COVID-19 and *Argumentum ad ignorantiam* or ''not everything goes''☆

COVID-19 y *Argumentum ad ignorantiam* o «no todo vale»

Dear Director,

After having read with interest the letter by Dr. Abril López de Medrano et al.,[1] which we wholeheartedly endorse, we would like to raise an alarm about a curious process of scientific thinking that, to our understanding, is happening in a generalized manner in the global management of treatment against COVID-19. It is the so-called *Argumentum ad ignorantiam* fallacy, which consists of thinking that ''lack of awareness of evidence contrary to an idea that we support counts as evidence in its favor.'' Nothing is further from the truth, and even more so given the capacity of generating multiple trial-and-error tests with unpredictable consequences, particularly in a disease that we unfortunately still know very little about.

Let's look at an example: a recently published preclinical study observed that the anthelmintic ivermectin achieves inhibition of SARS-CoV-2 replication *in vitro* in 48 h.[2] As no evidence against it has been published to date, the possible theoretical benefits of this drug in humans are to be expected. Nevertheless, if we review the work in detail, it is observed that the dose of ivermectin used *in vitro* is 5 μM. To achieve this concentration in a human being, oral administration on the order of 1000–1200 mg of ivermectin would be needed. According to the drug's technical datasheet, the dose tested in humans (healthy volunteers) is around 100–120 mg (single dose) and severe side effects due to intoxication include ataxia and seizures.[3] For this reason, it seems clear that it would not be possible to use this drug to treat SARS-CoV-2 in humans, as the levels required for it to be effective in humans would very probably also be highly toxic.

Let's suppose that this drug had been tested at the usual doses approved by the Spanish Agency of Medicines and Medical Devices (AEMPS, for its initials in Spanish) (thus below the therapeutic range for COVID-19) in a health center that had low mortality rates for the disease. In this scenario, it could have falsely been assumed that ivermectin played a decisive role in curing these patients. This is not so, as adequate therapeutic levels in the blood would not have been achieved.

Therefore, we must be on the alert to publications on ''sensationalist'' therapies supported by small case series (ozone therapy, vitamin D supplements, etc.) and, sometimes, by the doubtful methodology that, supported by the principal of *Argumentum ad ignorantiam*, promise fantasies of cures for COVID-19 disease.

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Ivermectin in COVID-19. *Argumentun ad ignorantiam*?☆

Ivermectina en COVID-19. *¿Argumentum ad ignorantiam*?

Dear Director,

In regard to the article ''COVID-19 and *Argumentum ad ignorantiam*, or 'not everything goes'''[1] I would like to make a few considerations.

Ivermectin has shown preclinical evidence of its efficacy against different types of virus, including SARS-CoV-2. Likewise, some authors suggest clinical evidence of the possible efficacy of the medication against COVID-19.

In a retrospective cohort study on 280 patients, Rajter et al.[2] showed a significant reduction in the overall mortality rate in the group that received ivermectin (15% vs. 25.2%; OR 0.52 [CI 95% 0.29—0.96], $p = .03$). In the regression analysis adjusted for confounding variables, the reduction in mortality remained significant (OR 0.27 [CI 95% 0.09—0.85], $p = .03$; HR 0.37 [CI 95% 0.19—0.71], $p = .03$). Notable methodological elements in that publication include the adjustment for multiple confounding factors, including sociodemographic variables, comorbidities, the severity of pulmonary compromise, and the use of hydroxychloroquine and azithromycin.[2]

The dose of ivermectin is calculated in micrograms/kilogram and not in milligrams/kilogram. Thus, even

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though concerns regarding the effective dose for SARS-CoV-2 have been raised, the study by Rajter et al.[2] showed the efficacy of the medication at a dose of 200 micrograms/kilogram, a dose that has been demonstrated to be safe. The widespread use of ivermectin that allowed for eradicating onchocerciasis as well as its use in treating parasitosis for more than 40 years provides evidence of a sufficiently safe pharmacological profile when it is used at a dose of 150–200 micrograms/kilogram.[3]

Though it is true that conclusive evidence is needed on the efficacy of the medication against COVID-19, to date (May 24, 2020), 14 ongoing investigations evaluating the possible efficacy of ivermectin are registered in ClinicalTrials.gov database. In this sense, its potential use outside the context of a clinical trial or research protocol for off-label medications that evaluate its efficacy and safety cannot be ruled out.[4]

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Reply to: Ivermectin in COVID-19. *Argumentum ad ignorantiam*?

Réplica: Ivermectina en COVID-19. *¿Argumentum ad ignorantiam*?

Dear Director,

After closely reading the letter by Carlosama-Rosero in which we were cited,[1] we observed some misinterpretations of the content of our publication[2] and we believe it would be useful to provide some clarifications.

In our previous letter, we reference the mental process known as *argumentum ad ignorantium*, which consists of believing that lack of awareness of evidence contrary to an idea that we support counts as evidence in its favor. At that time, we gave the example of the drug ivermectin in COVID-19 disease, whose previous success in a laboratory study would be difficult to extrapolate to clinical practice, as it would require toxic doses to reach the necessary therapeutic concentration.[2]

Although it is well-known that ivermectin dosing is in μg/kg of body weight, we gave the total necessary dosage in mg for reaching a concentration in human beings that is similar to what was effective *in vitro*, which would indeed be highly toxic (1000–1200 mg *vs* 10–20 mg, which is the dose habitually used in humans). At no point did we intend to categorically rule out ivermectin as a possible treatment for COVID-19, but rather refute inconsistent evidence in its favor. The work by Rajter et al.[3] that Carlosama-Rosero cites is a multicenter retrospective study of 280 patients treated with ivermectin which reported a significant reduction in the overall mortality rate in the group that received ivermectin (15% *vs* 25.2%; OR 0.52 [CI 95% 0.29–0.96], $p = 0.03$). Furthermore, on the regression analysis adjusted for confounding variables, the reduction in mortality remained significant (OR 0.27 [CI 95% 0.09–0.85], $p = 0.03$; HR 0.37 [CI 95% 0.19–0.71], $p = 0.03$). However, like all observational studies, it had some well-known selection and confounding biases, and therefore the results reported in that publication must be taken with great caution and of course after waiting for the results of ongoing clinical trials. This work unfortunately does not allow for drawing solid conclusions on the effectiveness of ivermectin at this time.

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