal models of bleomycin-induced pulmonary fibrosis (16, 17) and paraquat (PQ) (18). Although the anti-fibrotic effects of thalidomide in pulmonary fibrosis have been demonstrated, the precise mechanism of this effect remains unclear.

Thalidomide Mechanism of action in respiratory disorders

a)Effects on the inflammatory process

Thalidomide functions through a variety of actions of anti-inflammation, immunomodulation and anti-angiogenesis. Other studies have reported that thalidomide can suppress the production of inflammatory cytokines such as Tumor necrosis factor alpha (TNF-α), IL-8, 12, 18 and Inflammatory mediators.

Repeated lung injuries lead to irregular activation of growth/EMT pathways. EMT is a biological process in which epithelial cells lose contact adhesion and apical-basal polarity, change shape with dramatic cytoskeletal changes, and exhibit some mesenchymal characteristics of invasion, migration, and extracellular matrix production. As shown in Table 1, Inflammatory mediators, including cytokines and chemokines, trigger EMT, and EMT-derived fibrotic cells overproduce many pro-inflammatory factors (19). TGF-β, a multifunctional cytokine produced by all blood cell lineages, induces EMT through different pathways (TGF-β-induced epithelial to mesenchymal transition) (20).

Forming a regulatory loop leads to the persistence of EMT (21). Acute inflammation has two phases; 1) initiation (alpha) and 2) resolution (omega). Inflammation initiates by soluble inflammatory mediators such as complement, free radicals, cytokines including chemokines, vasoactive amines, and eicosanoids (including prostaglandins) by adjacent cells of the infected or injured part in the body (7, 22, 23). The inflammasome is a multiprotein oligomer responsible for activating inflammatory responses and consists of Nucleotide-binding oligomerization domains, Leucine-rich Repeat, and Pyrin domain containing (NLRP) proteins such as NLRP3, apoptosis-associated speck-like or known as ASC, and procaspase-1 (24, 25). The inflammasome can promote the maturation and secretion of interleukin 1β (IL-1β) and IL-18 (26). NLRP3 also participates in the regulation of EMT in bleomycin-induced pulmonary fibrosis (27). Antifibrotic effects of thalidomide may be due to a reduction in inflammatory factors, including interleukin-6 (IL-6). In addition, in another study, thalidomide decreased the expression of IL-6, TGF-beta, Vascular endothelial growth factor (VEGF), Angiopoietin-1 (Ang-1), Ang-2, and Collagen Type I Alpha 1 Chain mRNA in the lung tissues of bleomycin-treated mice (14). It also has the potential to improve therapeutic functions for sarcoidosis, sensitive pneumonitis, and idiopathic pulmonary fibrosis by reducing TNF-α, interleukin-12p40, interleukin-18, and interleukin-8 (10).

Table 1. Effect of paraquat and thalidomide on inflammatory and EMT biomarkers.

Biomarkers		Paraquat	Thalidomide
Inflammatory	IL-1	↑(28)	↓(29)
	IL-6	↑(30)	↓(31)
	COX-2	↑(32)	↓(31)
	NF-Kβ	↑(33)	↓(31)
	TNF-α	↑(34)	↓(31)
	VEGF	↑(35)	↓(31)
	TGF-β	↑(27)	↓(31)
EMT	E-cadherin	↑(36)	
	N-cadherin	↑(37)	
	vimentin	↑(27)	
	Fibronectin	↑(38)	

b) Effects on EMT processes

Several studies have suggested that alveolar epithelial cell apoptosis is an important factor in the pathogenesis of IPF and fibrotic lung disorders. Viruses are thought to induce epithelial cell injury and promote EMT, a process by which differentiated epithelial cells convert to a mesenchymal phenotype may play an important role in the pathogenesis of pulmonary fibrosis. EMT, a process whereby complete differentiated epithelial cells transition to a mesenchymal phenotype as fibroblasts and myofibroblasts.

Previous reports suggest that the anti-fibrotic effects of thalidomide on pulmonary fibrosis may be related to the suppression of the ERK1 / 2 signaling pathway (15). It is reported that thalidomide can inhibit Jun N-terminal kinase signaling in an animal model of pulmonary fibrosis (39). A previous study also suggested that thalidomide has an anti-fibrotic effect due to suppressing p38 and Smad3 signaling by TGF-β1 (40).

