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RECOVERY TRIAL AND HYDROXYCHLOROQUINE

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ABSTRACT— During the search for treatments for COVID-19, clinical trials for testing hydroxychloroquine were interrupted by the WHO already on May 25, 2020 after publication of a paper in the magazine The Lancet [2] that stated that patients who had received hydroxychloroquine presented mortality rates of 35% due to severe cardiac arrhythmias. This paper was withdrawn thirteen days after its publication because it was questioned by 120 scientists of various nationalities [3], both as regards the data collected and as regards the method, and on June 2, 2020 also eighty Italian medical doctors sent a letter to The Lancet and to the WHO in which they criticized the scientific contents of the paper. [4] Then, on June 3, 2020, Dr. Tedros Adhanom Ghebreyesus, Director-General of the WHO, allowed restart of recruitment of patients in tests regarding hydroxychloroquine in the Solidarity trial. [5] The Recovery trial then became the principal study on which the WHO based its final decision to confirm for all drug agencies suspension of use of hydroxychloroquine for the treatment of COVID-19.

KEYWORDS: Hydroxychloroquine Recovery Trail Covid Infection

1. INTRODUCTION

Why do we still want to talk about hydroxychloroquine as a treatment for COVID-19 when the Recovery trial [1] conducted in March 2020 by the prestigious University of Oxford and funded by the Bill and Melinda Gates Foundation declared on June 4, 2020 that this drug "had no benefit for patients hospitalized with Covid-19"? Why do we still want to continue to talk about it given that, also following upon this unquestioned result, the WHO decided to withdraw this drug for the treatment of COVID-19? [A] The answer is because to the best of our knowledge and judgment we believe that the Recovery trial is highly questionable, as regards its method and as regards the consequent results concerning hydroxychloroquine.

2. FOREWORD

During the search for treatments for COVID-19, clinical trials for testing hydroxychloroquine were interrupted by the WHO already on May 25, 2020 after publication of a paper in the magazine The Lancet [2] that stated that patients who had received hydroxychloroquine presented mortality rates of 35% due to severe cardiac arrhythmias. This paper was withdrawn thirteen days after its publication because it was questioned by 120 scientists of various nationalities [3], both as regards the data collected and as regards the

method, and on June 2, 2020 also eighty Italian medical doctors sent a letter to The Lancet and to the WHO in which they criticized the scientific contents of the paper. [4] Then, on June 3, 2020, Dr. Tedros Adhanom Ghebreyesus, Director-General of the WHO, allowed restart of recruitment of patients in tests regarding hydroxychloroquine in the Solidarity trial. [5] The Recovery trial then became the principal study on which the WHO based its final decision to confirm for all drug agencies suspension of use of hydroxychloroquine for the treatment of COVID-19.

3. RECOVERY TRIAL

This trial began on March 13, 2020 in the United Kingdom. [6] Approximately 11,500 patients were enrolled by 175 hospitals. These patients all manifested more or less severe respiratory symptoms and frequently presented a clinical picture of interstitial pneumonia of variable degree. Basically, all patients were in the so- called second stage or third stage of the disease, these stages being described in greater detail in the sequel of this letter. The trial was divided into various arms, and to all patients assigned to each arm a treatment was administered that basically consisted in A SINGLE drug.

