Médicos pela Vida
covid-19

DOCTORS FOR LIFE - BRAZIL

DOCTORS FOR LIFE IN BRAZIL SUPPORT BIRD'S POSITION AND CONCLUSIONS THAT CONTRADICT THE WHO AND CLAIM THERE IS MUCH EVIDENCE TO RECOMMEND IVERMECTIN FOR COVID-19, AND EACH POSTPONED DAY COSTS MANY LIVES

The potential therapeutic utility of Ivermectin has expanded over the past decade. It includes six important and well-demonstrated actions: antiparasitic, antibacterial, antiviral, anti-inflammatory, anticancer, and immunity modulator [7, 8], with antiviral being the most studied since the first SARS epidemic in 2012 and after COVID-19 became a pandemic. The European Medicines Agency (EMA) and the World Health Organization (WHO) recommended against the use of Ivermectin for the treatment of COVID-19 unless it was under controlled clinical trial. The EMA and the WHO considered that the favorable pieces of evidence on Ivermectin were still inconclusive, and the drug should not be used in the treatment of patients with COVID-19 and included this recommendation in their disease treatment guidelines. Janet Díaz, head of the U.N.'s COVID-19 clinical response team, said at a news conference: "Our recommendation is not to use ivermectin for patients with COVID-19, regardless of the level of severity or duration of symptoms." Moreover, the WHO has not recommended the use of Ivermectin to prevent and treat COVID-19, outside of "well-planned" clinical trials.

The WHO announced the statement o Ivermectin without the references to support their decision. The organization "Médicos pela Vida" (Doctors for Life - in English) does not agree with the conclusion considered by the WHO, to draw its recommendations, which did not consider all the evidence available now, and protest and support the actions of BIRD-British Ivermectin Recommendation Development.

In January 2021, Dr.. Tess Lawrie, director of Evidence-Based Medicine Consultancy Ltd (E-BMC), an independent medical research company in Bath, U.K., created The British Ivermectin Recommendation Development (BIRD) panel that analyzed all studies extensively, respecting the scientific methodological recommendations.

The WHO statement, March 31, 2021, with an unexpected recommendation against Ivermectin use in COVID-19 evidenced the disagreement on the conclusion of data review found by the Bird and the one published by Andrew Hill supported by the UNITAID. According to Dr. Lawrie, who led the BIRD review, at least five systematic review studies that she analyzed previously, together with Hill, met Cochrane criteria and could support the recommendation for the prevention treatment of COVID-19.

Delays in the WHO or EMA approval of Ivermectin as an antiviral and safe agent in COVID-19 may have catastrophic dimensions on the possibility of saving thousands of lives.

The DOCTORS FOR LIFE, Brazil, as many doctors and scientists around the world reaction in disagreement on the recommendation of the WHO and EMA to the use of Ivermectin in COVID-19, is based on data as listed below:

1) EVIDENCE

1. A systematic review and meta-analysis of Ivermectin for COVID-19 recently conducted by Tess Lawrie, together with a team of specialized systematic reviewers, resulted in a positive preliminary report released on the public domain website on January 3 [1].

2. A comprehensive article, including 21 RCTs (Controlled and Randomized Studies), was submitted to a peer-reviewed journal and is available on two preprint servers [2, 3].

3. On February 20, 2021, a group of 65 doctors, researchers, and patient representatives from 16 countries participated in the BIRD panel meeting convened by Dr. Lawrie and her team to evaluate the evidence Ivermectin for COVID-19. The results of the randomized controlled trial with Ivermectin from Zagazig University confirm the hypothesis that Ivermectin is an effective drug against COVID-19

4. Following the evidence structure for the standard "DECIDE" decision [4] for clinical recommendations, the BIRD concluded that there was sufficient evidence to recommend the rapid implementation of Ivermectin for COVID-19 [5, 6]. This recommendation has global implications and not only restricted to the United Kingdom or the European Union, considering it is related to a global pandemic.

5. The low cost of medication, the existence of large factories, and the capacity to expand their production quickly, as in Brazil and India, would allow the widespread use of Ivermectin to combat COVID-19 throughout the world, including in very low-income countries.

6. Doctors for Life in Brazil support the need to review the data supporting the reported WHO and EMA recommendations against Ivermectin to prevent and treat COVID-19. See below the gaps pointed by BIRD and supported by Doctors for Life Brazil:

6.1. According to the EMA, the results of some clinical studies showed no benefit, and others reported a potential benefit. They concluded that the currently available evidence was insufficient to support the use of Ivermectin in COVID-19 outside clinical trials. However, they did not evaluate all the studies available in the period they performed the review. Most of the studies included in the review were small and had methodological limitations, including different dosing regimens and concomitant medications in the control group that could interfere with the results.

