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Ethical Issues Regarding Investigational Drugs for the Treatment and Prevention of COVID-19

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Abstract

The challenging COVID-19 pandemic has witnessed the searches for treatment for a disease that had never been known before. Therefore, developing a treatment for the pandemic reflexively has gone beyond the usual methods due to limited time and the urge to benefit the patient. In cases where licensed drugs are insufficient, patients with serious and life-threatening diseases can have access to investigational drugs. These investigational drugs are used within programs such as Compassionate Use (CU) and Emergency Use Authorization (EUA) based on certain legal regulations. In terms of clinical and research ethics, it is a must to keep a balance between the necessity for the treatment to be tested for safety and effectiveness and the purpose of benefiting the patient. Such programs that are aimed at treatment are legitimate due to the concessions caused by the urgent need of treatment for a life-threatening disease in the crisis of a pandemic, however, ethical inquiries must be maintained and even increased in such challenging periods especially because of the need for rapid decision-making and information update. The ethical dilemmas that investigational drugs create have become more apparent, especially in this time of pandemic we are facing. The use of drugs within CU and EUA has ethical challenges. In our study, these challenges are discussed on the basis of beneficence, non-maleficence and justice, which are the basic principles of medical ethics. Regarding this basis, pharmaceutical industry, health authorities and physicians have a great responsibility.

Introduction

SARS-CoV-2 is a single-enveloped, single-stranded RNA virus that causes severe respiratory diseases in humans [1]. The coronavirus disease (COVID-19) was recorded as a severe pandemic that caused more than 4 million people's death around the world between December 2019 and August 2021. It has been reported that coronaviruses might cause respiratory, gastrointestinal and central nervous system diseases in humans and animals, might threaten human life and cause economic loss [2]. These viruses can also mutate and adapt to new environments and maintain their prevalence and efficacy for a long time[3].

Other coronaviruses, including SARS-CoV-2, cross the species barrier and infect humans, lead to outbreaks of severe and fatal respiratory diseases. Since the discovery of 229E and OC43, the first coronaviruses effective on

humans, in the late 1960s, the prevailing perception has been that coronavirus infection is largely harmless to humans[4]. This perception changed dramatically with the outbreak of severe respiratory syndrome coronavirus (SARS-CoV) in southern China in the winter of 2002 [5]. With the pandemic that originated from these viruses in 2002, about 20-30% of individuals with SARS needed intensive care units, and the overall mortality rate was around 15% [6]. In 2012, the findings detected in a 60-year-old patient in Jeddah, Saudi Arabia were similar to SARS, and it was seen that the isolated virus caused a new pandemic called MERS[7]. The overall death rate of MERS was around 36 % [2].

It is claimed that SARS-CoV-2, which affects the whole world today, emerged in the seafood wholesale market in Wuhan, China in 2019[8]. SARS-CoV-2 is the seventh member of the coronavirus family that infects humans and is different from both MERS-CoV and SARS-CoV. While some infections caused by human coronaviruses are mild and associated with the common cold, infections with COVID-19 have been recorded to be fatal, particularly in young children, the elderly, and immunocompromised patients [9].

The COVID-19 pandemic is a unique period in terms of the intensity of the development of new diagnostic and treatment methods [drugs, vaccines, etc.). Most of these treatment methods, which are predicted to be clinically beneficial, are investigational drugs. Drug repurposing, the process of identifying new uses of investigational drugs, is considered a very effective strategy for drug development as it requires less time and cost to find a therapeutic agent compared to the de novo drug development process[10].

While many of these products are undergoing accelerated clinical trials and regulatory review, there is pressure to ensure access as soon as possible to meet urgent patient needs is noted[11]. In such a backdrop, the drugs used for the diagnosis and treatment of COVID-19, and the production and application processes of protective vaccines have formed the basis of many discussions and are questioned within the framework of clinical research ethics. Our study includes the ethical evaluation of drugs and vaccines used in the research phase and in the COVID-19 pandemic.

