

ETHICAL ISSUES OF THE OFF-LABEL USE OF DRUGS FOR TREATMENT OF COVID-19

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The article discusses the issues related to the ethical aspects of the off-label use of medications for treatment of coronavirus infection, including in terms of conducting clinical trials of these medications. Furthermore, the article raises the issue of using drugs for treatment of coronavirus infection at the moment and discusses the related ethical principles. The major issue of this review is the ethical aspect of the search for benefits of using drugs not according to instructions in patients with emergencies and life-threatening conditions, such as COVID-19. The ethical role of the informed consent in both clinical trials and off-label prescription of drugs in general is also clarified. Several options provided in this review are proposed to address this issue.

Keywords: off-label, COVID-19, coronavirus infection, use not according to instructions, medical ethics

Author contribution: Severova YaG developed the concept and the structure of the article, reviewed the literature and wrote the text; Teplova NV contributed to the article concept development, provided academic supervision, finalized the text and approved it before publishing.

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Received: 25.07.2022 **Accepted:** 26.08.2022 **Published online:** 30.09.2022

DOI: 10.24075/medet.2022.055

ЭТИЧЕСКИЕ ВОПРОСЫ OFF-LABEL ПРИМЕНЕНИЯ ПРЕПАРАТОВ ДЛЯ ЛЕЧЕНИЯ COVID-19

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В статье рассматриваются вопросы, касающиеся этической стороны применения off-label препаратов для лечения коронавирусной инфекции, в том числе и в ключе проведения клинических исследований с данными лекарственными средствами. Помимо этого в данной работе затронут вопрос применения лекарственных препаратов для лечения коронавирусной инфекции в настоящее время и связанные с этим этические принципы. Основная проблема данного обзора заключается в этическом вопросе поиска пользы применения препаратов не по инструкции при экстренных и жизнеугрожающих состояниях, таких как COVID-19. Также уточняется этическая роль добровольного информированного согласия как на проведение клинических исследований, так и в целом на назначение off-label препаратов. Для решения данной проблемы было предложено несколько вариантов, представленных в данном обзоре.

Ключевые слова: off-label, COVID-19, коронавирусная инфекция, применение не по инструкции, медицинская этика

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Статья поступила: 25.07.2022 **Статья принята к печати:** 26.08.2022 **Опубликована онлайн:** 30.09.2022

DOI: 10.24075/medet.2022.055

Coronavirus infection is a dangerous rapidly developing and spreading infection that has caused one of the world's greatest pandemics. As of September 2022, a total of 20,535,057 COVID-19 infection cases have been reported in the Russian Federation. This amounts to 3.32% of the total number of infected people, and the disease lethality is 1.88% [1].

The lack of efficient medications for treatment and prevention of coronavirus infection was an important public health problem soon after the emergence of COVID-19, which resulted in the active off-label use of drugs (i. e. not according to instructions). Drug therapy of coronavirus infection was based not on the empirical evidence of clinical trials (CT), but on the physicians' assumptions. The major issue associated with prescription and use of drugs not according to instructions (off-label use) is as follows: despite the fact that the health risks of these drugs (based on the use in accordance with the confirmed indications) are generally predictable, the efficiency of their use according to the new indications, i. e. for treatment of COVID-19, was not predictable and provided nothing close to evidence in terms of efficacy and safety. While it was natural that the off-label use meant primarily gaining the benefits in

the form of beneficial therapeutic effect for the patient. That is why the study was aimed to review the legal and ethical aspects of the off-label drug use, clinical trials of the off-label drug use for treatment of coronavirus infection, and the ways of addressing issues associated with the use of drugs not according to instructions.

LEGAL AND ETHICAL ASPECTS OF THE USE OF DRUGS FOR TREATMENT OF COVID-19 NOT ACCORDING TO INSTRUCTIONS

Today, according to the latest update of the guidelines on the coronavirus infection prevention and treatment and the guidelines issued by the World Health Organization (WHO), it is possible to prescribe drugs that are assumed to be efficient when used off-label for etiotropic therapy (i. e., the drug medical use does not meet the guidelines on medical use). However, the drugs must be prescribed in accordance with the ethical standards recommended by the WHO and based on Federal Law (FZ) No. 323-FZ, FZ No. 61-FZ, GOST R ISO 14155-2014 "Good Clinical Practice", the order of the Ministry of Health

(MH) of the Russian Federation (RF) No. 200n, and the World Medical Association (WMA) Declaration of Helsinki on the ethical principles of research involving human subjects declared during the 64th WMA General Assembly, Fortaleza, Brazil, 2013. [2]. According to the WHO, the off-label use of drugs is justified in cases of severe conditions when there is evidence of potential benefits, but there is no standard therapy, the patients are informed and have given consent (in writing wherever possible), and the patients are under supervision due to safety reasons [3]. However, it is worth emphasizing that in the RF the off-label use of drugs in children is allowed by the Federal Law No. 482 on Amendment to the Federal Law "On the Basics of Protecting the Health of Citizens in the Russian Federation", while the established list of disorders that includes COVID-19 is set out in the Decree of the Government of the Russian Federation No. 1180-R [4,5]. Based on this Law, the use of drugs not according to instructions within the legal framework is possible only in people under the age of 18. This contradicts the data of the guidelines on prevention and treatment of coronavirus infection. Anyway, parents must submit a written consent to make possible the off-label use of drugs in children. As for adults, based on legal precedents, physicians do not have an obligation to inform patients or their families about the unintended use, addition or replacement of the drug during treatment, since there is a chance this could affect the patient's decision [6]. However, the informed consent is a fundamental principle of medical law and ethics, that is why physicians must obtain the patient's consent prior to treatment. It is worth noting that in terms of ethics the off-label use of drugs for treatment of coronavirus infection without the results of CTs should be considered only in cases of emergencies and life-threatening conditions when there is no effective evidence-based treatment; when the informed consent is available; when all treatment stages are documented. Active cooperation with the Federal Service for Surveillance in Healthcare in terms of pharmacovigilance should be also taken into account.