6.2. Since April 2020, the number of pieces of evidence on Ivermectin use for COVID-19 increased rapidly, including observational and randomized trials. A review [9, 10] by the

Front Line COVID-19 Critical Care Alliance (FLCCC) summarized the results of 27 randomized controlled trials (RCTs) and 16 observational studies on Ivermectin for the prevention and treatment of COVID-19. They concluded that ivermectin "shows a strong sign of therapeutic efficacy." In addition, Ivermectin is the only therapy so far that has shown efficacy in all stages of the COVID-19 clinical course, from prophylaxis, preventive, early symptomatic, to the treatment of the post-COVID-19 inflammatory phase and symptoms.

6.3. Dr. Lawrie and a team of experts subsequently conducted a systematic review and meta-analysis [2, 3]. Twenty-one RCTs involving 2,741 participants completed the inclusion of the review, according to strict criteria, and the subsequent meta-analysis of 13 studies found that Ivermectin reduced the risk of death (compared to no ivermectin) with an average Risk Ratio of 0,32 [95% confidence interval (CI) 0.14 to 0.72; n = 1892; I2 = 57%]. Adverse events were rare and generally attributable to other auxiliary drugs. These findings suggest Ivermectin reduces almost a third of the COVID-19 death risk to about a third compared to the risk without using this drug. Suggesting that to every nine patients who would die from COVID-19, six could survive when treated with Ivermectin. Likewise, the risk of healthy people using Ivermectin as prophylaxis to contracting COVID-19 could be reduced to a seventh of the risk compared to other healthy people with similar exposure without using Ivermectin. This result means only one out seven expected to contract the disease would be affected when taking Ivermectin.

6.4. In addition to the narrative review by Kory et al. [9, 10] and the rigorous meta-analysis by Bryant et al. [2,3], three other systematic reviews have been carried out so far, namely: Hill et al. [11] (commissioned by WHO); Castañeda-Sabogal et al. [12]; and Nardelli et al. [13]. Nardelli's is brief but consistent with BIRD's analysis. Therefore, of the five reviews so far, only Castañeda-Sabogal presented negative results, and, in the methodological assessment against the AMSTAR 2 criteria [15], it scores very poorly, as does Hill's [11, 2, 3]. Hill et al., however, report a 75% reduction in mortality, although they are inconsistent with the view that "the results are insufficient for review by regulatory authorities". Significantly, the review by Bryant et al. [2, 3] (on which the IBRD recommendation is based) is the most up-to-date systematic review and meta-analysis. It is also the first, and so far, the only, to use the rigorous Cochrane systematic review methodology [16]. However, it is not clear in Bryant et al. [2, 3] review, restriction to report Randomized Controlled Trials (RCTs), considered of highest quality evidence by regulators.

6.5. Researchers and organizations to determine the efficacy of a treatment or intervention under ideal conditions frequently use evidence obtained in randomized controlled trials (RCTs). Moreover, they use observational studies to measure the effectiveness of an intervention in non-experimental, 'real world' scenarios at the population level. Thus they are complementary to develop recommendations. The Cochrane [17]) shows that high-quality OCTs are as reliable as RCTs in their findings and showed little difference between the RCTs and observational results.

6.6. Finally, "real world" case reports like the described in Peru [18] show impressive reductions in deaths and infections related to COViD-19 after the implementation of distribution of Ivermectin on a large scale in the country. We currently have 25 countries using Ivermectin against COVID-19, 15 of them widespread the country with official endorsement [19]. Several Indian states have adopted Ivermectin as an official policy,

serving a total population of around 400 million. In the E.U. itself, and three other countries have already adopted Ivermectin (Bulgaria, Czech Republic, Slovakia).

In summary: The data above support the need for reevaluation of the recommendation of EMA and WHO. That is also incongruous with the policy already adopted in 25 countries, including three E.U. Member States.

2) DOSAGE AND SAFETY

Ivermectin is generally well tolerated with mild side effects in usual doses (150–200 mcg/kg), mostly used for filarial and *S. stercoralis* infections and approved in doses of up to 400 mcg/kg against infections with *Wuchereria bancrofti*. Doses above 400 mcg/kg are being evaluated to improve efficacy in other diseases like malaria by achieving higher peaks and/or extending the intervals with detectable drug levels as it may be required to obtain concentrations of Ivermectin in the lungs more effective against the virus. A recent meta-analysis evaluated the safety profile of higher doses. It concluded that the safety of high-dose Ivermectin appears to be comparable to standard doses, but yet, not enough data to support a recommendation for its use in higher-than-approved doses.