4. AN APPARENT DIGRESSION

We shall depart momentarily from the discussion of the study to clarify a fundamental aspect, which, without a preliminary explanation, might not enable easy understanding of our criticisms. In the pathogenic evolution of COVID-19 it is possible to distinguish three stages. [7] The first stage is the one in which viral replication prevails (the virus penetrates into the human body and replicates inside its cells). It may not give rise to any symptoms at all, or else it may give rise to symptoms similar to those of classic influenza syndromes, such as malaise, diffused arthralgia, fever, dry cough. Its prognosis is excellent, and its clinical course is benign in approximately 85% of the patients infected. The second stage is characterized by interstitial pneumonia, which very often affects extensively both lungs, and where there is a first inflammatory response with respiratory symptoms that may even be very serious. The prognosis in this stage is variable, and frequently hospitalization is required. The third stage, which may present in a small number of patients, is characterized by a progressing clinical condition caused by an inflammatory hyper-response (the cytokine storm), which causes, inter alia, a clinical picture of disseminated intravascular coagulation (DIC). In this stage the prognosis is critical. What needs to be said is that the WHO never gave any directive as regards a specific protocol to be applied in the case of COVID-19. Nevertheless, at a national level, various medical associations identified a mix of active principles to be used to treat the disease. Even though these indications differed from one country to another (but also, within one and the same country, they frequently differed from one hospital to another and from one region to another), they, however, envisaged a similar approach that contemplated combination, at the initial stage of the disease, of drugs that jointly achieved an immunomodulating and antiviral action. Starting from the first two or three weeks of March 2020, to treat the disease at each of the three stages, each treatment assigned at home or in hospital structures envisaged a combination of drugs that was similar, if not exactly the same, in many parts of the world. Usually, within the first seventy-two hours from onset of the symptoms, patients were treated at home by combining hydroxychloroquine with an antibiotic, specifically azithromycin. Instead, as the symptoms became more severe and during hospitalization, cortisone and low-molecular-weight heparin (LMWH) were added to the drugs used at the early stage. Use of hyperimmune convalescent plasma from patients who had recovered from the disease was then added to this mix of drugs, in a rather patchy way in some areas and in some hospitals. We have witnessed a phenomenon that is perhaps unique in the history of medicine, i.e., a convergence of medical practice throughout the world on the basis of clinical evidence encountered in field. [8,9,10,11] To sum up, albeit in the absence of a directive on the part of the World Health Organization, the various national experiences throughout the world converged towards one and the same approach, namely, a mix of drugs that synergistically responded to viral replication, to the excessive

non-specific immune response, and to intravascular coagulation, each drug having a specific role of its own. This clinical use in the various regions of the world was based upon a wide range of studies published over the last decade that witnessed to the antiviral effect of the active principle contained in hydroxychloroquine in regard to the SARS virus, to which SARS-CoV-2 is strictly related. [12,13,14] Thus the therapeutic strategy adopted, for example, in the IHU Méditerranée-Infection in Marseille France, and in all those realities that drew inspiration from this experience was based on these studies. Moreover, known to specialists in respiratory conditions was the synergistic action of the above active principles and those of specific antibiotics with immunomodulating activity and of anticoagulants, which all together are fundamental for treating symptoms that are similar to the ones caused by SARS-CoV-2 and that, albeit of another etiological nature (e.g., Mycoplasma pneumoniae), cause in the lungs damage comparable to the damage caused by COVID-19. [15]

5. CRITICISM OF THE RECOVERY STUDY

After this apparent digression, we shall now return to the Recovery trial.
Our criticism, given the reasons set forth above, is consequently based on three main points that characterize the trial:

- advanced stage of disease
- monotherapy
- excessive dose.

It is, to say the least, surprising that Oxford University made these choices to test the effectiveness of hydroxychloroquine in the patients treated and to study their mortality rate.

6. Advanced stage of disease

As emerges clearly from the ample clinical experience gathered all over the world, in the vast majority of cases where the mortality rates were contained within a percentage of 3% it is found that there was widespread use of hydroxychloroquine and azithromycin in the early stage of the disease (and of hyperimmune convalescent plasma in the advanced stage, or else corticosteroids, LMWH, etc.). Use of hydroxychloroquine and azithromycin in the early stage finds its justification in the antiviral and immunomodulating mechanisms of action of hydroxychloroquine[16], as mentioned above. Exploitation of these mechanisms in the first stage of the disease enables the drug to express the aforesaid properties at the moment when these are required, i.e., during viral replication within the host organism, and as direct consequence the reaction of the immune system takes place. Hydroxychloroquine counters the inflammatory response in a physiological way, modulating it and not suppressing it, and prevents onset of the cytokine storm. Hydroxychloroquine revealed in vitro or in animal models an antiviral effect through increase of the endosomial pH – which is a determining factor for virus-cell fusion –, thus blocking penetration of the virus into the cell. [16,17,18,19,20,21] Another mechanism of action of hydroxychloroquine for countering/combatting the virus consists in activating the innate immune signalling pathways of IFNβ, AP-1 and NF-κB, as well as in increasing the expression of antiviral genes and cytokynes such as interferon beta (IFNβ). [17] Furthermore, hydroxychloroquine produces an anti-inflammatory effect, which is due to inhibition of hyper- regulation of the mRNA of pro-inflammatory cytokines, IL-6, IL-1β TNF-α [22,23,25] and can block activation of T cells, interrupting T-cell-receptor-dependent calcium signalling. [24,25] If the drug is administered at a stage of evolution of the desease that is excessively late, this says nothing that militates against hydroxychloroquine, but rather calls into question the therapeutic choice. In these advanced stages, in fact, there is massive inflammation, and to prevent disseminated intravascular coagulation typical of COVID-19, clearly different interventions ought to be undertaken in the interests of a correct medical approach.

