Thalidomide-Revisited: Are COVID-19 Patients Going to be the Latest Victims of Yet Another Theoretical Drug-Repurposing?

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Abstract

The new pandemic coronavirus disease 2019 (COVID-19) is a worldwide threatening health issue. Early progression of this disease starts in the lung airways with an exaggerated inflammation, triggered by the viral infection and characterized by a “cytokine storm” that can lead to lethal lung injuries. In the absence of an effective anti-viral molecule and until the formulation of a successful vaccine, anti-inflammatory drugs might offer a complementary tool for controlling the associated complications and thus decreasing the subsequent fatalities. Drug repurposing for several molecules has emerged as a rapid temporary solution for COVID-19. Among these drugs, Thalidomide, a historically emblematic controversial molecule that harbors an FDA approval for treating Erythema Nodosum Leprosum (ENL) and multiple myeloma (MM). Based on only one-case report of positive outcomes in a patient treated amongst others with Thalidomide, two clinical trials on the efficacy and safety of Thalidomide in treating severe respiratory complications in COVID-19 patients were registered. Conversely, the absence of any substantial, promising evidence on Thalidomide usage in that context along with the discontinued studies on the efficiency of this drug in similar pulmonary diseases might cause a significant obstacle for carrying on clinical studies. In this review, we will discuss the theoretical effectiveness of this drug in attenuating inflammatory complications that are encountered in patients with COVID-19 while pinpointing the lack of evidence that is needed to move forward with this drug.

Introduction

The sudden epidemic outbreak of the new coronavirus disease 2019 (COVID-19) in Wu Han City, China, has rapidly spread all over the world, leading to one of the worst pandemic outbreaks since the Spanish Flu 100 years ago (Yang et al. 2020). The culprit infectious pathogen, which causes severe acute respiratory syndrome (SARS), is yet another coronavirus (SARS-CoV-2) very similar to the previous viruses that caused the epidemic SARS in 2003 and MERS (Middle-Est Respiratory Syndrome) in 2012(Jin et al. 2020). This highly contagious disease has spread throughout China and reached around 200 other countries within two months only (W. Zhang et al. 2020). Based on that, the World Health Organization (WHO) declared the COVID-19 outbreak as a pandemic on March 11, 2020. Till April 3rd, the confirmed number of cases surpassed 1 million globally and resulted in more than 50,000 deaths (WHO 2020). Fortunately, the severity of this disease is only encountered in about 20% of the cases where these patients develop respiratory failure, septic shock, and multi-organ dysfunction. According to the data reported so far, older adults, particularly those with severe underlying health conditions, are more prone to the lethal manifestations of this viral infection that are presented mainly by a severe inflammatory reaction (W. Zhang et al. 2020). In this review, we will discuss the pathological progression of this disease along with the activated inflammatory response that underlies the lethal complication of COVID-19. We will then evaluate the current status of Thalidomide usage as an anti-inflammatory therapy for COVID-19 induced pneumonia and acute lung injury (ALI).

COVID-19 and The Cytokine Storm: A Role for Anti-Inflammatory Drugs in the Treatment?

Since the human respiratory system is the primary target for coronavirus pathogens, abnormal respiratory findings are highly detected in COVID-19 patients. The initial pulmonary symptoms include a dry cough and coarse breathing sounds of both lungs(Rothan and Byrareddy 2020). The progression of this infection starts with mild manifestations in the lungs, including a) edema b) proteinaceous exudate with globules c) patchy inflammatory cellular infiltration, and d) moderate formation of hyaline membranes(Tian et al. 2020). In more advanced cases, pulmonary ground-glass changes are accompanied by bilateral diffuse alveolar damage with edema, pneumocyte desquamation, hyaline membrane formation, interstitial lymphocyte infiltration, and multinucleated syncytial cells in the lungs(R. Zhang et al. 2020; Yi et al. 2020). At the site of injury, extensive infiltration of neutrophils and macrophages is detected and is correlated with an increased number of neutrophils, monocytes, and the suppressed cell counts of CD4 and CD8 T and natural killer (NK) cells in the peripheral blood of patients with severe infection(Channappanavar and Perlman 2017; W. Zhang et al. 2020). The uncontrolled release of pro-inflammatory cytokines named as the “cytokine storm”, starts initially in the immunopathological lungs and spreads throughout the body via the systemic circulation(“Pathogenic T Cells and Inflammatory Monocytes Incite Inflammatory Storm in Severe COVID-19 Patients | National Science Review | Oxford Academic,” n.d.). This storm is accompanied by an exaggerated response from both T-cells and macrophages, all in all causing amongst others apoptosis of epithelial and endothelial cells and ending up with a lethal acute lung injury. Among the highly induced pro-inflammatory cytokines that are elevated in the epithelial cells of patients’ airway are: Interleukin (IL)-1β, IL-2, IL-6, IL-8, Tumor Necrosis factor-alpha (TNF-α), and Interferon alpha/beta (IFN-α/β) leading to an enhanced oxidative stress status(R. Zhang et al. 2020). This process will be followed by an extrapulmonary systemic hyper inflammation syndrome, which requires a blockage of the exaggerated cytokine storm to reduce the death rate among COVID-19 patients.

