Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Chapter 13

FDA Coronavirus Treatment Acceleration Program: approved drugs and those in clinical trials

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Chapter outline

13.1 Introduction

Coronavirus disease 2019 (COVID-19) is a highly infectious disease caused by the 2019 novel coronavirus (2019-nCoV) which is now officially recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to the family of *Nidovirales* which was first identified in Wuhan, China, with the symptoms of severe respiratory distress [1,2]. The World

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Health Organization (WHO) got the first report on COVID-19 on December 31, 2019, and on March 11, 2020, it declared it a global pandemic [3]. Presently, there are over 250 countries that have registered confirmed cases of COVID-19 despite the lack or insufficient testing kits. However, out of those countries, only 22 countries are seriously affected. As serious as it is, there are over 13.6 million confirmed cases of COVID-19 with over 586,896 deaths worldwide, as of July 2020 (Table 13.1) [4]. Graphical illustrations of confirmed cases as of June 2020 were presented in Fig. 13.1. The United States leads with 2.6 million confirmed cases with over 128,788 deaths [4]. This global pandemic brought challenges to clinical research because of its highly infectious nature and high mortality characteristics. The unavailability of therapeutics agents for its treatment also created anxiety in the general public and led to the collapse of the healthcare system in some places.

Investigators, industry sponsors, and institutional review boards/ethical committees are struggling to uphold the safety of participants and research team members taking part in ongoing clinical trials.

13.2 Food and Drug Administration

The Food and Drug Administration (FDA) or the United States Food and Drug Administration (US FDA) is a centralized agency of the United States Department of Health and Human Services that is responsible for maintaining, protecting, and endorsing public health by controlling, maintaining, and determining the quality of food products, food safety, dietary products, tobacco products, all types of pharmaceutical drugs, vaccines, medical devices, cosmetics, veterinary products, biopharmaceuticals, and blood transfusions.

TABLE 13.1 Current world situation report of COVID-19 cases and deaths by WHO according to WHO region [4].

Region	Total numbers of cases	Total number of deaths
Globally	13,150,645	574,464
Africa	506,124	8,650
Americas	6,884,151	290,674
Eastern Mediterranean	1,317,078	32,294
Europe	2,964,046	204,449
South-East Asia	1,231,014	30,570
Western Pacific	247,491	7,814

Source: WHO COVID-19 Situation Report-177, Data as received by WHO from national authorities by 10:00 CEST, 16th July 2020.

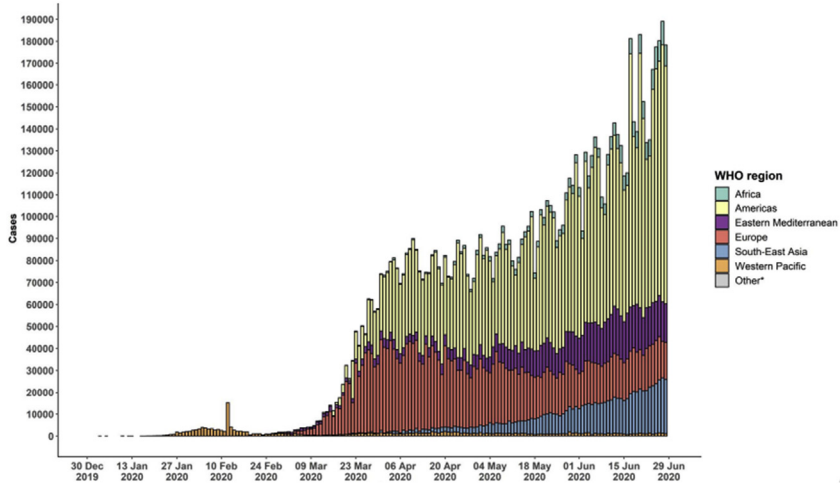

FIGURE 13.1 Status of COVID-19 cases by WHO as of June 29, 2020. *Source: WHO COVID-19 Situation Report-161, Data as received by WHO from national authorities by 10:00 CEST, June 29, 2020.*

The FDA has always been criticized for its very stringent approval guidelines to obtain FDA approval; hence, it is being too tough on industries.

