The pharmacokinetic rationale of Ivermectin for COVID-19 therapy.

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October 25, 2021

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Ivermectin can claim the title of 'wonder drug.' It has a significant impact on the health and well-being of humankind. Initially approved in humans in 1987 for onchocerciasis, Ivermectin has improved billions of people's well-being worldwide. Moreover, Ivermectin is used to treat billions of livestock and pets worldwide, helping boost the production of food and leather products and keep billions of companion animals healthy. Nowadays, Ivermectin is taken annually by close to 250 million people [1].

The "revival" of Ivermectin stems from its repurposing for COVID-19. The massive interest in this drug is evident from the hundreds of published studies that is only exceeded by its high presence in the press involving doctors, scientists, the general public, and health and global regulatory organizations such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the World Health Organization (WHO). We could summarize that scientific evidence suggests but does not prove its efficacy. From a regulatory and political perspective, the world's most influential health regulatory authorities, such as the FDA, the EMA, and the WHO, explicitly do not recommend its use outside of clinical trials. In the last of a series of publications entitled "*Timeline of ivermectin-related events in the COVID-19 pandemic",* the author concludes that the Ivermectin controversy for COVID-19 will remain out of reach if scientists are riddled with subconscious biases, fundamentally unsound methodologies, and dominancy of commercial interests [2].

Here we comment on the issue of Ivermectin dose, an overlocked pharmacokinetic (PK) key factor in the current clinical development of Ivermectin for COVID-19 therapy. In January 2020, Caly and colleagues reported that Vero-hSLAM cells treated with 5 μM Ivermectin after two hours post-infection with SARS-CoV-2 reduces the viral RNA load by 99.98% at 48 hours [3]. This finding initiated the avalanche of finished and ongoing clinical trials of Ivermectin for the disease. Of note, all trials have used the recommended standard dose as antiparasitic (usually 200-400 μg/Kg, or 600 μg/Kg the fewer) either a single dose or daily for three consecutive days. In March 2021, a letter published in BJCP stated that the 99.98% viral load reduction at 5 μM for 48 h concentration is not achievable clinically. The authors stated that at the highest reported dose of Ivermectin, approximately 1700 μg/Kg (8.5 times the FDA-approved dose of 200 μg/kg), the C_{max} was only 0.28 μM [4]. Since then, at the time of this writing, 26 clinical trials or meta-analyses argue on "unattainable C_{max}" as a partial explanation for the unsatisfactory results of Ivermectin for COVID-19 treatment. International press as well discourages its use, arguing that "horse doses" are needed.

Surprisingly, C_{max} and not the Area Under the Curve (AUC), which relates to both concentration and time, is taken as the determining PK parameter of the efficacy of Ivermectin for COVID-19. Antimicrobial agents are generally classified into three classes based on in vitro pharmacodynamics (PD) drug effect: 1) Time>MIC

(Minimal Inhibitory Concentration) -*time-dependent* - 2) Cmax/MIC

-*concentration-dependent* - or 3) AUC/MIC -*concentration/time-dependent* -. As

it can be seen, the factor of time of exposure is present in these three classes as

MIC accounts for concentration and time.

A key PK/PD aspect on the efficacy and toxicity of most drugs relates to the drug concentration-time at a receptor site to biological response. Since the drug concentration at the receptor site can rarely be measured directly, it is more usual to measure the drug concentration in the plasma and assume that it reflects that at the receptor site. From this, it can be appreciated that plasma concentration alone may mean nothing if time (duration of exposure) is not accounted for. Therefore, the C_{max} only informs on the plasma concentration's peak (amount of drug/volume) after a dose. Thus, what matters is how much drug is circulating in the plasma per unit of time (h/mL) and, therefore, be available to reach its potential site of action, which is measured by the AUC μg/h/mL (amount/time/volume).

Accordingly, the first randomized trial demonstrating improved survival in acute lymphoblastic leukemia in children used the AUC as a target and not the C*max* [5], which is not surprising as the in vitro cytotoxicity of antineoplastic drugs depend on both drug concentration and duration of drug exposure. Recent reviews show that for both cytotoxic and targeted anticancer agents, response and toxicity correlate with drug exposure, reflected in the AUC [6,7]. Translating this information to Ivermectin, it is clear that the C_{max} of 5 μM, which reduces 99.98% of the viral load, is not clinically feasible. However, the AUC (5,249 μM/h) that reflects the plasma concentration of the drug over time is achievable when using a dose of 2 mg/Kg. Table 1 shows these data estimated at different doses. It also shows that at a dose of 2 mg/Kg in a 5-day scheme, said concentration is reached since day 2 and on. Moreover, it shows that no significant dose accumulation occurs as the steady-state is reached at day 9.

In the Oncology arena, using the drugs pharmacokinetic information [8] and the IC50 to 1000 human cancer cell lines (https://www.cancerrxgene.org), we observe that among 32 agents, 28 have a C_{max} well below (18.3-fold less) the corresponding IC_{50} in cancer cell lines (median C_{max}1.0 μM (0.021-133), and median IC_{50} 13.8 μM (1.32-80.1). Despite that, these 28 drugs are FDA-approved because they are efficacious. Remdesivir, the only drug FDA-approved for COVID-19, shows an EC_{50} of 26.9 μM [9] while the C_{max} is 5.504 μM (5-fold less) [10]. Should C_{max} were the parameter to correlate with clinical feasibility and efficacy, none of these compounds, including remdesivir, could have developed.

In summary, the dose needed of Ivermectin to reduce 99.98% of the viral load in vitro is clinically feasible. It could be 2 mg/Kg, which appears safe. Ideally, a dose-finding study with PK/PD correlations should be done before beginning phase III clinical trials. As there is no commercial interest in developing Ivermectin and only independent researchers with limited resources can do it, it is imperative to optimize the studies to establish whether Ivermectin is useful for treating COVID-19. It is a fact that today, almost a third of the world population (28%) uses Ivermectin to treat COVID-19; hence the need for refuting or confirming its efficacy is paramount. (*https://ivmstatus.com*).

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`Table 1.docx` available at https://authorea.com/users/442741/articles/542926-the-pharmacokinetic-rationale-of-ivermectin-for-covid-19-therapy