Thalidomide decreases the expression of mesenchymal markers while increasing the expression of epithelial markers after TGF-β1 stimulation and reverses the morphological changes induced by TGF-β1 in alveolar epithelial cells. The effects of thalidomide suppression on TGF-β1-induced EMT may also be related to the inhibition of TGF-β1-mediated signaling pathways Smad2 / 3, Akt / GSK-3β, and MAPK. Today, more attention is paid to the EMT process and its possible role in the pathogenesis of pulmonary fibrosis (41).

The mechanism of EMT induced by TGF-β1 is complex because TGF-β1 signals are transmitted through various pathways, including Smad, MAPK, and phosphoinositide 3-kinase (PI3K) pathways (42).

In a study published in 2006, thalidomide inhibited TGF-β1-induced EMT in pulmonary epithelial cells by blocking the phosphorylation of both Smad2 and Smad3 (43).

EMT is essential for development and wound repair, which is also involved in PQ-induced and bleomycin-induced pulmonary fibrosis (14, 44). Pulmonary fibrosis is known to result from the differentiation of fibroblasts from pro-fibroblasts and the subsequent accumulation of extracellular matrix (ECM) proteins (45). Reports suggest that bone marrow-derived mesenchymal stem cells and alveolar differentiated epithelial cells can make phenotypic changes to fibroblasts through EMT (46, 47). EMT is a process that leads to the differentiation of epithelial cells into the mesenchymal phenotype, resulting in myofibroblasts and fibroblasts, and plays a crucial role in repairing damaged epithelial cells (48, 49). One of the primary events during EMT is the loosening of tight connections between epithelial cells, which leads to the onset of cytoskeleton reorganization and reduced epithelial cell polarity (44). During this process, the proteins involved in binding epithelial cells to each other, such as E-cadherin and Zonula occludens-1 (ZO-1), are reduced. At the same time, the morphology of the cells becomes spindle-shaped. The mesenchymal phenotype is characterized by the expression of cytoskeletal proteins such as vimentin and increased deposition of extracellular matrix proteins such as collagen and fibronectin. Mesenchymal markers include αSMA, vimentin, Fibroblast-specific protein (FSP-1), Desmin, procollagen, N-cadherin, and Matrix metalloproteinase (50). Recent evidence suggests that PQ induces EMT in extracorporeal and intrathecal models, which may be an important process in developing PQ-induced pulmonary fibrosis. In addition, TGF-β/Smad signaling may be involved in PQ-induced EMT (51). In a similar study, Tiegang et al. showed that EMT and the Notch1 signaling pathway could play an essential role in PQ-induced pulmonary fibrosis in A549 cells (44). A study published in 2006, reported that thalidomide is effective in vivo and in vitro models of interstitial lung fibrosis (ILF), which can be inhibited the upregulation of HYP protein, prolactin III mRNA, and α-SMA protein induced by TGF-β1 in HFL-F cells, and in addition, inhibits the expression of collagen III mRNA in differential (52). Another hypothesis has been suggested that thalidomide inhibits TGF-β1-induced EMT in AECs (40).

Based on a recent suggestion, Bleomycin induced EMT through downregulating ESRP1 by simultaneously increasing Basic fibroblast growth factor (BFGF) and TGF-β1 in pulmonary fibrosis (53).

c)Effects on cell death and survival pathways

Thalidomide with anti-inflammatory-anti-angiogenesis and pro-apoptotic properties seems to be a suitable candidate for the treatment of IPF. Inflammatory cytokines and angiogenesis have essential roles in the pathological progression of IPF, while the findings indicate that thalidomide has inhibitory effects on the cytokine profile in people with IPF (31, 54, 55). In this regard, Knobloch et al., reported that the underlying mechanisms of the anti-fibrotic effects of thalidomide include decreased regulation of bone morphogenetic protein signaling, increased Wnt and Akt activity, and increased resistance to apoptosis (56). The results of previous studies (shown in Figure1) indicate that the anti-fibrotic effects of thalidomide on pulmonary fibrosis may be related to the suppression of the ERK1/2 signaling pathway (57). In addition, another study showed that thalidomide has an anti-fibrotic effect by suppressing TGF-β1, which in turn induces Smad3 and P38 signaling (15).