Aim and Method:

It is a necessity in terms of clinical and research ethics to provide a balance between providing treatment to patients as soon as possible in emergency situations and the need for the treatment to be tested in terms of safety and efficacy. The ethical dilemmas that drugs and vaccines that have not yet received approval, whether it is a compassionate use (CU) program or Emergency Use Authorization (EUA), have become more apparent, especially in this pandemic period we are experiencing. In this study, the issues to be discussed in medical ethics -within the framework of the principled ethical approach- by applying the principles of beneficence, nonmaleficence, and justice are as follows: Ethical discussions on the use of investigational drugs with compassionate use or emergency use authorization, the Declaration of Helsinki, which forms the basis of research ethics, and a review of the literature published in PubMed over the past decade.

The Usage of Investigational Drugs in Treatment

Patients with serious and life-threatening diseases can be accessed to investigational drugs outside of clinical trials within certain programsin cases where licensed drugs are insufficient[12]. These programs are called Compassionate Use (expanded access) and Emergency Use Authorization.

Compassionate Use (CU) Program (Expanded Access)

It is the usage of an investigational drug for diagnostic, imaging or therapeutic purposes rather than collecting information about its safety and/or efficacy. This program is applied in more serious and directly life-threatening diseases or situations where there is no other possibility of treatment. What is meant by directly life-threatening is the possibility of death within a few months if no medical intervention is applied, and serious illness means that it has a significant morbidity-related impact on daily functioning[13].

In cases where the drug is withdrawn for safety reasons but the benefit outweighs the risks; for a similar but not yet approved (or approved by a foreign country) drug at the time of the drug shortage; Compassionate Use (CU) may also be applied where availability is limited within a risk assessment and mitigation strategy for diagnostic, monitoring or therapeutic purposes [13].

Under the Food and Drug Administration (FDA)'s current regulations, there are three categories of expanded use: a) Access to an individual patient: Early access for a single patient. b) Access to an average

patient population: Patients who are ineligible for a clinical trial (for example, with exclusion criteria) or who do not have access to a clinical trial (for example, who are geographically remote) are included in this category. c) Therapeutic Access: The investigational drug is allowed to be used for extensive treatment[13].

Medical countermeasures (MCMs) that are used by health authorities to combat threats of chemical, biological, radiological, nuclear and infectious diseases during public health emergencies to facilitate access to drugs, diagnostic tests or other essential medicinal products when approval and adequate options are not available [14].

In the US, the BioShield Act of 2004 created the comprehensive Emergency Use Authorization (EUA) program. Emergency Use Approval allows the FDA to apply the emergency use (including diagnostic) of drugs, devices, and medical products that have not been previously approved, registered or licensed[15].

The first emergency use approval took place in 2005. The U.S. Department of Health and Human Services has issued a statement pursuant to the Federal Food, Drug, and Cosmetic (FDA) Act to enable the emergency use of Adsorbed Anthrax Vaccine (AVA) for the prevention of inhalation anthrax. This decision was taken to reduce the risk of the exposure of US soldiers to anthrax [16].

Difference between CU and EUA

It is stated that the main difference between CU and EUA is that CU applies to patients who are not eligible to be included in the clinical trial (outside the inclusion criteria)—but in the EU there are no such criteria, the EU is part of medical treatment [17]. A drug can be used under both CU and EUA. However, the drug is not used as a CU after EUA approval. For instance, remdesivir was used within the CU program before receiving emergency use approval. Before the relevant randomized controlled trials were conducted and the results were published, remdesivir was provided to hospitalized severe COVID-19 patients within the scope of the CU program in the clinic, and the cohort results were published[18].

Overview of Investigational Drugs and Vaccines Used in the COVID-19 Outbreak Period

During the COVID-19 pandemic, numerous drugs were administered in treatment. In addition, countries have approved a large number of vaccines during the development phase. In our study, we include a few of these drugs and vaccines as examples. The common features of these drugs and vaccines are that they have been the subject of ethically controversial debates in this pandemic period.

Hydroxychloroquine and Chloroquine (HCQ and CQ)

Chloroquine is an antimalarial agent known for many years[19] For the treatment of COVID-19, an emergency use permit was granted by the FDA on March 28, 2020, and was cancelled on June 15, 2020. Based on the new information and other information discussed in the letter is presented, the FDA has concluded that it is no longer reasonable to believe that the oral form of HCQ and CQ can be effective in the treatment of COVID-19 and that it is no longer possible to conclude that the potential benefits outweigh the potential risks of these two drugs. They also reported that it cannot be used for treatment anymore [20].A meta-analysis of the effects of HCQ/CQ on survival in COVID-19 from all available published and unpublished RCT evidence (completed or discontinued) found that treatment with HCQ is associated with increased mortality in COVID-19 patients and there is no benefit of chloroquine [21].

