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THOUGHTS

Ethical issues related to the hydroxychloroquine treatment prescription for Covid-19

Problèmes éthiques liés à la prescription de l'hydroxychloroquine pour le traitement des malades Covid-19

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Summary The 2019-20 coronavirus pandemic (COVID-19) has led to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, no drugs have demonstrated safety and efficacy in randomized controlled trials for patients with COVID-19. Although the association between Hydroxychloroquine and Azithromycin efficacy lack of solid evidence-base, several governments have adopted it for all virology confirmed Covid-19 cases even for those who are asymptomatic. In the following, we aim to discuss some of the ethical issues associated with the use of this treatment association. We mainly tried to discuss the following controversial questions: Is it ethical not to treat a patient while a treatment exists and is used for other indications than Covid-19 for which it's not proven yet? If yes, is a randomized controlled trial to prove the hydroxychloroquine for the Covid-19 treatment, necessary, in the context of covid-19 pandemic? If no, is it the government's right to decide the hydroxychloroquine treatment for all covid-19 patients? And what should be the physicians' attitudes? Finally, what are the government, physicians, and patient's rights and responsibilities? The paper conclude that, since health authorities in some countries recommended this off-label use treatment, physicians are challenged by the requirement of veracity while providing care to their patients and the implications of such a requirement; they are facing the challenge of balancing this guideline and their own conviction. Furthermore, the fundamental principles of beneficence and non-maleficence, and respect for

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persons should underlie any reflection process to address this dilemma. In addition, in a pandemic context, the limits between the government's, practitioner's and patient's rights and obligations are not clear which could significantly endanger the universal ethical principles in clinical practice. It could also undermine any attempt to develop serious clinical trials to prove the considered off-label drug.

MOTS CLÉS
Covid-19 ;
Dilemmes éthiques ;
Traitement à l'hydroxychloroquine ;
Responsabilités ;
Droits

Résumé La pandémie de coronavirus 2019-2020 (COVID-19) conduit au syndrome respiratoire aigu sévère coronavirus 2 (SRAS-CoV-2). À ce jour, aucun médicament n'a démontré son innocuité et son efficacité dans des essais contrôlés randomisés pour les patients atteints de COVID-19. Bien que l'association entre l'hydroxychloroquine et l'azithromycine manque de preuves solides, plusieurs gouvernements l'ont adoptée pour tous les cas de Covid-19 confirmés, même pour ceux qui sont asymptomatiques. Dans ce qui suit, nous discutons certains des problèmes éthiques associés à l'utilisation de cette association thérapeutique. Nous avons principalement essayé de discuter les questions controversées suivantes: est-il éthique de ne pas traiter un patient alors qu'un traitement existe et est utilisé pour d'autres indications que le Covid-19 pour lequel il n'est pas encore prouvé ? Si oui, un essai contrôlé randomisé pour prouver l'hydroxychloroquine pour le traitement Covid-19 est-il nécessaire dans le contexte de la pandémie Covid-19 ? Si non, le gouvernement a-t-il le droit de décider du traitement à l'hydroxychloroquine pour tous les patients de Covid-19 ? Et quelles devraient être les attitudes des médecins ? Enfin, quels sont les droits et responsabilités du gouvernement, des médecins et des patients ? Le document conclut que, puisque les autorités sanitaires de certains pays ont recommandé ce traitement hors AMM, les médecins sont confrontés aux challenges de l'exigence de véracité de l'efficacité du traitement tout en prodiguant des soins à leurs patients et aux implications d'une telle exigence ; ils sont confrontés au défi d'équilibrer ces exigence et leur propre conviction. En outre, les principes fondamentaux de bienfaisance et de non-malfaisance, et le respect des personnes devraient sous-tendre tout processus de réflexion pour résoudre ce dilemme. Enfin, dans un contexte de pandémie, les limites entre les droits et obligations du gouvernement, du praticien et du patient ne sont pas toujours claires, ce qui pourrait mettre en danger de manière significative les principes éthiques universels dans la pratique clinique. Cela pourrait également saper toute tentative de développer des essais cliniques sérieux pour prouver le médicament hors AMM considéré.

Introduction

The 2019-20 coronavirus pandemic (COVID-19), has led to major morbidity in the form of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 265 862 deaths [1].