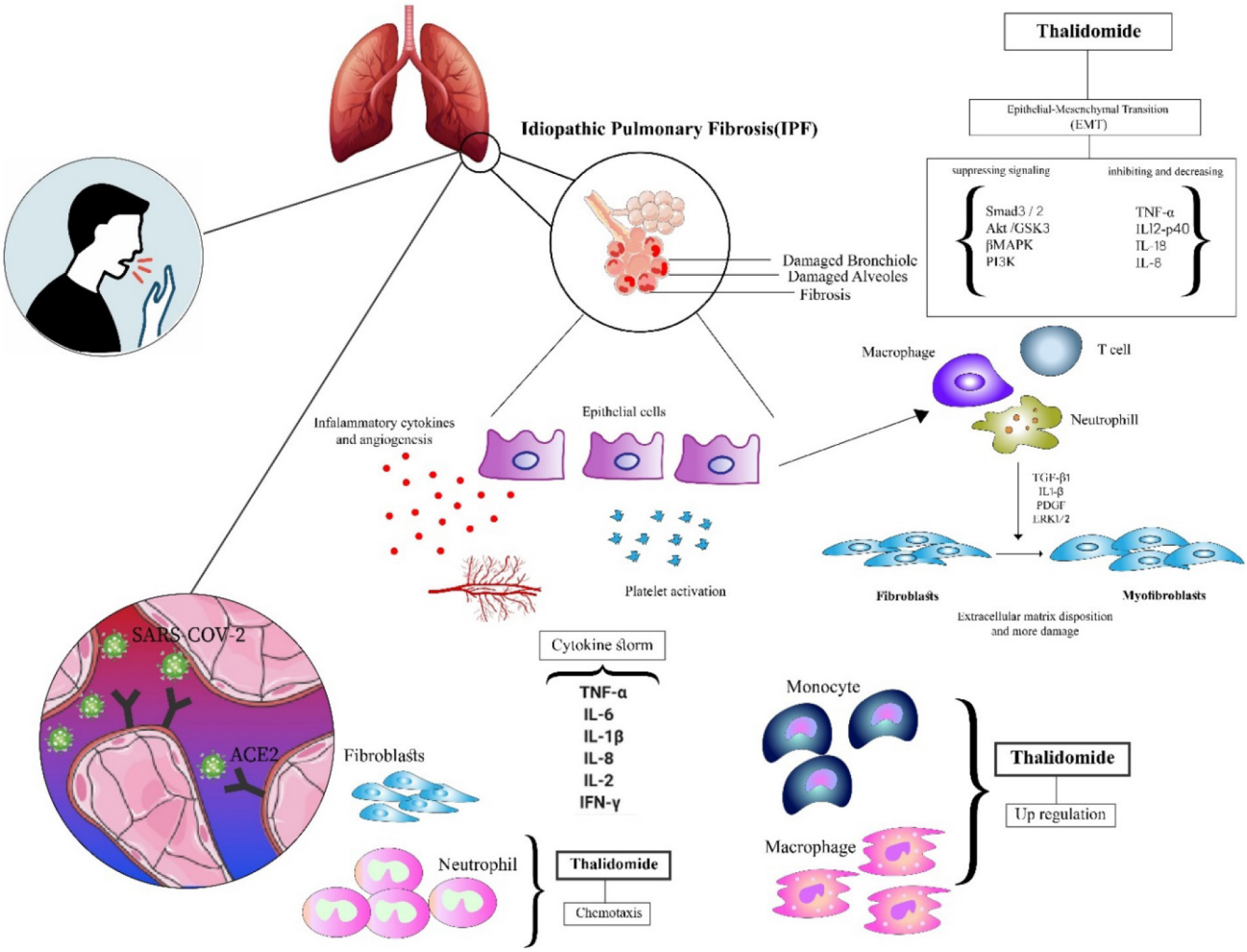

Figure 1. Thalidomide suppression on TGF-β1-induced EMT is related to inhibition of TGF-β1-mediated signaling pathways Smad2 / 3, Akt / GSK-3β, and MAPK. Moreover, by inhibiting and decreasing inflammatory factors including TNF-α, IL-12p40, IL-18, and IL-8 provides a possible role for this potential drug in the pathogenesis of idiopathic pulmonary fibrosis. In addition, thalidomide is known for its concomitant stimulatory effect on T cell proliferation after CD3 activation and its suppressive effect of thalidomide on pro-inflammatory cytokines including interleukin-6, TNF-α and interferon.

d)Effect on Covid-19

Recently, Wuhan, China, has become the epicenter of the new coronavirus (COVID-19) pneumonia, which causes an epidemic illness, that is associated with human-to-human contagious transmission of SARS-CoV-2 along with multiple organ failure, including acute respiratory distress syndrome (ARDS), acute heart damage, and shock (58, 59). Covid-19 pneumonia is the leading cause of death in hospitalized patients (60).

