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Promising COVID-19 therapies on examples of some antiviral, immunomodulatory and natural substances use - review

Krzysztof Bielewicz, Karolina Ryba, Kinga Kawalko, Anna Karaś, Kamil Pondel

Krzysztof Bielewicz krzysztofbielewicz1@wp.pl Faculty of Medicine, University of Rzeszow, Pigionia Street 6, 35-310 Rzeszow

Karolina Ryba karast3@gmail.com Faculty of Medicine, University of Rzeszow, Pigionia Street 6, 35-310 Rzeszow

Anna Karaś annamariakaras12@gmail.com Faculty of Medicine, University of Rzeszow, Pigionia Street 6, 35-310 Rzeszow

Kinga Kawalko kingakawalko@gmail.com Faculty of Medicine, University of Rzeszow, Pigionia Street 6, 35-310 Rzeszow

Kamil Pondel pondelkml@gmail.com Faculty of Medicine, University of Rzeszow, Pigionia Street 6, 35-310 Rzeszow

Abstract

COVID-19 is one of the biggest challenges to medicine ever. Because of its dissemination in population effective drug to cure it was needed. There were some trials on antiviral drugs like lopiravir/ritonavir, remdesivir, darunavir/cobicistat, favipiravir, molnupiravir, discovered originally in order to treat other diseases. Only remdesivir and molnupiravir seem to be beneficial for patients with COVID-19, both of them are approved in therapy in a large number of countries allover the world. [2]

Another very important group of drugs used in trials against COVID-19 was immunomodulatory drugs. Some of them, like chloroquine/hydrochloroquine was very promising, but finally there were no evidences of its benefits found. [2] Corticosteroids used in moderate and severe COVID-19 caused general improvement of clinical status and decreased mortality. Interesting and quite promising may be use of interferons but for now lack of evidences does not allow to make clear statement about its benefits.

There are some argumentations for natural methods of COVID-19 treatment. Dietary recommendations, vitamin and microelements supplementation may be helpful in the therapy and in addition may not have any adverse effects. Also, herbal mixtures, developed centuries ago in China found usage during COVID-19 pandemic. After analysis of thousands of cases

Traditional Chinese Medicine can be considered as one of the most successful attempt in combating COVID-19. [6]

Key words: COVID-19, SARS-CoV-2, lopiravir, remdesivir, darunavir, molnupiravir, favipiravir, chloroquine, hydrochloroquine, corticosteroids, interferons, natural therapy

Introduction and purpose

There is no doubt COVID-19 had and still is having enormous impact on every branch of human life and certainly on medicine. Since ending of 2019 till now number of doctors, scientists and also patients are trying to find the best, most specific anti-COVID drug. [1][2] There are some substances, which were used in some clinical trials, with various outcome, in COVID-19 treatment [2], so that we want to present you short review of literature, which is focused on that subject. We firmly believe in COVID-19 vaccine efficacy, but this article will describe only drugs or methods of treatment infections.

State of knowledge

The most important and certainly promising group of drugs used in COVID-19 treatment is group of antiviral drugs. Because of some similarities between SARS-CoV-2 and known before 2019 SARS-CoV-1 and MERS [2] the scientists used some drugs, which had been used to treat patients during MERS epidemic in 2003.[4]

Lopiravir/ritonavir (LPV/r) is protease inhibitor originally approved of HIV infection treatment. During SARS epidemic LPV/r led to reduction of the risk of progression to ARDS [5], but some clinical trials and case series from Asia during COVID-19 pandemic show that this therapy does not give an advantage in the COVID-19 treatment [3][7]. Use of LPV/r in some cases caused gastro-intestinal disorders like nausea, vomiting, diarrhea and liver enzymes elevation in plasma.

Remdesivir, antiviral drug from the group of adenosine analogues, was also widely tested in clinical trials in therapy against COVID-19. [4][2]. This initially used in Ebola treatment drug is seemed to be not beneficial to patient with mild, moderate COVID-19 and the patients who do not need respiratory support.[7] Some clinical trial show justified use of Remdesivir in COVID-19, but under condition of the drug intake on early stages of disease. Then it can lead to significant decrease of clinical signs and general status improvement.[2] There are two indications of remdesivir use – patient must be over 12 years old and there is need of hospitalization because of COVID-19. Remdesivir is approved in over 50 countries, among others in USA and EU countries. [8]

Another drug used against HIV, second-generation protease inhibitor, also used in clinical trials against COVID-19 is darunavir/cobicistat (DAR/COB). It was considered as alternative therapy for patients with contraindications to LPV/r therapy. It was noticed during clinical study, that DAR/COB increased virological clearance rate after one week since the diagnose of COVID-19. The main limitation of the trial was that it was made on small group of patients, so the benefits can't be representative to general population. [2]

Potential clinical benefits of favipiravir, new generation inhibitor of the RNA-dependent RNA-polymerase (RdRp) were seen in two clinical studies. It caused improvement of clinical signs, CT imaging and viral clearance after two weeks. [2] During favipiravir use psychiatric and gastro-intestinal adverse effects were seen. This drug is approved in COVID-19 treatment in China, India, Russia, Japan and many other countries. [1]

Promising results were seen in clinical trial with molnupiravir, prodrug of N-hydroxycytidine, which is active against RNA viruses including SARS-CoV-2. The MOVE-