To date and after the fifth months into the novel coronavirus pandemic, no drugs have demonstrated safety and efficacy in randomized controlled trials for patients with COVID-19. Several agents such as Hydroxychloroquine, Lopinavir, Ritonavir and Azithromycin are being used under clinical trial and compassionate use protocols based on in vitro activity (against SARS-CoV-2 or related viruses) and on limited clinical experience [2,3].

Although the association between Hydroxychloroquine and Azithromycin efficacy lack of solid evidence-base, it has been largely mediatized. Some experts are defending the efficacy of this association based on previous experiences on Malaria and also based on some of their observations made upon COVID-19 patients [4].

WHO refuted all allegations for the effectiveness of any drug and recommended only symptomatic treatment and monitoring for Covid-19. Many developed countries as China, European countries, and the USA are still very cautious about any proposed drug and are waiting for many ongoing clinical trials to be over [5].

Despite the doubt and uncertainty about a drug effectiveness for Covid-19, several governments have adopted the Hydroxychloroquine and Azithromycin association for all virology confirmed Covid-19 cases even for those who are asymptomatic [6]. This decision has raised many questions and some ethical issues related to the hydroxychloroquine treatment prescription might emerge during the Covid-19 patients' management. In the following, we aim to discuss some of these ethical issues associated with the use of this treatment association.

Is a randomized control trial necessary to prove the hydroxychloroquine—azithromycin association for the Covid-19 treatment in the emergency context?

It's admitted that all authorized drugs should be proven. In the case of hydroxychloroquine, it is not proven for Covid-19 yet. Its labeled indication is for the treatment of malaria. Its use in the Covid-19 is therefore off-label. That is why its use in the context of Covid-19 is rising many controversial questions: Is it ethical not to treat a patient while a treatment exists and is used for other indications than Covid-19 for which it's not proven yet? If yes, is a randomized controlled trial to prove the hydroxychloroquine for the Covid-19 treatment, necessary and feasible, in the context of covid-19 pandemic? If no, is it the government's right to decide the hydroxychloroquine treatment for all covid-19 patients? And what should be the physicians' attitudes? Finally, what are the government, physicians, and patient's rights and responsibilities?

First of all, randomization is the best way to avoid selection and information bias and equipoise is the main justification for randomization. It could be overlooked only when a treatment is clearly superior, and in this case, randomization will put one group of patients at a disadvantage. Many historical examples for effective treatment were based only on observational studies that were adequate enough to show effectiveness without recourse to randomization, e.g. penicillin for bacterial infections; smallpox vaccination. . .

In the case of hydroxychloroquine and COVID-19, we may ask if there is sufficient scientific and medical evidence to prescribe this drug as a treatment. A recent systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19 [7] concluded that there is sufficient pre-clinical rationale and evidence regarding the effectiveness of chloroquine for treatment of COVID-19 as well as evidence of safety from long-time use in clinical practice for other indications [8] to justify clinical research on the topic. Based on this conclusion, the question, related to the prescription of this drug as a treatment for covid-19, is not answered yet. However, one could argue that the worldwide emergency, the rapid spread of the disease, and the high rates of disease mortality mainly at the beginning of the pandemic [9], are sufficient reasons for prescribing this off-label treatment for Covid-19 patients. If the answer is yes, there remain the questions of what are the main ethical principles to be applied in this case? And is there other evidence based pathway other than Randomized Clinical Trial to support new purposes of this drug?

In the context of covid-19 pandemic characterized by a high case fatality rate (CFR) reported to be 15% in the initial period of the pandemic [9], health-care leaders and policy makers need such estimates of mortality and case fatality, even they were changing all over the time [10] and between cases illness severity [10], to be guided in forming strategies at national level from a public health perspective including patient care strategy. MEURI (Monitored Emergency Use of UnRegistered Interventions) Framework group stated that, in such emergency situation, it can be ethically appropriate to offer individual patients experimental interventions on an emergency basis outside clinical trials [11]. This is even more true when the best available therapeutic option fails, and patients demand new approach or new treatment and physicians promote patients' interests by prescribing products off-label [12], and also when the use of the ''best available drug'' is supported by some expert opinion [11], which is the case of the hydroxychloroquine. However, the clinical use of such drugs, should adhere to the MEURI framework [11] and the four principles of medical ethics (respect for autonomy, beneficence, non-maleficence, and justice) should be respected.