13.3 FDA coronavirus treatment acceleration program

The FDA regulations and guidelines for conducting clinical studies and trials have been changed after the announcement of COVID-19 Public Health Emergency by the US Department of Health and Human Services (HHS) on January 31, 2020 [5]. Under these guidelines, FDA, sponsors, investigators, and ethical boards have to respond quickly to understand the status of ongoing studies and to rearrange the research processes [6].

Amid COVID-19, demand for new clinical research studies is also increased [7] to learn more about the novel coronavirus and to evaluate or test the efficacy of new drug candidates and repurposing [8] of existing drugs against COVID-19 [9].

To decrease the regulatory burden on investigators during this pandemic and to accelerate the development of new investigational drugs, FDA has taken new attractive steps and launched Coronavirus Treatment Acceleration Program (CTAP) [10].

13.3.1 Aim of the CTAP program

The main aim of this special emergency FDA CTAP program is to provide early possible therapies for the treatment of COVID-19. The FDA had

strategically changed and redistributed a large number of its staff on the CTAP review team to facilitate the speedy development of treatments and preventive measures [10].

13.3.2 Important features of CTAP

1. The FDA generally responds within a day after obtaining a receipt or request regarding the development or evaluation of new investigational drug or biological therapies against COVID-19.
2. The FDA provides ultrarapid, interactive inputs on most development plans to the investigator.
3. Review of new application protocol within 24 h of submission.
4. Work closely with investigators and other regulating agencies for quality assessment of product for COVID-19 treatment.

13.3.3 Achievements of CTAP program

According to the latest updates, the FDA worked with researchers and companies in developing COVID-19 therapeutics and had filled more than

1. 144 active trials of therapeutic agents
2. Around 457 new development programs for therapeutic agents are in the queue.

13.4 Emergency use authorization approval of drugs by the FDA for combating COVID-19

Under Section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), Commissioner of FDA may allow the use of new unapproved or approved therapeutics or medical products for the diagnosis, treatment, and prevention of life-threatening disease when there is no approved, adequate, and available therapeutic alternative.

Recently, the FDA had approved the use of some drugs for the management of COVID-19 listed in Table 13.2. FDA approval of chloroquine and hydroxychloroquine under Emergency Use Authorization (EUA) for the treatment of COVID-19 has been canceled or terminated due to serious cardiotoxicity-related issues with these drugs.

13.5 Investigational antiviral agents under different clinical trials

Currently, various new investigation drugs (Fig. 13.2), biological products, and treatments are under different phases of clinical trials [11,12] against COVID-19 (Table 13.3). Besides therapies, new drugs, new molecules, vaccines, and

TABLE 13.2 FDA-approved therapeutics under the Emergency Use Authorization (EUA) for combating COVID-19.

S. No.	Date of first EUA issuance	Product	Authorized use
1	May 8, 2020	Propoven 2% (Fresenius Kabi)	Constant infusion of 2% Propoven to maintain sedation in hospitalized suspected or confirmed COVID-19 patients above 16 years of age who need mechanical ventilation in an ICU.
2	May 1, 2020	Remdesivir	Administered only to treat adults and children who are confirmed cases of COVID-19 and in severe patients with SpO_2 (blood oxygen saturation level) with or below 94% require external oxygen supplement.

Source: Official Site of US FDA, www.fda.gov.