OUT study were double-blind, randomized placebo controlled trial on 1433 unvaccinated adults with COVID-19 from 20 countries, who were not hospitalized because of this disease. The patients received 800 mg of molnupiravir or placebo twice daily for five days. They were asked to note presence of any signs and symptoms of COVID-19 within 29 days. They also were tested on virus presence six times during the study – on days 1,3,5,10,15 and 29. The results shown that the drug decreased risk of hospitalization or death because of COVID-19 in comparison with placebo. Also probability of progression of sign and symptoms were higher in placebo group. [9]

Chloroquine and its analogue, hydrochloroquine, which are used in malaria treatment were found to have in vitro activity against SARS-CoV-2. [2][8] Mechanism of this reaction is not clear. Clinical trials have not shown spectacular effect during COVID-19 therapy. [2] Even in combination with macrolide, mostly azithromycin, to avoid any bacterial co-infections the results do not allow to confirm that its use could be beneficial. Borba et al. [10] noticed dependency of chloroquine dose to ECG changes, like longer QTc (up to 500 ms) and elevation of CK-MB in plasma. Potential benefits were rather seen in patients with mild or moderate than severe COVID-19. [2] There are no evidences that the therapy can reduce mortality because of disease.

In opposite to some potential anti-COVID-19 drugs, which were tested in clinical studies, there are some evidences of beneficial use of corticosteroids. The clinical trials on moderate to severe, mostly hospitalized ill patients, show that corticosteroids can cause faster sign regression, improvement of oxygen saturation and reduce of mortality. These trials were based on various corticosteroids, like methylprednisolone or dexamethasone, but in general the mechanism is certainly rather anti-inflammatory than antiviral, so that no or little benefits were seen among patients with mild and not requiring respiratory support. [2] Also it is not recommended to use corticosteroids on the first disease phase. [11]

Interferons may be also beneficial in COVID-19 treatment. Its mechanism is based on natural skill of communication between cells to begin immune response, but they can also initiate viral degradation and cellular apoptosis. In general benefits of interferons in COVID-19 can be connected with contribution of cytokine storm and anti-inflammatory activity in lung tissue. [2] This mechanism was discovered during SARS and MERS. In addition to corticosteroids interferons helped to achieve faster lung recovery and need of respiratory support time. Lack of clinical evidences does not allow to claim that interferons can be useful in general population of COVID-19 patients. [12][13]

Herbs, vitamin supplements and natural product are very popular homemade solution to cure flu, cold or some infectious diseases. Very interesting outcome of one retrospective study show impact of diet, vitamins, and herbal on patients with mild COVID-19. Diet was completed by bone broth, beetroots and green vegetables. Oral supplements contain vitamins C, D₃, K, A and E, bacteria – *Lactobacillus spp.*, *Bifidobacterium bifidum*, *Streptococcus thermophilus* and herbal tinctures of *Inula helenium*, *Ligusticum porter*, *Echinacea purpurea*, *Echinacea angustifolia*, *Mahonia aquifolium*. IV therapy contained Magnesium chloride, Vitamin C, Zinc sulfate and Vitamin B₆. In this study total 30 patients were described. Half of them get completely recovered in ten days from the beginning of therapy, all of them finally get complete symptoms resolution. There were no reported side effects or presentation of new symptoms during treatment. [5]. It is important that only 16 patients were tested of COVID-19, 13 patients were thought as ill because of symptoms and contact with another person with COVID-19, one patient was diagnosed only by clinical condition. The patients only contacted with medics virtually or on parking lots, because of sanitary regime during pandemy.

Traditional Chinese Medicine (TCM) had been used for many centuries during several epidemics, so there were premises about its benefits in COVID-19. About 3100 TCM experts took part in treatment COVID-19 patients in Hubei province (China). They used decoctions,

acupuncture, Chinese patent medicine and more specific technics in the therapy. Also he special TCM wards were made and TCM experts were active participants in therapy planning with doctors and medical staff. Only till March of 2020 there were about 60000 cases of successfully cured COVID-19 patients. After TCM therapy in 102 cases of mild COVID-19 average time of symptoms was 2 days shorter, time of fever duration was approximately 1,7 days shorter and hospitalization could be ended 2,2 days earlier. Also CT improvement and clinical rate of successful treatment was significantly increased. In the therapy of severe patients stay in hospital and achieving negative result in COVID-19 test were shorter more than two days in comparison to average therapy without COVID-19 use. TCM is seemed to be “panaceum” for many diseases because its mechanism not only block virus but also regulate the immune system, reduce inflammatory response and help general recovery of the body. [6]

Discussion

COVID-19 forced medics and scientists all over the world to fast and effective treatment, like never before. We already know that some drug which theoretically should treat COVID-19 have very limited impact on the patients in clinical practice. The anti-COVID-19 drug seekers should always take into consideration that the golden standard drug can be not discovered or made yet. SARS-CoV-2 is very common in humanity, so there can be plenty of variants of this virus, because it can mutate spontaneously. One drug, which helped patient “A” overcome COVID-19, can be useless in patient “B” therapy, because this both of diseases can be caused by completely different variant of SARS-CoV-2 and differences can impact of drug activity. For sure combating SARS-CoV-2 will be very long and hard process, so it is justified to treat it by alternative drug, which mechanism is not only focused on antiviral activity. For now the most important and promising way to defeat COVID-19 is vaccination, which is the safest solution to get immunity against the disease. [14]

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