Convalescent Plasma

Convalescent plasma is the liquid portion of blood collected from patients who have recovered from the infection. Antibodies found in convalescent plasma are proteins that can help to fight the infections [22]. In a statement released by the FDA on April 3, 2020, it was reported that plasma therapy is being investigated for the treatment of COVID-19 because there is no approved treatment for this disease and there is some information showing that it may help some patients' recovery from COVID-19[23]. Thereupon, in a study conducted on 36 thousand patients between April 4 and July 4, 2020, it was shown that plasma therapy provides a lower mortality rate [17].

Remdesivir

Remdesivir has been used to treat RNA-based viruses, including the global epidemic *Coronaviridae* family viruses such as EBOV, SARS, and MERS [24]. In vitro and preclinical in vivo animal models have supported the efficacy of remdesivir against SARS-CoV-2 and related coronaviruses [25]. Immediately after the COVID-19

outbreak, clinical trials were started at two centres in China on February 5 and 6, 2020 [26][27]. In the first COVID-19 case reported in the USA on February 20, 2020, Remdesivir was used within CU program, the patient's fever decreased on the 8th day of hospitalization, and the PCR became negative on the 12th day [28].

After the National Institute of Allergy and Infectious Diseases (NIAID) announced the preliminary data on April 29, 2020, an EUA was granted by the FDA on May 1, 2020.

Bamlanivimab

Monoclonal antibodies such as bamlanivimab might be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high-flow oxygen or mechanical ventilation and are not authorized to be used in patients hospitalized for COVID-19 or requiring oxygen therapy. On November 9, 2020, FDA issued an EUA for bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients - Ages 12 years and older weighing at least 40 kg- [29]. Then, on April 16, 2021, FDA revoked the authorization for bamlanivimab, as the potential benefits outweighed the potential risks in the light of the data, particularly based on the continued increase of SARS-CoV-2 viral variants resistant to bamlanivimab alone, resulting in an increased risk of treatment failure[30].

Pfizer-BioNTech COVID - 19 Vaccine

On December 11, 2020, the FDA approved an EUA of an mRNA vaccine, Pfizer-BioNTech, for COVID-19 patients over the age of 16. On May 10, 2021, they stated that it can be applied between the ages of 12-15. On June 25, 2021, the FDA revised patient and company information sheets regarding the increased risks of myocarditis and pericarditis after vaccination [31]. Adverse effects that occur in any person after receiving the COVID-19 vaccine are reported to the Vaccine Adverse Effect Reporting System (VAERS). The FDA requires the vaccination company to report administration errors, serious adverse events, cases of multisystem inflammatory syndrome, and cases of COVID-19 resulting in hospitalization or death after administration of the COVID-19 vaccine under emergency use approval [32].

AstraZeneca/Oxford COVID-19 Vaccine

AstraZeneca released the first results of its phase III studies on March 5, 2021. It demonstrated statistically significant vaccine (an mRNA vaccine) efficacy of 79% in the prevention of symptomatic COVID-19 and 100% in the prevention of serious illness and hospitalization [33]. During phase III trials expected to be completed on February 14, 2023, on March 23, 2021, the United States Data and Safety Monitoring Board (DSMB) expressed concern about the information published by AstraZeneca about the initial data from the COVID-19 vaccine clinical trial. DSMB expressed concern that AstraZeneca included outdated information in this clinical trial, which may provide an incomplete view of efficacy data [34]. According to a news report in March 16, 2021, while researchers are investigating cases of blood clots among vaccinated people, several countries have reported that AstraZeneca has discontinued the use of the COVID-19 vaccine as a precaution [35]. A day after this news, the World Health Organization (WHO) made a statement and stated that it thought the benefits of the AstraZeneca vaccine outweighed the risks and recommended the vaccines to continue [36].

