REVIEW ARTICLE

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Evaluation the plausibility of repurpose of levamisole and niclosamide in treatment of Covid-19

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ABSTRACT

Since the world health organization declared the pandemic of covid 19, many drugs have been tested and re-evaluated to find effective treatment for the novel corona virus infection. Niclosamide and Levamisole which are FDA approved anthelmintic drugs have been evaluated by many researchers and agencies to repurpose of these drugs as additional options for existing treatment strategy used for patients with Covid-19. Hence we are trying in this review to introduce most reports that evaluated the use of Niclosamide and Levamisole for treatment of patients infected with Covid 19. We concluded that the encouraging studies regarding the repurpose of the two drugs may highlighting for further studies that can widening the options for existing treatment strategy used for patients with COVID-19.

1. INTRODUCTION

Niclosamide is an oral antihelminthic medicine that included in the essential medicines list of WHO. The drug was approved in 1982 by the FDA as a therapy for tapeworm diseases that infect humans [1]. The drug besides treating safely millions patients with parasitic infections worldwide, its broad clinical applications in the treatment of many diseases and manifestations such as cancer, bacterial, viral infection and various metabolic disorders, have been shown by recent studies [2-4]. Levamisole is an antihelminthic drug that was produced by Janssen and first used in 1969 as an active agent against many nematodes that infect animals and man [5-9]. The drug then was commonly applied to treat different infections caused by parasites, viruses, and bacteria [10]. Levamisole was used in 1970s and 1980s as an antirheumatic therapy for patients with rheumatoid arthritis [9]. In 1990 the drug got the approval by the FDA as an adjuvant treatment for colon cancer [11], since then Levamisole is prescribed together with other medicine as a therapy for various cancers [9,10]. The immunomodulatory effects of levamisole have been evaluated in attempt to study its effect in enhancing protective immune responses. The drug showed positive results with various rates of success in the treatment of various diseases in animals and human [10,12-14]. In 2000 Levamisole was withdrawn from the American market because the possibility to cause serious side effects [9].

Both drugs [Niclosamide and Levamisole] were found to have a role in suppression of viral infections through direct effect or by the immunostimulant effect respectively. Recently many research have been experimented the plausibility of repurpose of these drugs in treatment of patients infected with SARS-CoV-2. Hence we are trying in this review to introduce most reports that evaluated the use of Levamisole and Niclosamide for treatment of patients infected with Covid 19.

2. NICLOSAMIDE (NCS)

2.1. Niclosamide's Mechanism of Action

Niclosamide acts in prevent glucose consumption, oxidative phosphorylation, and anaerobic metabolism in the target worms [15]. Evaluation of the antineoplastic effect of NCS in many human malignant cancers indicated that NCS exerts anticancer activity by suppressing many oncogenic signaling pathways at the same time [4,16,17]. NCS action against viruses shows mainly through its role as a carrier of proton and that may lead to neutralize the acidity of endosomes which prevent endocytosis through influencing on trafficking of endosome and this inhibits the entrance of viruses [18,19,20].

2.2. Niclosamide Role in Viral Infections

Niclosamide has been evaluated against a wide scale of viruses and found to has a role in inhibition the entrance and the replication of many viruses including Herpes Simplex Virus(HSV-2) [18], Dengue Virus (DENV) [19,21], ZikaVirus (ZIKV) [22,23,24], Chikungunya Virus (CHIKV) [25], Lassa and Ebola Viruses [26], Epstein-Barr Virus (EBV) and Kaposi's Sarcoma-associated Herpesvirus (KSHV) [27], and Japanese Encephalitis Virus (JEV) [28]. Evaluation of Niclosamide against Coronaviruses was also studied. At a concentration of 1.56 μM, NCS found to be able in prevention SARS-CoV multiplication and completely terminated antigen formation of the virus. According to the study, the inhibiting activity was noticed even when NCS was added three hours following the inoculation of cells with SARS-CoV [29]. In Vero E6 cells, the cytopathogenic effect of SARS-CoV has been suppressed at 1 μM of NCS. And with an EC50 value of minimal than 0.1 μM, the replication of SARS-CoV was found to be inhibited [30]. Another study found that NCS didn't reveal clear inhibitory potency towards SARS-CoV(3CL protease) even up to 50 μM concentration. The study concluded that the drug may acts through different mechanism against the virus [31]. In Vero B4 cells, the evaluation of 10 μMNCS e against MERS-CoV demonstrated up to 1000-fold inhibition of MERS-CoV replication at 48 h p.i [32].

