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General review

Potential use of ivermectin for the treatment and prophylaxis of SARS-CoV-2 infection

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ABSTRACT

Purpose of the study: Currently no treatment has been proven to be efficacious for patients with early symptoms of COVID-19. Although most patients present mild or moderate symptoms, up to 5-10% may have a poor disease progression, so there is an urgent need for effective drugs, which can be administered even before the onset of severe symptoms, i.e. when the course of the disease is modifiable. Recently, promising results of several studies on oral ivermectin have been published, which has prompted us to conduct the present review of the scientific literature.
Methods: A narrative review has been carried out, focusing on the following four main topics: a) short-term efficacy in the treatment of the disease, b) long-term efficacy in the treatment of patients with post-acute symptoms of COVID-19, c) efficacy in the prophylaxis of the disease, and c) safety of ivermectin.
Results: The reviewed literature suggests that there seems to be sufficient evidence about the safety of oral ivermectin, as well as the efficacy of the drug in the early-treatment and the prophylaxis of COVID-19.
Conclusions: In the view of the available evidence, the Frontline COVID-19 Critical Care Alliance (FLCCC) recommends the use of oral ivermectin for both prophylaxis and early-treatment of COVID-19. Further well-designed studies should be conducted in order to explore the efficacy and safety of invermectin at low and high doses, following different dosing schedules, in both, the short and long-term treatment.

Introduction

Ivermectin is a macrocyclic lactone with a broad-spectrum antiparasitic pharmacological activity [1]. It is mainly indicated for the treatment of onchocerciasis, strongyloidiasis, ascariasis, cutaneous Larva Migrans, filariasis and scabies with a standard dose of 150-200 μg/kg) depending on the indication) [2]. It is the safest and most effective semi-synthetic derivative of the entire avermectin class. Marketed since 1981, its low cost, high efficacy and safety, and the marked helminth tropism (therefore with almost no impact on human biochemistry) have led to the inclusion of the drug in the 21st World Health Organization List of Essential Medicines [3].

In addition to the antiparasitic effect, it also appears to have an antibacterial effect [4], and antiviral and anticarcinogenic activity [5], and it is particularly useful for treating certain chronic diseases as allergic skin inflammatory diseases T cell mediated, (produced by inhibition of T−cell activation, proliferation, and cytokine production [6]).

Regarding the function as an antiviral agent, the efficacy has been demonstrated against several viruses, such as the Human Immunodeficiency Virus, type 1 - HIV-1 and the dengue virus, both *in vitro* and *in vivo*. Ivermectin performs its function mainly through inhibition of nuclear transport mediated by the imported heterodimer $\alpha/\beta 1$, which is responsible for the translocation of proteins of several viral species (Human Immunodeficiency Virus, type 1- HIV1, and Simian Virus 40 - SV40; a known oncogenic DNA), and such translocation is, in turn, essential for viral replication [7,8]. This inhibition appears to affect a considerable number of RNA viruses. It has recently been shown that ivermectin inhibits the replication of the SARS-CoV-2 virus *in vitro* [8, 9], although it is not clear how this occurs. However, since the causal agent of COVID-19 is an RNA virus, the interference with the same proteins and molecular processes described above can reasonably be expected. However, these studies were conducted at concentrations substantially higher than expected in the plasma and lungs of humans who receive the approved dose of ivermectin. Pharmacokinetic and pharmacodynamic studies suggest that in order to

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achieve the plasma concentrations required for *in vitro* antiviral efficacy, it would be necessary to administer doses up to 100 times higher than approved for human use [9, 10]. However, increasing the dose/kg of body weight may be a strategy to increase efficacy, the increase of the risk of toxicity is not conclusive [11, 12].

Currently, there is a noteworthy absence of efficacious treatments for patients with early infection [13]. Although most patients present mild or moderate symptoms, up to 5-10% may have a bad disease progression, so there is a pressing need for effective drugs to be administered early in the course of infection, even before the appearance of severe symptoms, i.e. when the course of the disease is more modifiable [14] to prevent disease progression and longer-term complications. In fact, it is known that the earlier the antiviral therapies are started, the greater the benefits for patients, in both influenza [15] and SARS infections [16], as well as, more generally, for all infections.