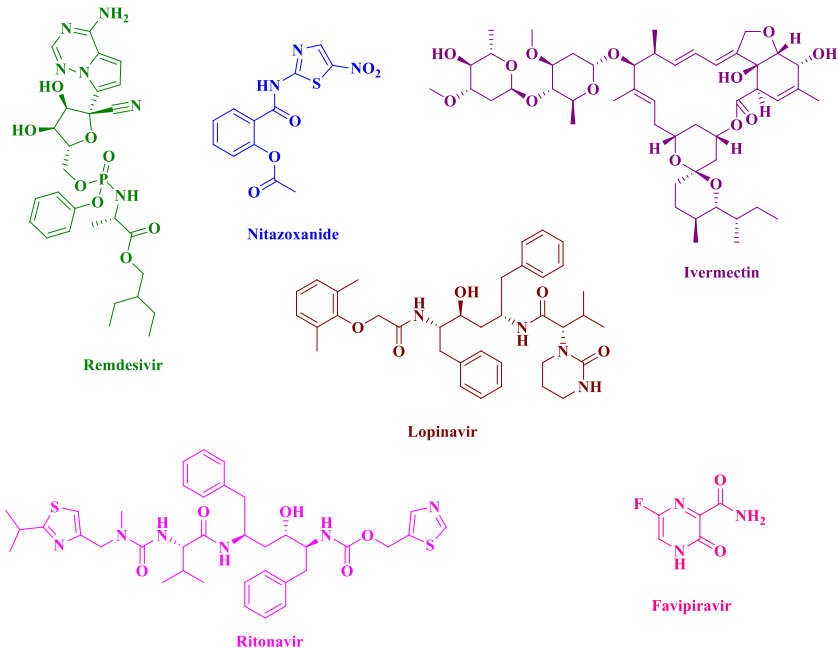

FIGURE 13.2 Some chemical structures of drugs that are under clinical trials.

TABLE 13.3 List of treatments, drugs, and vaccines for COVID-19 under clinical trials.

S. No.	Type of product—treatment	FDA approval, year	Molecular target	Clinical trials for COVID-19
Treatments				
1	Avastin (bevacizumab)	Yes, 2004 as anticancer agent (antibody)	Vascular endothelial growth factor (VEGFR) inhibitor	NCT04275414, NCT04305106
2	Programmed cell death protein 1 blocking (PD-1) antibody and thymosin	No	—	NCT04268537, ChiCTR2000030028
3	AiRuiKa (camrelizumab) in combination with PD-1 antibody	No	–	ChiCTR2000029806
4	Kevzara (sarilumab), interleukin-6 (IL-6) receptor antagonist	Yes, 2017, against rheumatoid arthritis (antibody)	–	NCT04315298
5	Actemra (tocilizumab), antibody	Yes, 2010, against cytokine release syndrome (systemic inflammatory response), arthritis, and rheumatoid arthritis	Antagonist of IL-6 receptor	NCT04317092, NCT04320615, NCT04310228, ChiCTR2000030894, NCT04306705, ChiCTR2000030442, ChiCTR2000029765
6	Convalescent plasma means blood plasma collected from patients recovered from COVID	No	–	NCT04321421, NCT04292340

Antivirals				
7	Favilavir or favipiravir	No, but used in Japan as antiviral for influenza	Viral RNA-dependent RNA polymerase inhibitor	NCT04303299, NCT04310228, ChiCTR2000029548, ChiCTR2000029496, ChiCTR2000029544
8	Lopinavir and ritonavir in combination	Yes, 2000, as anti-HIV agent	–	NCT04303299, NCT04255017, ChiCTR2000029548, R2000029539, NCT04307693, NCT04315948, NCT04252885
9	Remdesivir	No	–	NCT04257656, NCT04252664, NCT04292730, NCT04292899, NCT04280705, NCT04315948
10	Darunavir	Yes, 2015, as anti-HIV agent infection	Protease inhibitor	ChiCTR2000029541, NCT04252274, NCT04303299, NCT04304053
11	Lopinavir, ebastine with interferon alpha	No	–	ChiCTR2000030535

Continued

TABLE 13.3 List of treatments, drugs, and vaccines for COVID-19 under clinical trials.—cont'd

S. No.	Type of product—treatment	FDA approval, year	Molecular target	Clinical trials for COVID-19
12	Ritonavir, danoprevir with interferon alpha	No, but approved in China	Hepatitis C virus serine protease inhibitor	NCT04291729
13	ASC09	No	HIV protease inhibitor	NCT04261907
14	Emtricitabine and tenofovir	Yes, 2004, against HIV-1 infection	HIV-1 reverse transcriptase inhibitor	ChiCTR2000029468
15	Umifenovir	No, but approved against influenza virus in Russia and China	Virus membrane fusion inhibitor	NCT04252885
16	Baloxavir marboxil	Yes, 2018, against influenza	Polymerase acidic endonuclease inhibitor	ChiCTR2000029544
17	Azvudine	No	Antiviral drug (reverse transcriptase inhibitor)	ChiCTR2000030487, ChiCTR2000030424, ChiCTR2000029853
Cell-based therapies				
18	Mesenchymal stem cells	No		ChiCTR2000029990, NCT04315987, NCT04302519, NCT04288102, NCT04313322, NCT04273646,