Sinovac CoronaVac COVID - 19 Vaccine

CoronaVac is an inactivated vaccine against COVID-19 that stimulates the body's immune system without the risk of causing disease. In the efficacy demonstrated in the phase III study in Brazil, participants who received 2 doses of the vaccine 14 days apart had an efficacy of 51% against symptomatic SARSCoV-2 infection, 100% against severe COVID-19, and 100% against hospitalization starting 14 days after receiving the second dose [37]. This rate was reported to reduce prevention by 84% and hospitalization by 100% in a study conducted in Turkey [38]. The vaccine was approved for emergency use in Brazil on January 17, 2021, and in Turkey on January 13, 2021.

Ethical Framework for Investigational Drugs and Vaccines for the Treatment and Prevention of COVID-19

We will try to establish the ethical framework for investigational drugs based on three main principles: Beneficence, non-maleficence and justice.

1. Beneficence

The primary goal of medicine is to benefit the patient. As the basis of the promised benefit to the patient, the effectiveness of the interventions should be demonstrated by clinical studies. During a public health crisis such as a pandemic, in case that information is constantly evolving, the rationale for providing a drug that is still in the research phase to a patient who cannot be treated with current methods is the physician's aim to benefit the patient [39]. Although the risks of an investigational drug are great because the patient's life is in danger, the expected benefit outweighs the potential risks. Therefore, it is the utility purpose that justifies departing from the usual procedures in clinical trials in CU/EUA programs. According to Declaration of Helsinki, an unproven intervention may be used in the treatment of an individual patient in the judgment of the physician, when there are no proven interventions or where other known interventions are ineffective[40].

Programs such as CU and EUA, depending on their characteristics, are neither clinical research nor clinical practice. Since the logic of clinical research and clinical practice are different from each other[41], ethical evaluation of programs such as CU or EUA bring challenges arising from these differences.

Physicians have difficulties deciding which patients to use these drugs due to the fact that the current drugs were obtained EUA during the investigation of the indication for COVID-19 and they started to be used in patients, and the lack of information (causing uncertainty) obtained as a result of the research. For example, it was noted that it is not known how patients respond to remdesivir; - compared to patients with lower acuity - earlier disease status and patients with higher accuracy-late disease status, it is unclear which of them will have a better effect on the use of remdesivir [42]. This situation has been a target particularly regarding individual use programs such as CU, and since the physician is responsible for the supply of an unapproved drug to the patient, the importance of the qualifications of the physician who will perform the treatment and the patient selection criteria that the physician will use to determine which patient will be given this treatment has been emphasized[43]. According to the EUA definition, in addition to the difficulty experienced by the physician, the claim that there is no need to have sufficient information about efficacy and safety for approval[44] increases the uncertainty of the situation.

Concerns about the Endpoint of Clinical Research

The endpoint is defined as the overall outcome that a clinical trial aims to measure. This result can be a disease characteristic, health condition, symptom, or test (laboratory, radiological) results. At the beginning of the development and evaluation of an intervention, endpoints are used to determine the safety and biological activity of an intervention. Then, endpoints help decide whether a drug provides a clinical benefit or not[45].

A Discussion for Endpoint: An Example of Remdesivir

During the pandemic, there is an aim to get results from clinical trial as soon as possible. The decision on when to end the trial (how to determine the endpoint) is crucial and research ethics requires this decision to be questioned. Because, it is pointed out that a secret and bureaucratic process may be operating in making these decisions, as is often the case in clinical trials[46] For instance, how to determine this endpoint has been discussed broadly in the early part of the pandemic, in the remdesivir trial. It was emphasized that if the placebo group were cancelled without obtaining data on mortality, the main purpose of the clinical trial would not have been fulfilled and would limit the possibility of collecting further data on whether the drug would save lives.

According to preliminary data released by NIAID April 29, 2020, remdesivir reduces the median time to recovery (being well enough for hospital discharge or returning to normal activity level) 4 days compared to the placebo[47]. There was no statistically significant difference in mortality and the determination of the length of the median time to recovery as an endpoint has been an important discussion.