Given the need to find an effective drug that can mitigate the harmful consequences of COVID-19, a large number of studies are being carried out in order to assess the effectiveness of different existing drugs, including ivermectin, with promising results.

This narrative review summarizes and outlines the evidence-based effectiveness and safety of ivermectin in patients with SARS-CoV-2 infection, recommending the drug for the treatment of COVID-19 especially in the early stages of the disease.

Methodology

A literature search was conducted on MEDLINE, The Cochrane Library and EMBASE databases, using the following search strategy "COVID-19 treatment" or "ivermectin treatment for COVID-19" or "ivermectin treatment for SARS-CoV2 infection" between January and May of 2021. No further restrictions were applied to the search. In order to identify unpublished studies, a search, was also conducted on clinical trial registration platforms such as, Clinicaltrials.org.

Due to the narrative nature of the present review, no classification system was applied to the retrieved publications. Nevertheless, the authors reviewed the full texts of the retrieved studies and reviews and those articles with major methodological flaws were not included in the narrative review.

In order to facilitate the review, the retrieved articles were organized in the following four main topics: a) short-term efficacy in the treatment of the disease, b) long-term efficacy in the treatment of patients with post-acute symptoms of COVID-19, c) efficacy in the prophylaxis of the disease, and finally, c) safety of ivermectin. The results of the studies reviewed are presented as a narrative review.

Results

Short-term efficacy of oral ivermectin in the treatment of patients with COVID-19

By short-term or early treatment of the disease, we refer to the treatment administered immediately or soon after symptoms appear.

Recently, the WHO has commissioned a meta-analysis [17] to assess the clinical efficacy of ivermectin through the ACC Accelerator Program. The meta-analysis included 18 randomized controlled trials (RCTs) that evaluated doses up to 0.6 mg/kg of ivermectin, and conducted on a total of 2,282 RT-PCR positive patients (both, inpatients and outpatients), with mild to severe COVID-19 symptoms. Across six trials assessing the efficacy in survival in 1,255 patients, 14 of 658 patients (2.1%) died in the ivermectin arm versus 57 of 597 patients who died in the control arm (9.5%). The efficacy of ivermectin was assessed at doses of 200-400 μg/kg in a 1-5 day treatment schedule and a 75% reduction in mortality (Relative Risk-RR 0.25; 95% CI 0.12-0.52) was observed in patients treated with ivermectin, p<0.0002. Additionally, a reduction in hospital stay in five clinical trials 5-6.9 versus 6-18 days, p<0.05, was observed in ivermectin and control patients, respectively. In relation to the viral clearance, the effect of ivermectin on viral clearance was higher in clinical trials evaluating doses of up to five days of ivermectin. In these conditions, the authors have observed statistically significant differences in all three randomized clinical trials 5-9.7 versus 10-12.7 days, p<0.003 in ivermectin and control patients, respectively [18-20].

A real-time meta-analysis of 53 studies [21] conducted over a total sample of 17,582 patients with COVID-19 disease, assessing 27 RCTs, and 26 observational studies, described that all the studies included in the analysis reported positive effects. According to the results of the meta-analysis, treatment at an earlier stage of the disease (<=5 days after the onset of symptoms) is more successful, with an estimated 81% reduction in the measured effects (fever, death, no virological cure, no resolution of symptoms, need for ventilation, need for hospitalization, etc.) relative risk (RR) 0.19 [0.10- 0.039] [21]. It should be noted that, 96 % of the 27 randomized controlled trials (RCTs) included in the meta-analysis also report positive effects report positive effects, with an estimated improvement of 74% and 83% for early treatment and prophylaxis (RR 0.26 [0.16-0.42] and 0.17 [0.05-0.61]). Generally, antiviral drugs are only considered effective when used at the early stages of the infection, e.g. within 36-48 hours for oseltamivir, with longer delays not being effective [22, 23]. Equally, many viral infections such as influenza and herpes virus infections, treatment must be initiated soon, since symptom onset in order to confer benefit [24, 25]. Efficacy of antiviral drugs depends on the pathogenesis, transmission, and epidemiological characteristics of viruses. Antiviral treatment is not so effective for viruses with a very short period of incubation and that spread rapidly because it is difficult to complete diagnosis and initiate therapy early [26]. One of the reasons could be the inhibition of the formation of messenger RNA for interferon genesis [27]. On the other hand, Yeming Wang et al., [28] found a numerical reduction in time to clinical improvement in those treated earlier, Beigel et al., reached the same conclusion [29]. Severe COVID-19 typically manifests 8 to 12 days after symptom onset [30, 31], so antiviral agents administered after 9 days may be futile. In addition, evidence from a real-time meta-analysis showed that the improvement with the late treatment of ivermectin was only 43%; RR 0.57 [0.44-0.73] in the effects measured (fever, death, no virological cure, no resolution of symptoms, need for ventilation, need for hospitalization, etc.), while the early treatment resulted in an improvement of the 81% [21].