Others				
19	Methylprednisolone	Yes, 1955, as antiinflammatory agents	Corticosteroids	NCT04244591, NCT04263402, NCT04273321, ChiCTR2000029656, ChiCTR2000029386
20	Chloroquine and hydroxychloroquine	Yes, 1949, as antimalarial drug	Inhibits hemozoin polymerization	NCT04261517, NCT04303507, NCT04303299, NCT04304053, NCT04307693, NCT04316377, NCT04315948
21	Camostat mesylate	No, but approved in Japan against various ailments	Serine protease inhibitor	NCT04321096
22	Ruxolitinib	Yes, 2011, for the treatment of myelofibrosis, in 2014 for treatment of polycythemia vera	Janus kinase inhibitor	ChiCTR2000029580
23	Novaferon also termed as nova interferon	No, but approved for hepatitis B infection in China	Recombinant artificial designed antitumor and antiviral protein interferon	ChiCTR2000029573, ChiCTR2000029496
24	Fingolimod	Yes, 2010, for multiple sclerosis	Sphingosine 1-phosphate receptor modulator	NCT04280588
25	Rebif (interferon beta-1a)	No	–	EudraCT 2020-000936-23, NCT04315948

Continued

TABLE 13.3 List of treatments, drugs, and vaccines for COVID-19 under clinical trials.—cont'd

S. No.	Type of product—treatment	FDA approval, year	Molecular target	Clinical trials for COVID-19
26	Losartan	Yes, 1995, as antihypertensive	Angiotensin II receptor 1 1 (AT1) competitive inhibitor	NCT04312009, NCT04311177
27	Leukine (sargramostim, rhu granulocyte-macrophage colony-stimulating factor)	No	–	NCT04326920
Dormant/discontinued				
28	Washed microbiota Transplantation	No	–	NCT04251767
29	Recombinant angiotensin-converting enzyme 2	No	–	NCT04287686
Vaccines				
30	Nonreplicating adenovirus type 5 vector (Ad5-nCoV)	No	–	NCT04313127
31	RNA; LNP-encapsulated mRNA (mRNA 1273)	No	–	NCT04283461

Source: https://clinicaltrials.gov.

various medical devices, symptomatic treatments to support immune systems are also under clinical evaluation but these are out of the scope of this chapter.

13.5.1 Remdesivir

Remdesivir (GS-5734) is a broad-spectrum antiviral agent developed by Gilead Sciences in 2009. Originally, it was developed by the company for the treatment of hepatitis C virus diseases, but it was a failure [13,14]. Gilead Sciences repurposed and studied this nucleotide analog prodrug remdesivir for the treatment of Ebola virus, filoviruses, paramyxoviruses, Marburg virus, pneumoviruses, and recently against coronaviruses [15,16].

However, it had shown limited benefit against Ebola infection [17]. The US FDA approved the use of remdesivir on May 1, 2020 under EUA for emergency use in severe confirmed and suspected COVID-19 hospitalized patients [18,19].

During the in vitro screening and in animal models, remdesivir had shown a very high morbidity rate of different human coronaviruses, including Middle East respiratory syndrome coronavirus (MERS-CoV) as well as severe acute respiratory syndrome coronavirus (SARS-CoV) by inhibiting their replication [20].

According to the report of Adaptive COVID-19 Treatment Trial (ACTT) harmonized by the National Institute of Health (NCT04280705) on remdesivir, it had shown 31% faster recovery time than the placebo group. But this result was not statistically significant because the median time of recovery with remdesivir was 11 days whereas the recovery time of the placebo group patient was 15 days. Secondly, there was a nonsignificant decrease in mortality with the remdesivir group (7.1%) compared to the placebo group (11.9%) [18]. To rectify these statistical doubts, more numbers of clinical trials with a large group of population were carried out. Phase three clinical trials of remdesivir against COVID-19 are being conducted in South Korea, China, and the United States.

Remdesivir had shown superior in vitro antiviral activity against MERS-CoV than lopinavir/ritonavir when given with interferon beta (IFN-β). In mice, the prophylactic and therapeutic use of remdesivir reduced the virus load in the lungs and improved the pulmonary function and pathology [13].

13.5.1.1 Drug interactions

Chloroquine and hydroxychloroquine inhibited the intracellular metabolic activation of remdesivir and hence antagonize its antiviral activity. Therefore, combination and coadministration of remdesivir with these drugs are not recommended by the FDA [19].