Although this viral infection might be primarily beaten by anti-viral and respiratory supportive therapies yet, the cytokine storm that is associated with the severe form of the disease should be also tackled using anti-inflammatory drugs(W. Zhang et al. 2020). As such, drug repositioning for several known anti-inflammatory drugs emerged. The advantages of drug repositioning strategies rely mainly on the low costs, the reduced time to reach the market as the clinical trials on these drugs is already applied, and the existence of pharmaceutical supply chains for formulation and distribution(Phadke and Saunik 2020). For these reasons, several clinical trials have been conducted to inspect the efficiency of previously known anti-inflammatory and anti-viral drugs in treating COVID-19 lethal complications. Among the tested anti-inflammatory drugs are the non-steroidal anti-inflammatory (NSAID) drugs, glucocorticoids, chloroquine/hydroxychloroquine, immunosuppressants, and inflammatory cytokines antagonists(Favalli et al. 2020). Although some of these drugs have shown to be efficient in COVID-19 treatment, yet the accompanying adverse side effects or the reported non-significant outcomes did not support their further usage(Russell, Millar, and Baillie 2020; D. Wang et al. 2020; WHO 2020). So far, chloroquine and hydroxychloroquine usage have been highly applauded and was given an emergency approval by the FDA to slow the progression of COVID-19 among critical cases. Yet, the anti-viral and anti-inflammatory effects of these drugs still require more clinical and pre-clinical studies to confirm their effectiveness and to rule out any associated severe side effect that might limit their usage(W. Zhang et al. 2020). In particular,

we will review herein the potential of Thalidomide in diminishing the unpleasant outcomes of COVID-19.

Thalidomide Between the Past and the Present

Sixty years ago, a worldwide epidemic was attributed to the usage of Thalidomide (α-(N-phthalimido glutarimide), a synthetic glutamic-acid derivative. This drug was developed in Germany and was distributed to 46 different countries as a sedative drug for treating morning sickness in pregnant women(Nemer and Khalil 2019). From the time Thalidomide was marketed in 1957 till the date of its withdrawal in 1961, over 10,000 children were affected with severe congenital deformities including stunted limb development, cleft lip and palate, abnormal eyes and ears and congenital heart diseases(Khalil et al. 2017). In that time, Thalidomide safety was only tested in rodent models and was not approved by the FDA due to the reported peripheral neuropathy in adults(Matthews and McCoy 2003). Indeed, this drug caused a remarkable shift in drug testing strategies since it pinpointed for the first time on the existence of species specificity in reaction to medications.

Although Thalidomide was removed from the market at that time, research studies continued to tackle its effectiveness in other conditions, including autoimmune disorders, such as chronic graft versus host disease and rheumatoid arthritis(Ito, Ando, and Handa 2011). Moreover, its efficacy was revealed in several dermatologic conditions, including aphthous stomatitis, Behçet's syndrome, lupus erythematosus, prurigo nodularis, Kaposi's sarcoma, pyoderma gangrenosum, and lichen planus(Paravar and Lee 2008; M. Chen, Doherty, and Hsu 2010). The promising reported results encouraged further testing of this drug in treating tuberculosis, human immunodeficiency viruses (HIV), and several cancer cases like multiple myeloma, glioblastoma prostate, and lung cancer. While the outcomes varied between the tested diseases, the remarkable success in treating Erythema nodosum leprosum (ENL) and multiple myeloma (MM) guaranteed its FDA approval as a treatment of choice for these two conditions in 1998 and 2006, respectively(Semeraro et al. 2013). However, due to its known serious teratogenicity, the prescription and utilization of this drug are still under strict control by the System for Thalidomide Education and Prescribing Safety (STEPS) program that monitors prescribing, dispensing, and usage of this drug (Ito, Ando, and Handa 2011).