The main objection to the argument that the evidence on length of stay is "better than nothing", even if there is little evidence: the reason for locking down the entire community was not to allow COVID-19 patients to spend a few fewer days in the hospital; It was opposed on the grounds to prevent patients from dying and the right endpoint should be mortality [46]. The knowledge of whether the drug will save lives is the information that this study initially suggested but did not prove in the end, so the study would not have achieved its original purpose in this sense. According to those who think that determining whether the drug can prevent death can only

be determined by placebo control and therefore it is not appropriate to give remdesivir to the placebo group, with the disclosure of the endpoint, it is no longer possible to conduct a placebo-controlled trial to determine whether the drug has a benefit for mortality.

On the grounds that the basic rationale of conducting clinical trial is to conduct the experiment rigorously in order to provide the most accurate information about the right treatment, it was stated that it would be in the public interest to determine whether remdesivir could reduce mortality, but unfortunately, the opportunity to obtain evidence of mortality was missed [46]. In addition, it is dangerous at this point (as of the announcement of this endpoint) that it is still not clearly known (an uncertainty) who needs to be treated currently, despite this it is dangerous that it has now reached the status of treatment for everyone; doubts have been expressed as to whether this drug will now become a base drug and serve as a control and potent enough to become the standard of care [46].

Concerns about Earlier Approval

It is noted that the haste of approvals causes concern in the public and negatively affects confidence in these vaccines (for reasons such as the possibility of political pressure in the vaccine development process). It is emphasized that once public confidence in vaccines is compromised, it will be difficult to recover and distrust of one vaccine can fuel concerns about other vaccines [48].

At the beginning of the COVID-19 pandemic, the use of HCQ was first licensed and then revoked by FDA with an EUA. It is also emphasized that the licensing of COVID-19 vaccines, which were developed at an unprecedented pace in this process, should be evaluated within the framework of the lessons learned from the HCQ licensing process [49].

There have been public concerns about the safety and efficacy of vaccines developed through accelerated processes, and circuitously about the reliability of regulatory agencies such as FDA. FDA Chairman Stephen Hahn noted that the FDA may issue an EUA if it is felt that the risks associated with the vaccine are much lower than the risks of not being vaccinated[49].

Since drugs on clinical trials will never be complete theoretically, it would mean that a drug is used with data rather than a clinical trial.

Concerns about Long-Term Effects of Earlier Approval

Following the release of preliminary data of phase III trials, vaccine manufacturers sought regulatory approval for the emergency use of vaccines. Scientists are concerned that emergency use could jeopardize ongoing clinical trials aimed at conclusively showing how well vaccines work [50].

When a vaccine is authorized and given emergency approval, there is general encouragement for the placebo group to be vaccinated. But if too many people join to the vaccine group, companies won't have enough data to determine long-term data such as safety, how long vaccine protection lasts, and whether the vaccine prevents infection or just disease.

It is ethically unacceptable to continue research while there are still people in need of treatment. Once a certain level of evidence has been obtained, the obligation to give active treatment to the placebo group arises. It is questioned whether it is ethically justifiable to refuse to vaccinate vulnerable populations against an incurable infectious disease despite the availability of reasonably safe and effective vaccines, particularly due to the lack of phase III trial data[51].

Adding to the concerns above, Jerome Kim, executive director of the International Vaccine Institute in Seoul, says that early use of vaccines in high-risk groups will most probably save lives. The vaccines have only been tested for a few months, but it is too early to know how long they will be effective, he says[50].

2. Non-maleficence

Although the most important reason for CU/EUA programs is the purpose of usefulness, drugs that are still in the trial phase – and many drug candidates at this stage cannot provide sufficient effect and may not pass to the next licensing phase- are provided to patients in need. It is noted that the evaluation of CU programs as clinical practice, despite having the characteristics of a clinical trial, creates important inconsistencies due to the fact that data such as serious adverse effects from patients are not evaluated [52].

In order to decide on CU, it is only allowed in phase II and phase III stages of drug research, as the drug must not be fatal or completely useless [17]. However, it does not mean that the drug is harmless, because there are

uncertainties during the research process, such as serious side effects that have not yet emerged and unknown dosage levels of the drug.