Currently, no specific agents are available for the treatment of COVID-19, while some agents such as antivirals, chloroquine, and immune-regulating agents are under investigation. Moreover, the efficacy of antiviral drugs was not completely satisfactory or sufficient, especially in the later stages of disease progression. Among the available choices, thalidomide is a promising candidate (61-63).

Pulmonary fibrosis is one of the expected consequences after COVID-19 disease, which becomes more likely with underlying diseases, which was especially common in the elderly and high-risk patients. The majority of this population had residual lung tissue damage, severe respiratory pathology and reduced exercise tolerance.

On the other hand, Thalidomide modulates the immune system and is an anti-inflammatory agent (64), making it a possible candidate for reducing lung damage. Glucocorticoids have been consumed during the pandemic of SARS-CoV-2 to limit pulmonary inflammation and suppress immune system responses. Unfortunately, many side effects are associated with this therapy, including osteoporosis and secondary bacterial infections. Moreover, a high dose of glucocorticoids is not recommended as a beneficial approach to alleviating symptoms as they inhibit the immune system and the clearance of pathogens and Viruses (65). Uthoff et al., also studied the effects of thalidomide in lung transplanted dogs. They found that thalidomide was better than corticosteroids at suppressing the immune system early after surgery after lung transplantation, which was associated with a reduced incidence of pneumonia (66).

A recently published case report describes the beneficial effects of thalidomide (100 mg orally once daily) in combination with low-dose glucocorticoids. Due to the beneficial effects of thalidomide, it is necessary to try it in the case of Covid-19 as a therapeutic agent (22).

Thalidomide has been reported as an anti-inflammatory treatment with significant efficacy in many autoimmune disorders such as psoriasis, systemic lupus erythematosus, and inflammatory bowel disease in which the suppressive effect of thalidomide on pro-inflammatory cytokines including interleukin-6, TNF-α and interferon were indicated. In addition, thalidomide is known for its concomitant stimulatory effect on T cell proliferation after CD3 activation (23). The protective effect of thalidomide in combination with antiviral drugs and short-term glucocorticoids on lung damage and COVID-19-induced immune dysfunction has been reported (22).

The common downstream pathway between SARS-CoV2 and H1N1 is that infected cells can initiate a "cytokine storm," leading to severe post-infection complications (25).

There is no exact definition for cytokine storm. Cytokine storm syndrome refers to a hyperactive immune response condition characterized by releasing a large number of interferons, interleukins, tumor necrosis factors, chemokines, and several other mediators. These mediators are part of an innate immune response required for the efficient clearance of infectious agents (67). Cytokine storm causes injury to host cells due to high levels of released cytokines and reaching the appropriate treatment to regulate the immune system has become complicated and challenging.

After Cellular entry of SARS-CoV-2, the immune response activates inflammatory cytokine production accompanied by a weak interferon response. The pro-inflammatory immune responses of pathogenic Th1 cells and intermediate CD14+ CD16+ monocytes are also mediated by membrane-bound immune receptors and downstream signaling pathways (68). The penetration of macrophages and neutrophils into the pulmonary epithelial tissue ends up triggering a cytokine storm.

Activation of nuclear factor kappa-light-chain enhancer of activated B (NF-κB) leads to the upregulation of a variety of antiviral genes, therefore, it is commonly regarded as a major regulator of the innate immune system to infection. However, an uncontrolled immune response causes more damage to host cells than the replication of the virus would (69). The anti-inflammatory effects of thalidomide on the H1N1 influenza virus caused by lung injury in mice showed that thalidomide greatly improved survival, infiltration of inflammatory cells and cytokines (e.g., IL-6, TNF-α), and Reduces chemokine and inhibits p-NFκB p6 activation (26, 70).

Conclusion

Through our study different aspects of thalidomide's ability as a promising drug have been observed. Therefore, it might be a potential drug agent that can reduce persistent cough and lung damage, improving the quality of patients' life. It appears to process the mechanism by blocking the inflammatory response and controlling damage in pulmonary tissue in pulmonary disease, especially in Covid-19. In further studies, researchers must focus on the clinical aspects of using this drug in Covid-19 management to improve the clinical presentation of Covid-19 patients.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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PLEASE CITE THIS PAPER AS:

Rashidipour N, Karami-mohajeri S, Farsinejad A, Alizadegan D, Taebi M, Amiri-Ardekani E. Potential Therapeutic Uses of Thalidomide for Pulmonary Fibrosis. J Pharm Care 2023;11(2):102-109.