7. Monotherapy

Notwithstanding the considerable properties just described of hydroxychloroquine as antiviral and anti-inflammatory drug, the numerous clinical experiences have shown that its effectiveness is potentially increased if it is used in combination with another active principle that acts synergistically with it. In the specific case of treatment of COVID-19, the drug that, together with hydroxychloroquine, has been found to contribute most to creating the combined effect that is most favourable for enabling recovery from the disease is azithromycin. Azithromycin is a macrolide, which, in addition to its antibacterial action, has shown an immunomodulating action [26], which differs from immunosuppressive or anti-inflammatory action in so far as it amounts to a non- linear adjustment of the inflammatory response that acts by modifying or regulating one or more functions of the immune system. We use the term "immunomodulation" to describe the downregulation of a hyperimmune or hyperinflammatory mechanism that acts without jeopardizing the normal immune or inflammatory response as a defense from the infection. The drugs hydroxychloroquine and azithromycin are both immunomodulators that synergistically prevent the deleterious effects caused by the massive inflammation induced by COVID-19. Therefore, these are two different drugs, which, however, present a similar activity and work synergistically. In addition, azithromycin is known for halting production of cytokynes, an intense flow of inflammatory mediators that trigger pulmonary inflammation, which is potentially lethal in COVID-19 patients. [27] Just as monotherapy is not practiced also in the case of other diseases, even more so it does not find any rational justification for being adopted in the case of infection from SARS-CoV-2, which has proven to be, as explained previously, a disease that is certainly complex but can be handled at each stage with tools that are adequate in relation to the severity of the disease, and not with monotherapy.

8. Excessive dose

Another aspect that requires some explanation regards the high dosage of hydroxychloroquine that was administered, which cannot be justified either by the clinical practice followed at the time or by the relevant literature. In fact, the doses were more than twice the doses normally administered for reference diseases (malaria, lupus erythematosus, rheumatoid arthritis). Any drug is safe if it is used at the doses envisaged and becomes potentially lethal for higher doses. The Recovery protocol envisaged a dosage of 2400 mg of hydroxychloroquine in the first 24 hours of treatment. The initial dose was then followed by administrations of 400 mg every twelve hours for another nine days, for a total amount of 9.6 g of drug in ten days. Just to make a comparison, Prof. Didier Raoult's team [28] in Marseilles used 600 mg per day for not more than ten days in 1061 patients with COVID-19, recording 8 deaths and a mortality rate of 0.75%. It should be mentioned that in Italy in the same period, at the level of territory medicine the daily doses of hydroxychloroquine used were 400 mg. [29] The above overdose of hydroxychloroquine and the monotherapy mode of administration does not find any medical justification in the treatment of COVID-19. It can thus be stated, beyond any reasonable doubt, that, in the Recovery trial in the United Kingdom hydroxychloroquine was used in a non-therapeutic dose, with consequent increased risk of side effects, such as heart disease and retinopathy, which is incomprehensible in relation to the medical approach currently adopted for this disease. Notwithstanding the extremely high and unjustified dose of hydroxychloroquine, no substantial difference in mortality rate was found as compared to the control arm. [30] The above is altogether at odds with the reasons previously put forward by the WHO for justifying suspension of hydroxychloroquine after publication in The Lancet of the paper that was then withdrawn; namely, that it was an unsafe and potentially lethal drug. In actual fact, hydroxychloroquine is an antiviral compound with a sixty-five-year track record for safety and effectiveness. It was developed from chloroquine, which is, in turn, the synthetic version of quinine. Chloroquine and hydroxychloroquine are inexpensive, globally available drugs that have been used all over the world since 1945 to treat malaria, autoimmune syndromes, and various other conditions. The trial, in fact, itself demonstrated the total safety of the drug given that,

with a dose more than twice the one normally used, did not cause a mortality rate higher than that of the control arm. In this perspective, acknowledging or rejecting a possible healing capacity for a drug in the case where the drug is used improperly and without exploiting the necessary synergistic effect obtained by combining drugs appears rather questionable. In such circumstances, it is consequently obvious that hydroxychloroquine was unable to prevent the death of many patients. Only if it is used according to current practice can it prevent aggravation of the disease and its complications or death of the patient.