Adequate concentrations of IVM in the lung or serum based on initial in vitro EC50 values reported by Caly et al. [20]) may not be achievable in vivo and may not be necessary to achieve benefits. Such controversy is well known in the literature [21]). Clinical trials have already shown consistent therapeutic effect at much lower dosages: no higher or twice the standard 200 mcg / kg recommended dose for strongyloidiasis [22]. The protocols used to study its usage in COVID-19 [5] do not exceed five times the package insert dose and, in most of them, only 2 or 3 times are the usual recommended dose. Many protocols standardize a fixed dose of 12 mg, corresponding to 200 mcg / kg only for a body weight of 60 kg.

The safety of Ivermectin is better established than almost any other drug in the pharmacopeia, having been distributed worldwide in "Mass Drug Administration" (MDA) campaigns for the control and elimination of tropical parasites [23]. The cumulative number of doses now exceeds 3.8 billion [24], approximately half of the world population. In addition, detailed safety studies [25] show that Ivermectin is well tolerated at doses up to 10 × the maximum dose recommended by the FDA for strongyloidiasis, giving a more than adequate therapeutic range.

Several other safety studies are available. An expert review report from more than 500 evaluated studies reported adverse events associated with the use of Ivermectin and found that adverse events were rare and mostly mild to moderate [26]. Many of the adverse reactions are related to the treatment of parasitic infections with inflammation and irritation caused by the decomposition of dead or dying internal parasites; these are, of course, completely irrelevant to the treatment of COVID-19.

In the prophylactic use, the weekly or fortnightly doses of Ivermectin recommended by the package leaflet are advocated, and it was questioned whether prolonged use would cause problems. But an extreme example of continuous administration of Ivermectin is its use in the treatment of childhood leukemia, where daily doses of 1 mg/kg or 60 mg (5x the strongyloidiasis dose, repeated daily) were continued for six months. The only complaint of the 13-year-old patient related to the smell of Ivermectin [27] A Phase 1 clinical trial validating the safety of continuous administration of Ivermectin, authorized by the Regulatory Agency for Medicines and Health Products (MHRA, the U.K. regulator), found no side effects with daily doses of 75mcg / kg for 28 days [28]. Records [29] show only 16 deaths from ingestion of Ivermectin since 1992. This drug has been used for 30 years, for various indications, in colossal amounts, with reports of adverse reactions that are at an exceptionally low rate or mild to trivial (for example, headache).

In summary: High doses of Ivermectin are clearly not essential (although dose optimization trials should undoubtedly be evaluated. Current COVID-19 doses are well within the previously established safety intervals.

Ivermectin is an exceptionally safe drug, although more pharmacovigilance is always welcome, with negligible rates of serious adverse events and only trivial common side effects, which must be compared to the symptoms and risks of the disease itself.

3) ON THE WHO AND EMA RECOMMENDATION OF RESTRICTION OF IVERMECTIN TO CLINICAL TRIALS

EMA and WHO concluded that the use of Ivermectin for the prevention or treatment of COVID-19 could not only be recommended in controlled clinical trials. However, as shown above, this recommendation should be reviewed. These recommendations go against the decisions of 25 countries, including three E.U. Member States, which have already adopted Ivermectin in the treatment of Covid-19.

The restriction to clinical trials limits its use and benefits urgently needed during a pandemic with elevated infection and deaths. Although the "certainty" of the evidence reported in the review [2, 3] on which the IBRD recommendation is base is low or "low to moderate", this does not mean that the effect is weak. Clinical trials and observational studies of real-life have reported that its effects are strong and predominantly beneficial. The evidence that there are positive benefits is already evident.

When treatment is considered effective, it is unethical to conduct other controlled clinical trials for a potentially fatal disease using a placebo arm, as they would violate protocols under international law, such as the Helsinki Protocols for clinical trials [30]. The next clinical trials to be carried out on Ivermectin should be restricted to:

(i) dose optimization tests,

(ii) trials comparing the effect of various adjuvant drugs commonly used at various stages of the disease (antibiotics, other antivirals, vitamins and minerals, anti-inflammatories and anticoagulants)

(iii) contact tests quantifying the reduction of contagion when used as a prophylactic.

Authorization for emergency use has been granted for therapies with far less positive evidence and more negative safety profiles than we currently have for Ivermectin (e.g. remedesivir). Ivermectin itself has been approved by WHO in the scabies indication and added to the list of essential drugs (including the list of children) in that indication, on an evidence base that is clearly weaker than the systematic reviews already available for COVID-19 [31].

In summary: it is time for regulatory authorities to recognize that the effectiveness of Ivermectin in COVID-19 has already been demonstrated and that its overall safety profile is extremely well known. In a pandemic situation, regulatory bodies must approve this very safe drug for routine use, at the clinical discretion of any licensed physician. Further delays will lead to more unnecessary loss of life.

The Evidence-Based Medicine Consultancy Ltd

Doctors for Life Brazil
Bath, England March 26 2021

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