Mohan-Padhy et al.,[32] carried out another meta-analysis of 4 studies and a total of 629 COVID-19 RT-PCR positive patients, to assess the therapeutic potential of ivermectin at a standard dose of 200 μg/kg for the treatment of COVID-19 as an adjuvant therapy to the standard care. The overall Odds Ratio (OR) of 0.53 (95% CI: 0.29 to 0.96) was reported for the primary outcome of all-cause mortality which was statistically significant (p=0.04) [32].

According to a recent meta-analysis based on 18 randomized controlled treatment trials of ivermectin in COVID-19, mortality, time to clinical recovery, and time to viral clearance were lower in patients treated with this drug (33). In other meta-analysis analysing mortality in 28 clinical trials, mortality was also lower in the ivermectin arm versus non-ivermectin arm (OR 0.39, 95% CI 0.22-0.70) [34].

In a new published meta-analysis the RR of 13 clinical trials evaluating the risk of death in 1,892 COVID-19 patients comparing ivermectin versus no ivermectin was 0.32, 95% CI 0.14-0.72; low to moderate-certainty evidence according to the GRADE approach [35].

In a multicentre case-control study [36] of 280 hospitalized patients, ivermectin administered in a single dose of 150 μg/kg to patients diagnosed with SARS-CoV-2 infection, achieved a significant reduction in intrahospital mortality in those patients treated with the drug (1.4% versus 8.5% (ivermectin *versus* non-ivermectin; Hazard Ratio (HR) 0.20, 95% CI: 0.11 to 0.37, p<0.0001) [36]. These results are very similar to those obtained by Cepelowicz-Rajter et al., [37] in a

retrospective study comparing the efficacy of two therapeutic strategies (at least one dose of ivermectin + hydroxychloroquine and/or azithromycin *versus* hydroxychloroquine and/or azithromycin). In the group of patients who received ivermectin at a dose of 200 μg/kg, a reduction in mortality was observed (15.0% versus 25.2%, OR 0.52, 95% CI: 0.29 to 0.96, p=0.03). In the same study, the subgroup of patients with severe lung disease showed an even lower mortality (38.8% *versus* 80.7%, OR 0.15, 95% CI: 0.05-0.47, p=0.001) [37].

In both studies described above, the standard dose was administered (i.e., 150-200 μg/kg for most filarial infections and *S. stercoralis* and up to 400 μg/kg for *Wuchereria bancrofti* infections) [38, 39]. This contrasts with the very high doses of ivermectin employed in the *in vitro* experiment conducted by Caly et al., [9] with COVID-19-infected cell lines, indicating that it appears that standard doses might also be effective in reducing mortality.

In another interventional study conducted by Isho et al., [40] in 30 hospitalized patients with mild to moderate COVID-19, no difference was observed in the percentage of cured patients among those treated with 200 μg/kg in a single dose of ivermectin at the admission day + hydroxychloroquine + azithromycin and those treated with hydroxychloroquine + azithromycin. On the contrary, it was observed a difference in the length of hospital stay (7.62 $\pm$ 2.75 versus 13.22 $\pm$5.90 days, p=0.00005) and no adverse effects were reported [40].