The Potent Anti-inflammatory Properties of Thalidomide

Numerous studies aroused concerning the mechanism of action of this drug, yet its exact mechanism, whether in treating these diseases or in triggering congenital malformations, is still debatable and not fully understood(Khalil et al. 2017). Among the most successful adopted mechanisms of Thalidomide is its potent anti-inflammatory activity that is achieved by its extensive involvement in both innate and adaptive immune systems. Basically, Thalidomide can downregulate the phagocytic activity of immune cells, inhibit antimicrobial mediators' release from neutrophils, and enhance the number of natural killer cells(Paravar and Lee 2008). Regarding neutrophils, Thalidomide can inhibit their chemotaxis to the site of inflammation, suppress their reactive oxygen species (ROS) generation, and modulate their interaction with the endothelial cells at the site of inflammation(Kumar and Chhibber 2008; Paravar and Lee 2008)

As for cytokines and chemokines, Thalidomide has proven to have a key regulatory effect on their production mainly through inhibiting cyclooxygenase enzyme-2 (COX-2) and downregulating soluble levels of mediators such as Prostaglandin E2 (PGE2), TNF-α, IL-1, IL-6 (Paravar and Lee 2008). Among the most affected pro-inflammatory cytokines stands TNF-α as the primary target. The latter could be either degraded at the mRNA level or downregulated as a subsequent effect to the inhibited NF-κ β pathway that is highly disrupted by Thalidomide. (Majumder et al. 2012). Regarding the adaptive immunity, studies on the impact of Thalidomide on B cells is not well elaborated, but a demonstrated downregulatory effect on antibody production was presented by the decreased serum IgM concentrations(SHANNON et al. 1981). On the other hand, studies on the involvement of T cells moved an extra mile to demonstrate an independent co-stimulation of T-cells by Thalidomide, which was difficult to interpret, given its proven ability to treat inflammatory disease conditions. Thalidomide was initially thought to be associated with increased production of IL-4 and IL-5 and a decreased IFN-γ production as it primarily promotes T-helper cells type 2 (Th2). Afterward, an overwhelming amount of data supported the differentiation of T-helper cells type 1 (Th1) and the subsequent increase in IFN-γ and IL-2 levels. Moreover, some studies done on alveolar macrophages from patients with interstitial lung disease revealed a suppressed IL-12 production in response to Thalidomide (Paravar and Lee 2008).

Thalidomide as an Immunomodulatory Drug in pulmonary Diseases and Lung Injuries

Thalidomide effectiveness was tested in several pulmonary diseases and lung injuries. Among these studies is the one done on the induced acute lung inflammation by *Klebsiella pneumoniae* in mice. The effective anti-inflammatory activity was presented by the decreased neutrophil influx to the lungs, the suppressed production of malondialdehyde as well as nitric oxide, and the inhibited myeloperoxidase activity(Kumar and Chhibber 2008). Similarly, Thalidomide treatment for mice with Paraquat (PQ) induced pulmonary inflammation and fibrosis revealed a decreased production of inflammatory and fibrogenic cytokines in lung tissue including TNF-α, IL-1β, IL-6, TGF-β1 as well as myeloperoxidase (MPO), nitric oxide (NO), and hydroxyproline contents which prevented the progression of PQ-induced pulmonary injury(Amirshahrokhi 2013). Likewise, Thalidomide was able to reduce macrophages, and lymphocytes count in bleomycin (BLM)-induced pulmonary fibrosis mice model and to suppress IL-6, IL-8, TNF-α, and TGF-β levels in the bronchoalveolar lavage fluid (BALF). The detected attenuated pulmonary fibrosis and the inhibition of the collagen deposition in the BLM-treated mouse lung tissues were attributed to Thalidomide effect on suppressing inflammation and oxidative stress(Dong et al. 2017). On the clinical level, 23 patients with Idiopathic pulmonary fibrosis (IPF) reported an improved cough and respiratory quality after being treated with Thalidomide. At the same time, the associated side effects were tolerable, including only constipation, dizziness, and malaise(Horton et al. 2012).