ETHICAL ISSUES OF CONDUCTING CLINICAL TRIALS OF THE OFF-LABEL USE OF DRUGS FOR TREATMENT OF CORONAVIRUS INFECTION

To conduct the CT of the off-label drug use, it is necessary to consider certain ethical and scientific principles, ethical guidelines and ethical approval even in case of unexpected dangerous outbreak, such as COVID-19 outbreak. In the RF, the MH issued the letter explaining how to conduct CTs during the COVID-19 pandemic. According to the letter, it may be difficult to perform the procedures of the CT protocols due to challenging current situation. In such cases the drug CT managers together with the researchers and local ethics committees can adjust standard operating procedures on behalf of the CT participants taking into account the guarantees of data reliability [7]. Thus, in the RF favipiravir was registered in accordance with the registration procedure for drugs intended for use in the context of threat of emergency situation or emergency response, but about it a little later.

Of course, the MH places a priority on the CT participants' safety and reasonable risk-benefit balance for research subjects. The MH recommends the CT managers to consider alternative possibilities of conducting CT, such as shifting to online monitoring methods (virtual visits, telephone conversations, etc.), home delivery of medications, careful documentation of all anomalies, protection of personnel involved.

Thus, when discussing the ethical issue of conducting CTs of the off-label use of drugs for treatment of coronavirus infection,

several examples are worth mentioning. For example, in the CTs of hydroxychloroquine treatment resulted in no beneficial clinical effects, while the rate of side effects was almost twice larger compared to placebo. In these cases, patients in the treatment group had a high risk of suffering from the harmful effects of the drug and would have got minimum benefits when using this drug [8]. In contrast, another group of patients enrolled in other CTs, such as the CT of remdesivir, recovered faster and showed fewer side effects [9]. Such situation in the group, receiving, for example, hydroxychloroquine, would be a "lost opportunity" in contrast to participants of other CTs showing more beneficial results. The other problem is that in some cases patients with severe and critical conditions admitted to the intensive care unit are unable to give a verbal consent or have very little time to give the consent. In such cases the consent given by relatives or legal representatives does not always correspond to the patient's desire. Thus, to address the ethical issues related to the CTs of the off-label use of drugs for treatment of COVID-19, it is necessary to implement the adaptive research planning model, i. e., the study of several medications within the framework of one CT. This would make it possible to transition all groups to the more efficient and safer drug. Furthermore, the more precise legislative regulation of CTs is required within the framework of consent or refusal of participation in cases of pandemics and life-threatening conditions.

PRESENT-DAY ETHICAL ISSUES OF TREATING CORONAVIRUS INFECTION

As has become clear from the above, there were no data on the effective and safe treatment confirmed by CTs in the beginning of the COVID-19 pandemic, that is why the medical community had to rely on their own clinical experience and prescribe drugs off-label. However, after more than two years since the beginning of the pandemic, the clinical and epidemiological features of the disease are intensively studied, and the new means for prevention and treatment of coronavirus infection are developed. Today, according to the guidelines issued by MH of the RF, etiotropic therapy is used along with the pathogenetic and symptomatic therapy. There are several drugs that could be used for treatment of COVID-19: favipiravir, molnupiravir, nirmatrelvir + ritonavir, remdesivir, synthetic small interfering ribonucleic acid (siRNA) [double-stranded], umifenovir and interferon-alpha [2].

However, in terms of evidence-based medicine, the drugs recommended by the MH of the RF at least cannot be considered effective, despite the fact that these are not used off-label. To prove his statement, the randomized double-blind multicenter placebo-controlled CTs of favipiravir were reviewed. The study results showed no decrease in the time till viral clearance or showed just a non-significant trend toward the increase in viral clearance along with no significant therapeutic benefits. The independent data and safety monitoring board (DSMB) recommended to withdraw the drug due to futility of interim analysis [10, 11]. According to the Directory of Medicines, the instructions to favipiravir have been developed based on the limited clinical data on the drug use and would be amended as new data become available [12]. It is worth noting that the drug is used according to instructions in hospital settings, but there are many cases of prescribing favipiravir in outpatient settings, which means favipiravir is used not according to instructions. In this way, even if we consider this drug as relatively safe, the data of CTs show it is inefficient, and it is questionable whether the use of this drug is feasible from the ethical and medical point of view. Despite the fact that the

drug is included in the guidelines on treatment of coronavirus infection and is not an off-label drug, the use of this medication cannot be considered reliable.

CONCLUSION

In conclusion, it should be noted that prescription of drugs not according to instructions or during clinical trials is considered

unethical unless proven otherwise. However, it is worth mentioning that in the context of the pandemic the ideas about the off-label prescription of drugs could be revised due to emergency and lack of evidence-based treatment. To adhere to ethical standards, it is necessary to improve the legislative framework of the off-label use of drugs and implement the adaptive CT model. Furthermore, it is necessary to think critically about the existing guidelines on treatment and prevention of coronavirus infection.

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