The Ebola outbreak in the Democratic Republic of Congo is a good example illustrating this reasoning where vaccine trials have been conducted under the scrutiny of the MEURI method [13]. Some results from these trials suggest robust vaccine efficacy within 10 days and good tolerance when administered to healthy, non-pregnant adults [14] while some authors deplore that none of the promising treatments used in Ebola field trials could so far be convincingly confirmed as curative [15] and the MEURI circumstances should not substitute for properly designed trials. Having said that, Agarwal propose a pluralistic evidence instead of a Randomized Clinical considering all available sources and types of data, including laboratory studies on mechanisms of action, in vitro experiments on human biopsies, in vivo animal models, quality of life data, clinical trials of off-label drug use, etc [16]. The pluralistic evidence approach may be feasible and acceptable in the covid-19 pandemic. It can provide: data of sufficient quality to ''fill the evidence gap'' for the efficacy and safety of such off-label medicine, a more complete causal association while minimizing the potential biases, and practitioners can be more confident and less reluctant for its prescription.

What are the government, physicians and patients' rights and responsibilities?

For government

In modern societies, the government's duty to provide healthcare is established by law. Does this mean that the government has the right to decide whether a treatment even not proven yet, should be prescribed as a treatment?

In habitual situations, authorities monitor off-label drug uses, regularly collect and publicize information about off-label uses, and consider proposals to regulate certain off-label uses as well as other proposed policy measures that could decrease risky and ineffective off-label prescribing. [12]. However, in the covid-19 pandemic, the government is promoting the off-label drug prescription. In doing so, decision-makers should be guided by any available scientific evidence about the intervention expected benefits and harms [11]. When specific evidence is not available, decisions should be based on reasoned and evidence-informed substantive arguments from analogous situations, to the possible extent [11]. However, at some point in an emergency context, decisions are still very difficult to make especially when it comes to the weight to be given to treat patients

in pandemic context compared to other important public health priorities [17]. This should not be a reason to not include clinicians and patients in this decision-making process. Otherwise, this decision may be considered unacceptably paternalistic.

For doctors

Many doctors are currently facing the dilemma of a choice between the two options: either prescribing not yet proven treatment with many unanswered questions on the one hand or to be limited to symptomatic treatment as recommended by WHO on the other. They may ask what might be the ethical implications of doing so?

While the government has decided on the treatment prescription, some doctors may feel forced to prescribe a treatment regimen of which they are not necessarily convinced and may feel double challenging: should they strictly follow the therapeutic protocol as dictated by their government? Should they present that treatment to their patients as experimental or as therapeutic?

The physician's duty is to provide clear clinical information to his patient in accordance with the universal rules of ethics. In addition, in ''standard'' situation, ''responsible off-label prescribing requires physicians to:

- evaluate whether there is sufficient evidence to justify an off-label use;
- press for additional information and adequate evidence;
- inform patients about the uncertainties and potential costs associated with off-label prescribing'' [12].

However, explaining the risks and benefits in detail, and explaining also that, although this treatment has had good results in other indications, its effectiveness for Covid-19 is not yet proven, is not an easy task in such context. In addition, some could argue that taking the time to explain all details about the complexities of off-label drug use in an emergency context could distract from shared clinical goals [18,19]. This challenge is even more complicated in developing countries, considering the context of multicultural specificity (different dialects), medical paternalistic decisions often required by patients, the social vulnerability which is deepened more and more by the pandemic (high level of illiteracy, low socioeconomic level). In addition, because in some countries [6], the treatment has been recommended for all patients even for those who are asymptomatic, some doctors argued that the treatment should be given only to moderate to critically ill patients. Such targeting of the treatment, however, may be viewed from a public health emergency perspective, as to be less effective in reducing the spread of the disease in the contact patients and the whole population. Such attitude may undermine the public health goal as individual interests outweigh the collective ones.