9. A note on dexamethasone

For the reasons that will be clarified hearinafter, it is instead worthwhile describing briefly the report regarding another drug used in the Recovery trial, namely, dexamethasone. [31] According to the Recovery research group at Oxford University, this drug is described as being the first drug to be shown to reduce mortality rate in a significant way. The data, however, do not appear to support the adjective “significant” used above. The patients treated without dexamethasone after 28 days showed a mortality rate of 41% in the case where they required mechanical ventilation, of 25% when they required only oxygen, and of 13% when no respiratory treatment was required. Dexamethasone was found to be fundamental in saving 1 patient out of 8 under mechanical ventilation and 1 patient out of 25 under oxygen, whereas no beneficial effect was found in patients in a better clinical condition who did not require oxygen. We thus fail to understand the emphasis given, upon conclusion of testing with dexamethasone, by Prof. Peter Horby and Prof. Martin Landray on its effects, as if it were a sensational discovery. The error made in the study conducted by Oxford University, which regards the entire Recovery trial, is monotherapy, namely, testing of only one drug or type of treatment. Especially with regard to dexamethasone, the Recovery trial has failed to bring out sufficiently the real importance of corticosteroids in saving lives in the second and third stages of the disease, when they are used in combination with other drugs. As we have said, corticosteroids have always been the elective drug in interstitial pneumonia and have proven to be very useful in dealing with the COVID-19 epidemic, it should be introduced at the moment when the so-called cytokine storm is about to occur in the second stage of the disease together with hyperimmune plasma, immunomodulating therapy, and anticoagulants, and has also proven useful in the third stage of the disease. Use thereof envisaged by the Recovery trial for the treatment of COVID-19, in monotherapy regimen, has devalued its real scope and importance. We wish to emphasize that cortisone has been used for some 50 years now all over the world in the case of interstitial pneumonia. Moreover, not even its use in relation to COVID-19 is a discovery that can be attributed to the Recovery trial in so far as dexamethasone analogues have been used, together with other drugs, in practically all hospital structures at a worldwide level, starting from March 2020. The above treatments, which are based upon a combination of drugs, have provided COVID-19 patients with benefits far exceeding the ones reported by the Recovery trial. Finally, it should be said that the effectiveness of the use of dexamethasone in the early stage of the disease remains altogether to be verified.

10. CONCLUSIONS

It should be said with extreme clarity that many European hospitals have seen mortality rates that during the epidemic are not so high as those of the Recovery trial. This statement alone would be sufficient to demonstrate that the underlying arguments of the Recovery study are wrong. As we have clarified in our objections, the Recovery study does not prove either the ineffectiveness of hydroxychloroquine or the effectiveness of dexamethasone. What the study does show, instead, is only the ineffectiveness of use of hydroxychloroquine at an inappropriate stage of the disease, at excessively high doses, and in monotherapy for combatting COVID-19. Demonstrated at the same time is the inadequate effectiveness of dexamethasone unless it is included within the framework of a protocol that associates it with other drugs. It is thus shown that even a hypothetical “life-saving” drug fails to be such if it is used alone. The only true demonstration useful for the medical and scientific community to which the Recovery study leads appears to be the

confirmation of the evidence based upon clinical practice, developed during the epidemic, that has led the doctors engaged in the front line to employ a combination of drugs, the use of which rapidly spread all over the world. Clinical practice has witnessed, in the situations where the mortality rate was contained within extremely low percentages, the constant presence of hydroxychloroquine, azithromycin, cortisone, anticoagulants, and, in certain cases, hyperimmune convalescent plasma. What is particularly perplexing is the fact that the WHO bases its own decisions – as it did with the paper published in The Lancet and subsequently withdrawn – on studies that provide clear evidence of the fact that this disease is treated as if it were a disease completely unknown in its manifestations and clinical evolution. The total absence of a medico-clinical approach to COVID-19 in the Recovery study necessarily requires the WHO to reconsider the decisions adopted as a consequence of this study; otherwise, it will itself be responsible for an increase in deaths throughout the world. The decision to ban yet again a drug that has now proven to be safe and of ascertained effectiveness in the initial stage of the disease contributes to increasing the death toll of persons who could otherwise have been successfully treated and healed, as well as to prolonging the pandemic. This, although unacceptable under any circumstance, emerges as an intolerable harm and tort above all in the poorest countries, where hydroxychloroquine represented the main therapeutic drug in the early stages of the disease.

11. NOTES

As a result of this decision, all regional and national drug agencies gave orders in their own territories to limit use thereof to clinical trials alone. The WHO declared that its own decision was taken on the basis of the results of the Recovery trial but also on the Solidarity trial and a Cochrane rewiew of other evidence on hydroxychloroquine.

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