2.3. Evaluation of Niclosamide on Covid-19

Due to prior studies that described NCS as an encouraging efficient therapy or SARS-CoV infection [29], and since SARS-CoV-2 genome sequences have been found to match with SARS-CoV in about 79.6% [33]. Besides that Covid-19 threat is still push scientists around the world to find more than successful therapy. All these reasons as well to NCS wide effects against viruses gave envision that NCS may be repurposed and developed as effective antiviral drug against COVID-19 if approved experimentally and clinically [34]. Recent study suggested that NCS may have a feasible activity towards COVID-19 probably through prevents the entrance of virus via changing the pH of endosomes and suppresses the multiplication of the virus via autophagy prevention. This plausible mechanism need to be confirmed clinically to evaluate the efficiency of NCS against COVID-19 [35]. Group of researchers in The University of Texas at Austin, Division of Molecular Pharmaceutics and Drug Deliver are attempting to develop a mechanism that make the intake method of NCS reach directly to the lungs. This mechanism could demonstrate effectiveness at management and control the critical manifestations in COVID-19 patients [36]. Recently, an inhaled NCS -Lysozyme formulation has been developed and revealed encouraging results in vitro and in vivo against SARS-CoV-2 [37]. Another developed nanoparticles formulation of NCS demonstrated an in vitro effectiveness against SARS-CoV-2 replication [38]. Another group of investigators in clinical trial which still waiting to be approved hypothesized that the antiviral activity of NCS may be extended to COVID-19 [39]. A recent study suggested that NCS may potentially inhibit the entrance of SARS-CoV2 through the interference with pH-dependent endocytic pathway that the

virus depends on during its entrance [40]. South Korean Daewoong Pharmaceutical Co. Ltd. has collaborated with other companies for conducting Phase I clinical trial of a long-acting intramuscular formulation of NCS. The injectable intramuscular (IM) formulation of NCS demonstrated promising results that successfully removed the virus from lungs in animal tests. Daewoong researchers worked on quick development of the formulation to reach the stage of "First-in-Human" evaluation. The successful completion of this work can immensely facilitate COVID-19 disease treatment [41].

3. LEVAMISOLE (LMS)

3.1. Levamisole's Mechanism of Action

The paralytic effect of the drug is the main antiparasitic action against the target worms. The drug acts as neuromuscular blocking agent (their revocable, noncompetitive depolarization type) which results in persistent contract of the worm somatic muscles leading to paralysis. It is also prevents succinate synthesis [42]. Chemically the immune-stimulant effect of LMS shows through forming a thymopoietin-mimetic tertiary structure. Thymopoietin compound influences several immunological cells such as neutrophils, macrophages, and lymphocytes; hence the enhancement of phagocytosis and regulatory T cells are probably the medicinal effect of this compound [43].