Safety

Although there is a certain level of safety in the use of a drug in a new indication, which is currently used with the original indication for another disease, this may not be sufficient. Although the current drug has a previously established clinical safety profile, there is a need for a comprehensive safety (such as drug interactions, dosing) evaluation as well as efficacy evaluation specific to COVID-19 treatment. For example, CQ/HCQ has been used for many years in indications such as malaria, so it is known that the safety profile of this drug is at a certain level. However, it is noted that the quality of the evidence in published studies regarding the clinical efficacy of this drug, either alone or in combination with other drugs, is low due to insufficient sample size, clinical results, and lack of randomization[53].

It is emphasized that a data-based strategy on the off-label use of vaccines, independence of randomized controlled trials, may fail in the long run, and may also raise public doubts about the effectiveness of the vaccine campaign, with the risk of creating false feelings of safety in patients. On the other hand, it is pointed out that in case of infection in vaccinated individuals, with the decrease in voluntary adherence to the vaccine, significant harm may occur in the entire vaccination campaign in terms of public confidence [54].

The key point of safety concern is that patients at risk of COVID-19 complications are also at the highest risk of drug interactions and drug-related toxicity. As a matter of fact, these are people over the age of 60; persons with comorbidities such as arterial hypertension, diabetes, chronic lung disease, malignancies, and immunosuppressive conditions; and those taking drugs with potential for drug interactions or additive toxicity at the same time, and it has been emphasized that extreme caution should be exercised in the use of CQ/HCQ in these vulnerable populations [53].

Transparency

Different challenges occur for CU and EUA in reporting adverse effects. It is relatively easy to report adverse effects when CU is applied more often in physician follow-up and on a small number of patients. However, in drugs and vaccines that have received EUA, feedback will be insufficient due to the population load and the expectation of notification from patients.

It is crucial to obtain more comprehensive efficacy and safety data on the use of EUA drugs in treatment, where evidence of efficacy is weak. All care processes (order of medication, duration of treatment, etc.) of patients receiving EUA should be reported in detail and carefully in order to ensure the level of transparency required for backward reviews[55]. Meticulous data acquisition and rapidly scaling clinical trials are critical to establishing a quality evidence base during pandemics. In the study that aims to shed light on the data acquisition process in the research of antiviral treatments for the prophylaxis and treatment of viral infections for the management of the COVID-19 pandemic, it is pointed out that the data collected from patients by modelling the influenza pandemic are underreported. It is also suggested that tolerance to treatment is incompatible with the commitment to collecting high-quality data for treatments, which is a failure to the standards expected of modern evidence-based medicine. It is indicated that patients are treated with drugs that are not registered for the indication of pandemic influenza (H1N1). This is not under high-quality data acquisition conditions, and the reliance on use under compassionate conditions leads to constant uncertainty about the potential benefits and harms of antiviral therapy[56].

During the phase-III trials of the COVID-19 vaccine developed by AstraZeneca, DSMB reported their concerns about the information published on preliminary data of its clinical trial. DSMB made a statement their concern that AstraZeneca contained out-of-date information in this clinical trial, which may provide an incomplete view of efficacy data[34]. Nevertheless, we have witnessed a good example of transparency led trust during the use of the vaccine belonging to the same company. Earlier in September, a multi-country clinical trial of a leading vaccine candidate being developed by AstraZeneca and the University of Oxford in the UK paused as researchers assessed a possible safety risk affecting one of their participants [57]. Pauses in such trials are pretty common. This is a sign that auditors strictly follow the security protocols. Given that scientists are under pressure to test this vaccine rapidly, this is reassuring.

Informed Consent

In clinical practice, the patient must be informed about the interventions to be made and give their consent. When it comes to clinical trials, it is not possible to

inform the patient as in clinical practice. According to the Declaration of Helsinki, the subject must be adequately informed of both the anticipated benefits and the potential risks that may occur[40].

Patient consent should be more sensitive in the case of an unapproved investigational drug that may lead to serious adverse effects. Patients should be asked clearly if they are willing to take the drugs used within the EUA [55] because EUA differs from routine clinical practice standards in terms of the level of evidence and risks. For this reason, it is essential to make sure that the patient fully understands those different and particular statuses. Similarly, distinguishing EUA from CU and clinical trials properly during the information will be a facilitating for the patient's decision-making.