Gómez-Hernández et al., [41] observed in a retrospective cohort of 325 patients diagnosed with SARS-CoV-2 infection, a better disease progression in patients treated with ivermectin at a single dose of 12mg within 24-h after hospital admission. In particular, it was observed a lower incidence of respiratory distress: 3 patients (2.5%) *versus* 21 patients (15.8%) p<0.001, and a lower need for intensive care: 1 patient (0.9%) versus 11 patients (8.3%) p<0.001[29]. Furthermore, the length of hospital stay was also lower in the group treated with ivermectin plus standard care (9 (7-10) days) compared to standard care alone (15 (12-19) days) (p<0.001) [41].

Morgenstern and co-workers conducted a retrospective study that evaluated the mortality of 3,099 patients with a definitive or highly probable diagnosis of infection due to COVID-19 (both inpatients and outpatients) treated with ivermectin and found a mortality-rate of 1.3%, which contrasts with the world average mortality-rate of 2.2% [42]. Ivermectin dosage varied depending on the type of patient. Outpatients were administered ivermectin at 400 μg/kg, orally in a single dose in the Emergency Service, and azithromycin 500mg orally (PO) per day for 5 days. Hospitalized patients received ivermectin orally at 300 μg/kg, at days 1, 2, 6 and 7. Patients also received azithromycin 500mg PO daily, for 7 days.

The routine prophylactic administration of ivermectin in Peru starting from May 2020 was also associated with a reduction in mortality due to SARS-CoV-2 [43]. Hashim et al., in a randomized controlled study conducted on 70 COVID-19 patients also observed a reduction in recovery time and a reduction in mortality in severe patients treated with doxycycline and ivermectin [44]. The treatment regimen was 200ug/kg of ivermectin orally per day for 2-3 days along with 100mg of oral doxycycline twice per day for 5-10 days in addition to the standard therapy,

A non-randomized intervention evaluating the efficacy of ivermectin combined with azithromycin and cholecalciferol, showed that the recovery-rate was 100% in patients treated with the drug at the early stages of the disease [45].

The results of the clinical trial carried out by Chaccour et al., [46] in 24 patients who received a single dose of 400 μg/kg of ivermectin or placebo, have been recently published. No difference was found in the proportion of patients with positive PCR at 7 days (RR 0.92, 95% CI: 0.77 to 1.09, p = 1.0). Patients in the ivermectin group had fewer days of symptoms as compared to those in the placebo group (171 versus 255 patient-days). The observed difference was mainly due to two symptoms, anosmia/hyposmia and cough. There was no difference in the days of fever, malaise, headache, or nasal congestion between the two groups. In contrast, the ivermectin group presented more days of gastrointestinal symptoms (21 versus 6) and less days of respiratory difficulty (3 versus 15) [46].

Long-term efficacy of ivermectin in the treatment of patients with post-acute symptoms of COVID-19

Approximately 10-45% of people suffering from COVID-19 will continue with symptoms after the acute stage of the disease [47]. The more common are cough, fever, dyspnea, musculoskeletal and gastrointestinal symptoms, and total loss of smell (anosmia) and/or altered sense of taste (dysgeusia) [47, 48]. In one study [49] carried out in 179 patients with persistent COVID-19, the 87,4% reported persistence of at least 1 symptom, particularly fatigue and dyspnea. In other study carried out by Rosales-Castillo et al., [50] the more common symtomps in the acute phase of disease were fever (84.7%), cough (65.3%), dyspnoea (61%), diarrhoea (50.8%), ageusia (50.8%), myalgia (49, 2%), anosmia (42.4%), chest pain (34.7%), headache (34%) and expectoration (13.6%). The 28% of 118 patients assessed, 50 days after hospital discharge presented two or more of the symptoms specified above.

Aguirre et al., [51] carried out another study in 33 patients with subacute symptoms of COVID-19 between weeks 4 and 12 from the onset of symptoms. They received two consecutive daily doses of ivermectin 200 - 400 μg/kg depending on the severity of the symptoms. An improvement of symptoms (total or partial) was observed in 94% of patients, and a total improvement in 87.9% of them. Patients whose main symptoms were musculoskeletal, such as fatigue due to muscle weakness, diminished muscle strength and myalgia (muscle pain) were excluded from the study. If any symptoms were present after the second dose (12.1% of patients), 2 additional doses were administered, reaching a 94% of success in the complete resolution of the symptoms after the fourth dose [51].