For patients

The first concern when it comes to patients is related to the principle of beneficence and non-maleficence. To address this concern, we need to answer two questions:

- the first question is whether there is enough evidence as to the benefits of the hydroxychloroquine. Reluctancy regarding the use of this drug for the treatment of patients with Covid-19 is justified by the absence of a high level of scientific evidence namely randomized controlled clinical trials proving the superiority of this drug for this indication, as we discussed above. In the presence of such a crisis, waiting for the results of randomized clinical trials might be considered a luxury;
- the second question is to what extent the risks related to hydroxychloroquine are acceptable and justifiable by the benefits. It comes to how much we know about this drug safety and tolerance. In the particular case of hydroxychloroquine, the drug is known and has been used for so many years for malaria treatment and prophylaxis as well as some autoimmune conditions [3]. This means it has been used among large patients' populations and clinicians have long experience with prescribing it and monitoring its side effects.

In the effort of trying to address these concerns, we would want to provide the best care for patients considering available knowledge and at the same time; generate valid evidence for the future. The off-label and unlicensed use of drugs is quite common in medical practice. Several reasons explain this phenomenon. In a recent paper, Agarwal discusses a pluralistic method for ethical and efficient evidence generation for off-label medication use in a real-world situation [4].

The very specific conditions of a global public health threat such as the current Covid-19 pandemic do not allow us to wait for generating high-quality evidence before proposing promising drugs. A recent example is the recent Ebola outbreak in the Democratic Republic of Congo that has raised similar discussions. The World Health Organization advised the monitored emergency use of unregistered interventions (MEURI) [16]. Bhadelia et al. also proposed a set of recommendations on how to choose among available options and to collect data to build the evidence [20]. Such perspectives and examples can be considered for translation in the situation of the Covid-19 pandemic.

Since the beginning of this pandemic, scientists started exploring the available options [20,21]. To date, there is no proved vaccine or treatment for covid-19. But several papers supporting the rationale for Chloroquine use have been published [22]. Some articles reported on preclinical data [4] or preliminary clinical data [23]. In many countries, the use of hydroxychloroquine is recommended by health authorities, as this is the case in Morocco [6]. Finally, clinical trials are ongoing to provide further evidence [24], which will provide a supplementary argument for ethicists to solve this question.

The second concern is related to the principle of ''respect for persons'', with an emphasis on patients' autonomy and healthcare providers' transparency or veracity.

Off-label prescription is considered legal and is quite frequent. A common example is the prescription of many drugs among children because those drugs were not tested and evaluated among this population [7]. Another example is Aspirin which was prescribed to prevent cardiovascular events for many years before it was licensed by the FDA for this indication.

On the other hand, it is recognized that off-label prescriptions can be dangerous and are generally more

expensive. Thus, it is important to emphasize informed consent and shared decision-making [25]. In the case of chloroquine, it is a cheap drug, but the probability of side effects is present.

Several arguments for requiring consent for off-label use were proposed including that it is a means to respect the patient's autonomy, to account for the potential risk to patients related to the lack of scientific evidence. Another set of arguments could be discussed for not requiring this consent: the procedure of obtaining approval for all different uses might be considered not cost-effective for pharmaceutical companies. The use of licensed drugs is not without risks. It is also possible that discussing the off-label nature of the use confuses the patient [26].

Obtaining valid informed consent requires that the patients should be informed that the proposed treatment is not licensed for this indication, with available rationale and data justifying its consideration for the situation. Appropriate information and consideration for the patient's autonomy should lead to shared decision-making. Achieving informed consent and shared decision-making is the application of the principles of patient autonomy and veracity.

Conclusion

This paper highlighted some ethical issues related to the prescription of an off-label drug in the pandemic conditions. In such context, the limits between the government's, practitioner's and patient's rights and obligations are not clear which could significantly endanger the universal ethical principles in clinical practice. It could also undermine any attempt to develop serious clinical trials to prove the considered off-label drug.

Since health authorities in some countries recommended this off-label use, physicians are challenged by the requirement of veracity while providing care to their patients and the implications of such a requirement. Furthermore, physicians are facing the challenge of balancing this guideline and their own conviction. The fundamental principles of beneficence and non-maleficence, and respect for persons should underlie any reflection process to address this dilemma.

Hence, there is an urgent need for guidance to encourage proper off-label use of drugs in an emergency situation. This step should be taken only considering grounded ethical and legal principles, and if the important decisions about the drug prescription is taken through a process that is transparent, inclusive, and appropriately communicated to practitioners as well as the general public [27] with the development of culturally-sensitive communication strategies, this may be achievable with relatively modest resources.

Disclosure of interest

The authors declare that they have no competing interest.

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