For instance, in the case of a recommended EUA use of COVID-19 vaccines, informing patients including indications shouldn't be that different from foreign or supranational regulatory agencies and relevant supporting studies. The meaning of the type of authorization issued by regulatory agencies (FDA, EMA, etc.) should also be included in informed consent. It is claimed that there is currently no data available on the sudden or long-term adverse effects of vaccines. It is emphasized that any complications identified in pharmacovigilance activity - within self-determination- should be immediately integrated into the label and informed consent[54]. One of the suggestions for the off-label implementation of COVID-19 vaccines is the need to encourage practicing health professionals to report adverse and drug-related incidents in order to ensure accurate pharmacovigilance effectiveness [58].

When an investigational drug needs to be used in treatment, the information for the patient is expected to be comprehensive enough [40]. This is possible for the individual patient access within the CU program. However, it is a controversial issue whether the information provided for a drug that has been authorized for emergency use is comprehensive enough. There might be various reasons for this and these include the intense need for medication due to the burden of a massive patient population (density of health centers during the pandemic), to the lack of sufficient time and due to the insufficient willingness of health workers, these information processes may not be given the due care.

Another important reason is that patients are less likely to encounter health care workers. During the pandemic, drugs were mostly delivered to quarantined patients, by other officials not by healthcare professionals.

3. Justice

There are challenges in providing investigational drugs to patients fairly.

Which patient will it be prescribed to? Is it the doctor who will determine this? According to what?

The first of these concerns is about the challenges experienced due to weak evidence for investigational drugs. The lack of evidence on the drug creates uncertainty about the patient population who will benefit from the drug. A detailed ethical framework is needed for the allocation of the drug prescribed in the EUA. For instance, although it was stated in the EUA for remdesivir that people eligible to use the drug should have a "severe" illness, it was indicated that the eligibility criteria in the EUA were broad enough to cover almost the entire clinical spectrum of respiratory disease [55]. The healthcare professionals in the hospital will decide whether the patient meets the specified drug eligibility criteria, and when these criteria are not defined in detail will complicate the decision processes. In order to address these uncertainties, institutions try to create an allocation framework with detailed guidelines created by their own ethics committees. Although they can provide a certain level of solutions in practice, it is not possible to say that they completely eliminate ethical concerns.

The problem of determining the criteria according to which patients will be selected and how one should be prioritized[59] is not limited to the interventions of treatment. Similarly, the uncertainty of these criteria is largely effective at the basis of this difficulty in determining the allocation framework in preventive interventions such as vaccines. Answers to who should be get vaccinated first, what is the legitimate basis for prioritizing in society (the superiority of one over another), requires these criteria to be defined in detail. Otherwise, those who need the drug/vaccine more and urgently will not be able to access the drug/vaccine. Drug shortage can occur if there is no regulation of access to drugs for patients or people at higher risk.

For instance, it has been stated that recommending CQ/HCQ for the treatment of COVID-19 based on weak evidence may cause patients to use the drug without consulting a physician, taking an overdose, or the inability to provide medication for those who need it due to drug shortages [53][60]. Although it was indicated that

HCQ can be effective in COVID-19, it was emphasized that there will be a shortage of supply and will make it difficult to treat patients for indications that it was originally developed and approved [61].

Prioritization of Patients Using the Drug With the Original Indication

During the pandemic, it might be possible to use a drug with a new indication other than the original indication through drug repurposing or off-label uses. However, difficulty in accessing drug treatment is considered a risk for patients using drugs with the original indication, who are part of vulnerable populations, and it is criticized especially in terms of the principle of justice [62].

In this inquiry, the weakness of medical evidence is used as an argument and it is argued that if prioritization is required for the allocation of the drug, the indication with stronger evidence should be prioritized. Accordingly, the level of medical evidence supporting the efficacy of drugs for the original indication is stronger than the new indication, as well-designed, controlled randomized controlled trials have been performed for the original indication, and large-scale retrospective analyzes using real world data are available and provide warranted results on long-term efficacy [62].

In emergency situations, low quality study results may serve as the basis for the large-scale use of drugs. In this case, it is argued that evidence-based medicine would be violated if indications with poor medical evidence were given more priority than anything else and that the assessment of drug effectiveness would remain scientifically weak. There is criticism that drug repurposing will be a simple off-label use, devoid of both ethical and scientific support[62].