In another study carried out by the same authors, 21 adult patients with persistent symptoms of anosmia or hyposmia received ivermectin at a dose of 200 μg/kg of body weight per day for 2 days. If symptoms did not disappear after the second day of ivermectin treatment, patients received two more doses of 400 μg/kg (in days 5 and 6). Among the 21 adult patients with persistent anosmia or hyposmia treated with ivermectin, 66.7% had an overall clinical improvement after the two first days of ivermectin treatment, and this percentage increased to 85.7% after two more doses of ivermectin and acetylsalicylic acid for 5 days [52].

Efficacy of ivermectin for infection prophylaxis

The scientific literature provides evidence regarding the use of ivermectin as a prophylactic agent. We searched for studies in which the medication was regularly taken following different schedules in order to prevent or minimize SARS-CoV-2 infection. We found a real-time meta-analysis of 14 studies showing high effectiveness for the prophylactic use of ivermectin, which reported a 85% reduction in the risk of acquiring the disease on a sample 8,789 patients RR 0.15 (0.09 to 0.25) [20]. The meta-analysis included 4 RCTs and 10 observational studies. The results regarding prophylaxis remain very similar when only the three RCTs included in the meta-analysis were taken into consideration, showing a 83% reduction in the risk of a COVID-19 case (RR 0.17 (0.05 to 0.61)). Further, two of the studies included in the meta-analysis also investigated the risk of death as the main outcome measure reporting a 96% improvement (RR 0.04 (0.00 to 0.58)) [53].

On the other hand, countries with prophylactic administration of drugs on a routine basis against parasitic infections (filariasis [54] and onchocersis [55]) have less incidence of COVID-19. Thus, a study conducted by Hellwig et al., collecting data from countries that use

prophylactic drug therapy for the treatment of other infections, detected a lower incidence of COVID-19 in patients treated with ivermectin at 150-200 μg/kg doses ($p<0.05$) [56], without observing any remarkable difference between doses. This could be partly due to the relatively short half-life of ivermectin and the little added effect of higher doses [56]. Additionally, the hypothesis of activation of alternative routes when using lower dose, should be also considered [57].

In addition, it should noted that the prophylactic administration of ivermectin at a weekly single dose of 200 μg/kg up to 8 weeks in 74 people (residents and workers in nursing homes) produced IgG titers for SARS-CoV-2 of 5 to 10 times higher than the standard titers in 85% of cases. Workers included in the study would had been in contact with the virus, asymptomatically, but their immune system was able to produce antibodies against SARS-CoV-2 [58, 59].

Safety

The safety of ivermectin at high doses (>400 μg/kg) appears to be comparable to standard doses (<=400 μg/kg) according to a meta-analysis of RCTs conducted by Navarro et al. (60) (OR 1.16, 95% CI: 0.89 to 1.52). The severity of adverse reactions was similar in both dosage groups and was mild or moderate in almost 100% of the cases. Only one study reported a severe anaphylactic reaction in the standard dose group and a prolongation of QTc (corrected QT interval) in the high dose group [60]. Among the studies included in the meta-analysis only one study on onchocerciasis (river blindness) treatment showed an increase in eye reactions (transient blurred vision, itching, eye pain, dyschromatopsia) (IR-incidence ratio 2.797, 95% CI 1.226 to 6.377) [61]. These observations are in agreement with the side effects reported by other research groups [12, 62, 63]. In the clinical trial carried out by Chaccour et al., [46], 12 patients received a single dose of 400 μg/Kg of ivermectin and 12 patients received placebo. Patients in the ivermectin group reported more patient-days of dizziness (7 versus 1) and blurred vision (24 versus 1), although it should be taken into account that the blurred vision was reported in a single patient [46].

Veit et al., reported in 2006 the case of a 20-year-old patient with microfilaria symptoms, treated with a single dose of ivermectin of 300 ug/kg, who developed severe hepatitis, probably induced by that single dose [64].