Regarding pulmonary viral infections, Thalidomide was able to suppress the induced pulmonary inflammation of the H1N1-induced lung injury in mice. The anti-inflammatory activity was achieved through suppressing the expression of cytokines and chemokines released by epithelial and inflammatory cells such as TNF-α, IL-6, RANTES, IFN- α, and IP-10. This inhibition was attributed mainly to the suppressed NF-κ β activity that usually promotes inflammation and viral gene expression(Zhu et al. 2014).

Thalidomide and COVID-19

Since Thalidomide revealed a promising outcome in several cases of pulmonary diseases and lung injuries, this drug was suggested as a potential anti-inflammatory drug for COVID-19 patients. Hypothetically, the potent anti-inflammatory activity of this drug and the mechanism of action that it follows for attenuating exaggerated inflammation and cytokine storms, makes it a good candidate for treating COVID-19 respiratory complications. The above-experimented cases are characterized by similar disease manifestations, pathogenicity, and progression as that encountered in COVID-19 cases. For example, diffuse interstitial lung disease (ILD) is characterized by pulmonary fibrosis that includes inflammation, fibroblast proliferation, and excessive collagen deposition. Since inflammation and oxidative stress are responsible for the high mortality rate associated with this disease, Thalidomide as an immunomodulatory drug was proposed as a potential treatment for this lethal condition(Dong et al. 2017). Similar to COVID-19, Paraquat (PQ) poisoning is known to be associated with respiratory distress due to the alveolar epithelial cell disruption, the hemorrhage, and the infiltration of inflammatory cells into the interstitial and alveolar spaces which ends up with fibroblastic proliferation, collagen deposition, and progressive fibrosis. The exaggerated inflammatory process in PQ poisoning is mainly induced by the generation of reactive oxygen species (ROS), induction of intracellular transcription factors such as NF-kB mediators, and the de-regulation of many pro-inflammatory agents including inducible nitric oxide synthase (iNOS), inflammatory cytokines, and cyclooxygenase (Amirshahrokhi 2013). In both (PQ) and (BLM)-induced pulmonary fibrosis models, the core pro-inflammatory cytokines of the underlying pathogenicity are common with known targets of Thalidomide, such as TNF-α, IL-6, IL-1β, and TGF-β (Dong et al. 2017; Amirshahrokhi 2013). On the other hand, the phase of similarity between COVID-19 and H1N1 is that cells infected with any of these two viruses can initiate a “cytokine storm,” leading to severe post-infection complications(Q. Liu, Zhou, and Yang 2016). Based on the above, Thalidomide was suggested among the potential drugs to be tested in treating respiratory complications associated with COVID-19.

What is the Current Status of Thalidomide in the COVID-19 Crisis?

Recently, a case report presented a single Chinese patient with severe COVID-19 pneumonia treated with Thalidomide in combination with low-dose glucocorticoids and anti-viral therapy(C. Chen et al. 2020). Apparently, these results presented Thalidomide as a promising therapeutic strategy to treat COVID-19 severe complications. The administrated 100 mg of Thalidomide, along with the low dose methylprednisolone, improved the clinical condition by increasing the oxygen index rapidly and by inhibiting anxiety, nausea, and vomiting without any reported side effect. The anti-inflammatory and immunoregulatory activity of Thalidomide was revealed by the reduced inflammatory cytokines (IL-6, IL-10, and IFN-γ) and the recovered lymphocytes count, which caused a reduction in pulmonary effusion symptoms. On the other hand, the sedative nature of this drug and its antiemetic activities helped in calming down the anxious patient, thus, reduced oxygen consumption, and alleviated the digestive symptoms(C. Chen et al. 2020). Meanwhile, a couple of phase II clinical trials are registered to evaluate the effectiveness of Thalidomide as an immunomodulatory drug for treating patients with COVID-19 infection. The first clinical trial (NCT04273581) is concerned about the efficacy and safety of this drug in combination with low-dose hormones for treating severe COVID-19 cases while the second trial

(NCT04273529) will investigate the efficacy and safety of this drug as an adjuvant treatment for moderate new coronavirus (COVID-19) pneumonia(Xia 2020a, 2020b).