13.5.2 Nitazoxanide

Structurally, nitazoxanide belongs to the class of thiazolides and recognized as FDA-approved broad-spectrum antiparasitic (antihelminthic and antiprotozoal) and broad-spectrum antiviral agent. It also has been repurposed for the treatment of influenza and hence suspected to have great antiviral activity. Recently, Romark Laboratories has found the in vitro broad-spectrum antiviral activity of nitazoxanide against respiratory viruses including SARS-CoV-2 [21]. It inhibits the replication of the COVID-19 virus. On this basis, Romark Laboratories has conducted clinical trials with nitazoxanide extended-release tablets (NT-300) against COVID-19 [22]. Two phase 3 clinical trials with the prevention perspective of COVID-19 are started in high-risk populations and a third trial is also planned for the early treatment of COVID-19 by the company [23,24].

13.5.3 Ivermectin

Ivermectin is an FDA-approved antiparasitic drug. It showed in vitro reduction of viral RNA in Vero-hSLAM cells infected with SARS-CoV-2 within 48 h at a concentration of 5 μM [8]. But the pharmacokinetic data showed that the inhibitory concertation (IC_{50}) to kill the virus is not likely to be attained in human plasma with the FDA-approved normal dose of ivermectin [25]. In a retrospective cohort study with 280 confirmed SARS-CoV-2 hospitalized patients, a significant decrease in the mortality rate of 15% with ivermectin in comparison to 25% in placebo patients was documented [26,27].

Vero/hSLAM cell is a tissue culture cell line derived from African green monkey kidney epithelial cells containing an expression plasmid (pCAG-hSLAM) encoding the human signaling lymphocytic activation molecule.

13.5.4 Lopinavir/ritonavir

Lopinavir and ritonavir are antiretroviral (anti-HIV) protease inhibitors that are generally used in fixed-dose combinations. Currently, these drugs are under clinical trials for evaluation of efficacy against COVID-19. In a randomized clinical trial, lopinavir/ritonavir (400 mg/100 mg) combination in COVID patients fails to give statistically significant results [28,29]. Therefore, recently "National Institute of Health (NIH) Panel for COVID-19 Treatment Guidelines" recommended against the use of HIV protease inhibitors like lopinavir/ritonavir or others in the treatment of COVID-19 [30,31].

13.5.5 Favipiravir

Favipiravir is an antiviral drug that belongs to the class of pyrazinecarboxamide derivatives, and in 2014, it is approved for the treatment of the influenza

pandemic in Japan [32]. Its mechanism of action is not well understood but is considered to act as a selective inhibitor of viral RNA-dependent RNA polymerase. In different countries, clinical trials are conducted taking favipiravir alone or in combination with other drugs against COVID-19.

Phase three clinical trial has been started of favipiravir against COVID-19 in Japan [33]. In the United States, clinical trial phase 2 has been started with small numbers of COVID-19 patients. The clinical trial phase three of a combination of favipiravir and umifenovir is already started in May 2020. Favipiravir is already approved in China (in March 2020) and India (in June 2020) for the treatment of COVID-19. In India, it is manufactured by Glenmark under the brand name Fabiflu.

13.6 Future projections

COVID-19 outbreak is an uncontrolled highly infectious disease. There is an urgent need to develop new drugs, biological therapies, and vaccines to protect people from this deadly viral disease. The softness of US FDA in its regulatory guidelines would help the investigators, scientists, researchers, and academic institutions/universities to develop and evaluate the efficacy of new drug candidates, biological therapies against COVID-19. A huge number of clinical studies and trials are allowed by the FDA to find and develop an effective therapeutic alternative against COVID-19. This cooperation and involvement of the FDA with investigators, scientists, and academic institutes will help in the development of new effective treatment of COVID-19 in the future.

13.7 Conclusion

FDA CTAP is a very good and attractive initiative by the US FDA which defiantly increases the thinking power of scientists and researchers by understanding the novel coronavirus in many different aspects. This program not only provokes investigators but also common researchers to actively participate in clinical trials because of the new cooperative policies of FDA in the development of new effective therapeutics against COVID-19.

List of abbreviations

2019-nCoV 2019 Novel coronavirus
CTAP Coronavirus Treatment Acceleration Program
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
US FDA United States Food and Drug Administration
WHO World Health Organization

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