Generally, ivermectin is well tolerated causing mainly dizziness, nausea, headache, skin rash, and appears to be dose-dependent [65, 66]. Since the approval of the drug in the 1980s, the drug has been distributed for the treatment of river blindness (onchocerciasis) through the Mectizan program, administering more than 3 billion treatments over the last 30 years, with an excellent safety profile. Most adverse reactions are mild, transient and associated with the death of the parasite rather than the drug itself [67]. Despite this, Chandler [68] described a series of 28 cases with severe neurological reactions after ivermectin treatment outside the onchocerciasis-endemic areas. One of the possible causes may be a variation of the MDR-1 gene, which may have allowed ivermectin to penetrate the central nervous system [68].

Ivermectin has affinity for glutamate-gated chloride channels, which are only present in invertebrates. Mammals only express a similar channel that could potentially cross-react with ivermectin, but such channels are only expressed in the central nervous system and are protected by the blood-brain barrier thanks to the P glycoprotein, a product of the MDR-1 gene, in humans [69]. This protein is located in the endothelium of the brain capillaries. Its function is eliminating substances or toxins found on the plasmatic membranes before they penetrate the cell, or to eliminate toxic substances that have managed to enter the cellular cytoplasm [70].

Since the majority of safety data on oral ivermectin are with single doses of 150 to 200 μg/kg, it was necessary to assess the security profile with higher doses. Guzzo et al., [12] carried out a study to obtain additional information at doses up to 10 times the 200 μg/kg dose through a multiple rising dose, double-blind and placebo-controlled clinical trial. Subjects were sequentially assigned to one of four treatment panels and were randomized to receive ivermectin or placebo within with doses of ivermectin from 333 μg/kg up to 2,000 μg/kg; doses much higher than the usual 150-400 μg/kg. The 24% of participants from ivermectin group (n=12) and 35% from placebo group (n=6) reported at least one clinical adverse experience.

All clinical adverse experiences were transient and mild. The most commonly reported were headache, nausea, dizziness, and rash, occurring in both, ivermectin and placebo-treated groups [12].

Discussion

The scientific evidence reviewed in this manuscript seems to indicate that ivermectin is effective in the short-term treatment and prophylaxis of COVID-19. The debate now focuses on selecting an effective dose with the best safety profile and lowest possible toxicity. The doses used across the different studies included in the present narrative review range from 150-600 μg/kg, administered as a single dose or in a 1-7 days schedule. According to the scientific evidence available, the standard dose (150-200 μg/kg depending on the indication) could be effective and has a lower probability of causing adverse reactions, especially at eye level [67]. In relation to the dosing schedule, it appears that a multi-day pattern would produce better results than the single dose [21].

It should be noted that the high quality evidence from meta-analyses of randomized controlled trials [21] is also corroborated by other studies (i.e., observational studies) reviewed in this article. Evidence shows that non-RCT trials can also provide reliable results [71]. The authors showed that the results of well-designed observational studies (with either a cohort or a case−control design) do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. So far, no individual clinical trial conducted to date is large enough to clearly establish the efficacy of ivermectin for the treatment of COVID-19. Nevertheless, the meta-analysis of 18 RCTs conducted by Hills and colleagues [21] includes a sample of 2,282 patients with COVID-19, providing stronger evidence on the efficacy of the drug. Two possible limitations should be also noted: firstly, that there is a possibility of publication bias, due to almost all published studies report positive results in relation to the ivermectin treatment would be published and secondly, that several clinical trials included in the meta-analysis are open-labelled and therefore, the potential investigator bias cannot be ruled out.

With the available evidence, the Frontline COVID-19 Critical Care Alliance (FLCCC) recommends the use of ivermectin in both prophylaxis and treatment of COVID-19 [33]. It should be noted that recently the American NIH (National Institutes of Health) has upgraded the recommendation and has issued a statement on the use of ivermectin within the COVID-19 Treatment Guidelines [71]. Despite, the NIH Guidelines do not recommend either for or against the use of ivermectin for the treatment of COVID-19, they now allow treatment of COVID-19 patients with ivermectin in the U.S.A. It should be noted that the results of the recent systematic review of RCTs commissioned by WHO [16] have not been taken into consideration by the Guideline Panel. The WHO, in the last revision recommends against the use ivermectin except in patients participating in clinical trials [72]. The WHO's decision was based on 16 of the 27 published RCTs with ivermectin involving 2,407 people [21, 73]. However, in the real time meta-analysis authors reflect on the WHO's decision but conclude that ivermectin is an effective treatment for COVID-19. The probability that an ineffective treatment generated results as positive as the 53 studies to date is estimated to be 1 in 167 trillion ($p = 0.000000000000006$).