Critical Limitations to be considered When using Thalidomide in COVID-19 Cases

So far, numerous studies were conducted on the efficiency of Thalidomide in treating hundreds of diseases, yet, the FDA approval remains limited for only two conditions that are MM and ENL cases. Although this anti-inflammatory orphan drug has proven its effectiveness in some pulmonary inflammatory diseases, including IPF, severe H1N1-induced pneumonia, and paraquat poisoning lung injury, however, these studies were discontinued and stopped at the *in vivo* levels. None of the deliberated results was able to secure the testing of Thalidomide on the above diseases at a clinical level. For example, and back to 2014, treating mice infected with H1N1 by Thalidomide resulted in an auspicious outcome, but studies in this area were stopped without any explanation(Zhu et al. 2014; Amirshahrokhi 2013; Horton et al. 2012).

Similarly, the recommendation for using Thalidomide to treat IPF associated cough did not pass the panel vote for treating interstitial lung disease associated cough as per the CHEST guideline methodology (Birring et al. 2018). Moreover, our group has recently raised concerns about worsening the health condition of lung cancer patients by Thalidomide based on an identified potential molecular target in that context(Nemer and Khalil 2019). Thus, using this drug for treating a respiratory condition such as that encountered by COVID-19 should be further investigated before proceeding.

Currently, the available case report for Thalidomide usage in treating severe COVID-19 is not sufficient to promote this drug usage due to several reasons. Aside from being a non-peer reviewed article tackling only one COVID-19 patient, Thalidomide combination with corticosteroids might be a drawback since the latter was reported to cause lung injury, and thus, its usage is not clinically supported (Russell, Millar, and Baillie 2020). Moreover, the two clinical trials that aim in studying the efficacy and safety of this drug in COVID-19 patients were initiated by the same author who published the discussed single case-report. These two trials were registered on February 18,2020, but to this date, none of them has started the recruitment procedure. This delay in initiating such trials at a stage where thousands of severe cases are in need of promising treatment might question Thalidomide potentials in this area. Additionally, no studies were previously carried on the beneficial use of Thalidomide on the related SARS-Covid2 viruses, namely those which caused SARS and MERS, casting more doubts about its potential. In addition, the known teratogenicity of this drug should be highly taken into consideration when assigning the target population who can benefit from this treatment. Excluding pregnant and breastfeeding women and patients with severe liver disease, thromboembolism, or lung cancer might discourage further investigations (Nemer and Khalil 2019)

On a separate note, it is well known that in such cases of viral infection, an effective treatment approach should comprise both anti-viral and anti-inflammatory activities. This combination will prevent the replication and progression of the virus in the host cells and, at the same time, will suppress the overactive cytokine production and reduce the disease aggravation. (X. Wang and Ding 2020; J. Liu et al. 2020) Thus, since Thalidomide lacks an anti-viral effect, further

investigations on its usage should take into consideration combinational approaches to help overcome the virus burden.

Conclusion

Although the ideal solution for this crisis remains to be an effective vaccine against COVID-19 or at least a new molecule that prevents the entry of the virus to human cells and/or its destruction early on, yet these strategies are time-consuming. The rapid progression of this crisis is forcing temporary compensatory actions such as drug repurposing approaches and/or combining adjuvant-efficient anti-inflammatory drugs with anti-viral therapies. Yet, repurposing Thalidomide based on the first glance at its proven efficiency in some pulmonary inflammatory conditions is inadequate, especially if we look in-depth on the reported results and try to question the outcomes of these data at the clinical level. Moreover, when dealing with anti-inflammatory drugs that lack anti-viral activity, like in the case of Thalidomide, one should always consider combinational approaches for a more promising outcome.

All in all, although theoretically the anti-inflammatory and the immunomodulatory properties of Thalidomide allow this drug to be a potential candidate for treating the complications of COVID-19, yet many limitations should be resolved before proceeding into a clinical setting. At this stage, the devastating rapid outcome of COVID-19 is exceptionally granting the utilization of some drugs on the basis of "possible benefit that can outweigh the risk". However, this urgent need for rapid solution should not permit hasty medical decisions as this might lead to an additional man-made crisis. Thus, repurposing some drugs could be beneficial only if appropriate interpretation of literature is accompanied by supportive data from well-designed clinical trials.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

All co-authors (AK, AK and GN) have made significant contributions to writing this manuscript.

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