3.2. Levamisole Role in Viral Infections

The role of LMS in viral infection has been evaluated through its action as immune-stimulant agent. The drug found to enhance the host defense mechanisms in10-day-oldrats and gave the rats protection against HSV-2 [44]. Using of LMS alone demonstrated stimulation of antibody formation against influenza A and B viruses. The stimulation is probably due to provoking of immunocompetent memory cells [45]. Studying the ability of LMS to enhance monocyte chemotaxis in vitro, demonstrated that the drug efficiently prevented the chemotaxis dropping induced by influenza virus when incubated with normal monocytes. LMS also showed improving in monocyte chemotaxic reaction in vitro. The cells were taken from confirmed acute influenza cases, which indicate that LMS may be helpful in acute influenza cases through boosting the performance of cellular immunity [46]. LMS also found to enhance production of IFN-γ through its role in macrophages activation which in turn provokes the growing of cells participated in cellular mediated immunity [47,48]. Another study noticed an increase in CD4 (+)/CD8 (+) ratio after one course therapy with liniment LMS, and stated that the drug acts in boosting cellular immune role in chronic hepatitis B individuals [49]. Other published paper found that giving LMS alone to chronic hepatitis B children at 2.5 mg/kg/day per os, three fold weekly for 90 days; didn't show any cellular immunostimulation in them. While a combination of LMS plus HBs Ag vaccine demonstrated a notable increase CD3, CD4 and CD4/CD8 ratio with remarkable depression in CD8 in chronic hepatitis B sets [50]. More studies found the same encouraging results on chronic hepatitis B (CHB) persons and healthy carriers if received LMS and vaccine [51]. For inactivated viral vaccines, humoral and cell-mediated responses found to be improved by using modified LMS adjuvant [52]. LMS and killed-virus-based antiviral vaccines combination may contribute in to promoting Th1-biased immune responses depending on the optimal LMS dosage [53]. A research included serious forms of influenza demonstrated that LMS can induces interferon efficiently, and advised the usage of the drug in combination treatment, particularly for those with a severe course [54]. After repeated regimen administration with LMS, the experimentally infected quails with H9N2 AI viruses showed CMI responses enhancement towards H9N2 AI viruses with reduction in virus discharging duration [55].

3.3. Evaluation of Levamisole on Covid-19

Very limited number of published reports indicated the assessment of LMS on covid -19. As an antiviral agent, LMS found as an effective therapy in treating diarrhea [56], and in improving cough and dyspnea in COVID-19 patients [57]. A study, based on the effect of LMS as an immune-stimulant, concluded that this drug may help the immune system of COVID-19 patients to overcome the hidden virus by establishing a strong response [58]. Few clinical trials in study level that are still waiting to be published is tested the immune-stimulant activity of LMS on patients

with COVID-19. One of these trials suggested that LMS can play a role in enhancing the immunity in covid-19 patients through increasing the number of lymphocytes and can also interferes with virulence factors of the virus [59]. Other trials have been evaluated the prophylactic and the therapeutic role of LMS on COVID-19 patients and the results is still expected [60,61]. Evaluation of LMS as antiviral and immune-stimulant drug for patients with covid-19 needs further studies to recognize the specific role of the drug during infection.

4. CONCLUSION

Considerable and exceptional global researches have been undertaken during the SARS-CoV-2 pandemic. Facilitating cooperation with coordination between scientists and global health professionals and accelerating efforts by WHO has been achieved on a scale not seen before. All these efforts have been succeeded in December 2020 to provide the first vaccine that paved the road to initiate a mass programme of vaccination around the world and until now around 13 types of vaccines are available and taken in different countries [62]. Although up to the 25 January 2022, about nine and half billion vaccine doses have been provided, COVID-19 virus extensively expanded to more than 200 countries, infected around 350 million cases and resulted in more than five and half million deaths [63,64]. The huge increase in numbers of infected and dead people as well the continuous appearance of different variants of the virus is still urges the need to find an effective treatment that eliminate COVID-19 entirely and is also still fuels the researchers around the world to search for promising drugs that can participate in the control of COVID-19 outbreak completely. So we believe that highlighting on the latest encouraging studies of evaluation of Niclosamide and Levamisole and their plausibility of repurpose in treatment of patients with Covid 19, may attract more attention for wider clinical studies on these drugs. Testing each of these drugs alone or in combination with other drugs should also consider in these studies. Providing a promising treatment for COVID-19 from already existing drugs may give additional options for existing treatment strategy used for patients with COVID-19.

AUTHOR CONTRIBUTION

Concept: ABA, SEK; Design: ABA, SEK; Supervision: SEK; Data Collection and/or Processing ABA; Analysis and/or Interpretation: ABA, SEK; Literature Search: ABA; Writing: ABA; Critical Reviews: SEK..

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CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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