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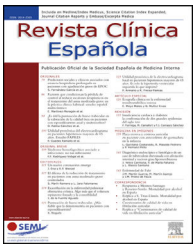

CORRESPONDENCE

Treatment of the COVID-19 pandemic: Preventing a missed opportunity☆

El tratamiento de la pandemia por COVID-19. Ante la expectativa de evitar una oportunidad perdida

Dear Director,

In a recent opinion article,[1] the author describes in quite an informative manner the need to be able to take advantage of the enormous professional capacity that was set in motion to fight the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in order to launch clinical trials that will allow us to progress in the therapeutic repositioning of drugs with indications for other infections and diseases which may be useful for the control or cure of SARS-CoV-2 infection. The design of new drugs specific to this disease or the development of vaccines are much more interesting options, but do not have a possible practical application in the medium term.

The author uses the example of the Ebola crisis in 2014, in which the slowness of bureaucracy impeded the timely development and implementation of any clinical trials. After that outbreak, we were left without quality evidence that would have allowed us to advance in future management of the disease.

Currently, there are multiple treatments used against SARS-CoV-2 infection, an unprecedented infection in our history.[2] Both antiviral drugs (lopinavir/ritonavir, remdesivir, etc.) and drugs used in inflammatory diseases (hydroxychloroquine, glucocorticoids, anti-interleukin-6 antibodies, gamma globulins, etc.) are being prescribed, all without scientific support. We constantly receive series or retrospective studies with conflicting results, inadequate designs, and serious difficulties in the interpretation of results.

We have seen the publication of a clinical trial in a highly prestigious journal[3] with a possible beta error due to a lack of power conditioned by an insufficient sample size. The conclusions included in the abstract and those obtained following a detailed analysis based on the evidence are absolutely contradictory, which ends up generating more questions than answers after reading it. As the journal's editorial proposes,[4] this trial should lead to taking what has been learned and using it to develop a new study, not for the drug to be suspended in all clinical scenarios.

The situation in our area is much the same. Given the Herculean task of adapting to a new reality, with the creation of multidisciplinary working groups to treat the disease and a significant number of professionals affected or infected, it seems impossible to conceive of having time for developing clinical trials that would allow us to obtain reliable results in the upcoming months. We are witnessing a kind of Stupor-Based Medicine (SBM), in which different local committees adopt their own protocols. The majority are based on recommendations from the Ministry of Health,[5] but include, in some cases, compassionate use of drugs that are not only not indicated, like the rest of the drugs we are using, but have not even been recommended by scientific societies[6] or the aforementioned ministry.[5]

A paradigmatic case is treatment of the so-called ''cytokine storm'' that occurs in a small percentage of patients. It is a very severe complication in which rapid clinical decline, mainly characterized by an increase in dyspnea, is accompanied by a laboratory profile that suggests marked inflammatory activity (elevation of interleukin-6, D-dimer, C-reactive protein, etc.). Since the start of the crisis, the Ministry of Health has authorized the use of tocilizumab, a monoclonal antibody against the interleukin-6 receptor, seeking to halt this ''storm.'' Given its scarcity, in recent weeks, other therapies have been tried, such as steroids, despite the fact that organizations such as the World Health Organization (WHO) are against their use.[7] Steroids are being used with different guidelines and doses based on extrapolation of the doses that are effective in other contexts, either inflammatory or infectious, but without a clear indication in SARS-CoV-2 infection itself.

At this time, we may be letting the opportunity slip by to put all of our efforts at the service of generating new evidence that will allow us to face this crisis with objective data. Sharing local protocols is not enough. It is necessary to unify protocols among different centers and, most of all, launch multicenter clinical trials. Different local experts establishing their own combinations, each one based on a personal judgment, is nothing to be proud of. It is a tragedy that we are not able to put all of this to work in a coordinated manner. In the face of very severe patients for whom there is no treatment with demonstrated efficacy, it is difficult for clinicians to try not to act, to do something rather than doing nothing. When compassionate use drugs are given these patients, clinicians tend to think that if the patient progresses favorably, it is thanks to the drug, but if the patient progresses poorly or dies, it is due to the disease. On many occasions, this interpretation is not correct and lacks a scientific basis.

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We are before a unique, once-in-a-lifetime opportunity to do things as best as possible, to cooperate among centers, and to include the greatest number of patients in clinical trials. Before starting to try to innovate, we must search clinical trial registries, such as the Spanish Clinical Studies Registry (REEC, for its initials in Spanish).[8] As of today, April 2, 2020, there are 13 ongoing clinical trials in the REEC, two of which seek to evaluate the use of steroids, in addition to international initiatives such as the WHO's SOLIDARITY trial. Before including any compassionate use drugs in our protocols, we are ethically obligated to try to join any clinical trial that may be testing its potential.

Within three months, we could have an answer about what drugs will work in future outbreaks, what the right moment to start each of the treatments is, and what their dose and durations are. Alternatively, within three months, we will only have the cacophony of multiple local studies—retrospective and contradictory—that are impossible to interpret; we will be filled with regret in the shadow of a missed opportunity. The choice is in our hands.

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Obesity and 2019-nCoV: A risky relationship☆

Obesidad y coronavirus 2019nCoV: una relación de riesgo

Dear Editor,

Obesity is a multifactorial, complex, chronic metabolic disease[1] associated with chronic inflammation that plays an essential role in the development of type 2 diabetes mellitus (DM2), dyslipidemia, hypertension (HT), cardiovascular diseases (CVD), and cancer.[2]

Currently, the 2019-nCoV coronavirus is devastating the planet. It has diverse clinical manifestations including, most notably, lung disease. The risk factors for infectious diseases depend on the host, the pathogen, and the environment. Various factors associated with the severity and a worse prognosis of 2019-nCoV infection have been described, such as age, presence of chronic diseases such as DM2 or HT, and diseases that compromise the immune system.[3] In the few series that have been published, obesity is also included among these factors, especially for those younger than 65 years of age.[3–5]

Obesity is associated with a worse immune response and a poor prognosis for respiratory infections, as was observed during the influenza A (H1N1) epidemic in 2009.[6] At baseline, people with obesity have an associated low grade of chronic inflammation; they have decreased concentrations of anti-inflammatory adiponectin and elevated concentrations of proinflammatory cytokines such as interleukin 6, tumor necrosis factor alpha, and leptin, which are produced in visceral and subcutaneous abdominal fatty tissue, especially in males. All are associated with greater severity of disease caused by 2019-nCoV.[7] This ''inflamed'' microenvironment predisposes people with obesity to an abnormal cellular and humoral immune response leading to, on one hand, greater susceptibility to and delay in resolution of the infection and, on the other hand, the onset of severe lung injury and lesser immunization coverage.[8] Associated with inflammation, obesity predisposes the body to a state of hypercoagulability, in this case boosted by 2019-nCoV. It is also important not to forget abnormalities in respiratory dynamics, also especially of note in males, as it confers greater predisposition to respiratory diseases such as asthma

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