Contrary to the WHOs recommendation, the Health Ministries of India, Macedonia, Bulgaria, Eslovaquia, and several South American

countries have already approved the use of ivermectin for the treatment of COVID-19 [74].

Recently, another meta-analysis has been published analyzing mortality in 28 clinical trials. The odds of death was lower in the Ivermectin arm compared to the non-Ivermectin arm (OR 0.39, 95% CI 0.22-0.70; I2=81%) [34]. A total 22 studies reported mortality-rate in patients receiving ivermectin (252/2778) versus no ivermectin therapy (1265/8038). In the meta-analysis of mortality, the odds of death were lower in the Ivermectin arm compared to the non-Ivermectin arm (OR 0.39, 95% CI 0.22-0.70; I2=81%), but evidence was graded very low. Similarly, in the subgroup analysis conducted of 12 RCTs (mild/moderate and severe/critical subgroups), a similar benefit was observed in the mild/moderate subgroup (OR 0.10, 95% CI 0.03-0.33, p=0.002), however, mortality benefit was not statistically significant in the severe/critical subgroup (OR 0.53, 95% CI 0.23-1.23, p=0.14). This could suggest that ivermectin could be an effective adjuvant therapy to reduce mortality, particularly in patients with mild-moderate clinical presentation of COVID-19. Our review is in line this and other meta-analysis and reviews like Ōmura et al., 2015 Novel Price [17, 21, 75].

Several clinical trials are underway to further evaluate the efficacy of ivermectin in the management of SARS-CoV-2 infection using different dosing patterns. Further investigations should be conducted in order to explore the above mentioned aspect, by means of carrying out well-designed studies that would allow the assessment of the efficacy and safety at low and high doses, following different dosing schedules. Such studies should make a special emphasis on the incidence of ocular and neurological adverse reactions, and should also identify the profile of patients where these adverse reactions occur most frequently.

Evidence regarding the effectiveness of ivermectin for the treatment of persistent COVID-19 symptoms is provided by two prospective observational studies conducted in 33 and 21 adult patients with post-acute symptoms of COVID-19, respectively [51, 52]. Nevertheless, it is important to point out that the studies mentioned above have serious methodological limitations. Firstly, both studies lack a control group and have very small sample sizes. Secondly, the assessment of the main outcome measures was subjective and has not been clearly specified in the published papers. Therefore, the evidence in favor of the treatment with ivermectin for long-term COVID-19 is very weak due to the serious limitations of the studies conducted by Aguirre-Chang and co-workers. Given the high number of patients with persistent COVID-19 symptoms, further investigations should be carried out, in order to unequivocally prove the effectiveness of ivermectin in long haulers. In this regard, it is crucially important to carry out well designed controlled clinical studies.

Given the significant upsurge in cases of SARS-CoV-2 infection that has occurred in recent months, the use of ivermectin could reduce transmission-rates, as well as decrease short term morbidity and mortality in mild, moderate and even severe phases of the disease [33]. In this regard, it has been shown that treatment with ivermectin could produce IgG titers for SARS-CoV-2 around 5 to 10 times higher as compared to the titrations of untreated patients in 85% of people who had come into contact with the virus asymptomatically [58,59].

However, although ivermectin appears promising for the treatment of COVID-19, it should not be used massively and for long periods as a prophylactic agent, until results of well-designed clinical trials are completed. The effects of the long-term use of ivermectin have not been sufficiently studied. In this regard, there is a serious concern that the recommendation of a weekly dose to prevent SARS-CoV-2 infection could lead to an excess of confidence among the general population, which in turn could lead to neglect the recommended biosecurity measures [76].

Declaration of competing interest

The authors declare no conflict of interests.

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