Conclusions and Recommendations :

Whether under CU or EUA, although the use of investigational drugs for treatment purposes is not evaluated as a clinical trial, they should be evaluated in a different status from standard medical care, largely due to their clinical trial features and poor level of evidence in practice. It should be noted that any data collected during the treatment process are tools that will help strengthen the evidence in hand in terms of safety and efficacy.

In an emergency, both in the process of developing a new drug and determining a new indication of an existing drug, well-designed research (including endpoint determination, etc.) should be approached with higher attention than routine.

A good endpoint in a clinical trial should be clinically relevant, capable of following the disease of the patients closely, rich in information, sensitive (liable, differential and well distributed). It should have (precise, low-variable, and reproducible) reliable information, be resistant to missing data, not affecting the treatment response, and be practical (measurable in all patients and affordable)[45].

Some authors emphasize certain requirements that must be met in order for the use of the research drug in treatment to be ethically appropriate. These requirements are a justifiable need for use, not having a threat for the clinical development of the drug, adequate scientific evidence, the benefit of the patient as the primary target, the patient's informed consent, fair access, independent ethics review, and the declaration of treatment results [63].

Unlike any medical intervention where information to the patient is expected to be complete, actual and understandable to the patient about the benefits, risks, and possible alternatives of the provided any medical treatment, informing the patient should be done more sensitively than a standard clinical care practice. It is necessary to make sure that the patient understands that the drug has a much weaker level of evidence compared to a drug that has been in use for many years in large populations and for a certain indication, where extensive data on its safety and efficacy have accumulated over time. However, thanks to such good information, the patient will be able to understand a realistic benefit-risk assessment for itself and make an autonomous decision about whether or not to accept the treatment.

The pharmaceutical industry in particular must provide a higher standard of transparency in the reporting of clinical trials in order to build and maintain vaccine confidence. They need to respond to the concerns of experimenters, researchers and the public, ensure confidentiality in trials and show respect for the privacy of participants. Also, the fact that the experimenters do not share the details of the research for confidential reasons of information, leads to the lack of desired transparency. By publishing actual clinical results and making the results public with execution policies, data can be evaluated apart from the research and the reported results and claims can be verified[48].

It should be prevented from advertising the drugs and preventing anyone who needs/does not need it from

rushing to that drug, causing subsequent shortages. For instance, it has been indicated that recommending CQ/HCQ for the treatment of COVID-19 based on low-quality data may lead patients to use it without consulting, using overdose, and inability to provide medication for those who need medication due to shortage in pharmacies[60].

Consequently, the lack of information about the pandemic that emerged in 2019 with great uncertainty also raises concerns in terms of its treatment and prevention. In order to relieve these concerns, pharmaceutical companies, health authorities and physicians have crucial duties.

Considering the fact that pharmaceutical companies continue their experimental processes against the pandemic, the greatest expectation from them is to be fully transparent and accurate in the presentation of the data they collect and produce.

In the face of a sudden epidemic, the existence of drugs and vaccines is not expected, but the information on the development processes of new drugs developed against the new epidemic should be reliable. This includes basic obligations such as designing the right research, determining the right endpoints, working with the right group of patients, and not advertising their own medications.

The primary duty for health authorities is to control the drug development and application phases by conducting strict supervision of pharmaceutical companies. Another duty is to ensure a fair distribution of approved drugs and vaccines for use. This will prevent shortage of pharmacies and ensure that those who need it most have access to it. Current guidelines and protocols to be published by health authorities are crucial for the effective use of health resources. Another duty that health authorities are responsible for is to inform and guide the community properly. It is of great importance that the population affected by the pandemic is accurately informed by both media organs and direct statements and guided to the right health institutions in order to eliminate the possible health issues.

Because they are the first contact with the patient, the duty for physicians is to accurately inform the patient or people who are likely to be affected by the pandemic and to treat them in a compassionate and altruistic way. The right information would allow the person to make the right decision for themselves. The greatest responsibility of informing the patient and society about investigational drugs and vaccines is on the physicians. For this reason, physicians should also have access to actual and accurate information in this period. Physicians are the most reliable way to reach the patient with rigorously collected and synthesized information.

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