Drug repositioning as an alternative for the treatment of COVID-19 and future pandemics

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Drug repurposing or drug repositioning is a technique by which existing drugs are used to treat emerging and challenging diseases (1). The SARS-CoV-2 coronavirus outbreak has caused a major public health problem worldwide, so the use of drugs intended to treat other diseases became a suitable approach to fight COVID-19 disease. In this review we explore some of the drugs that have been postulated to be repurposed and their clinical implications, highlighting some that are potential candidates not only because they exhibit anti-SARS-CoV-2 effects, but also because they are economical, safe, easily accessible as well as indicated for the general population, and easy to administer. We also analyze the implications of vaccination schedules and their conjugation with COVID-19 treatment.

Introduction

Three highly pathogenic coronaviruses have emerged in the past 20 years, Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV) and, the most recent of these, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 was first isolated in December 2019 and was quickly identified as causing coronavirus disease 2019 (COVID-19) (1). The emergence of SARS-CoV-2 caused a public health emergency, and because of its rapid spread, in March 2020 the World Health Organization (WHO) declared it a pandemic that has so far been attributed with more than 530 million confirmed cases and 6.3 million deaths worldwide (https://COVID19.who.int/, accessed on June 2022).

Since the emergence of SARS-CoV-2, there has been increased interest in finding effective treatments for COVID-19. Although humans have been regularly infected with seasonal coronaviruses (usually causing mild respiratory illness) (2), the development of a specific treatment or a preventive vaccine was not considered a priority as they were not considered a major threat. Thus, there are currently no specific antiviral drugs approved against SARS-CoV-2, nor against human coronaviruses in general (3).

The understanding of diseases, the discovery of new compounds with biological activity, as well as the development of new therapeutic options, is a long and complex process that can take several years. On average,

clinical studies for the development and introduction of new drugs take about 12 years from therapeutic target identification to marketing authorization (4,5). Therefore, the identification and development of new drugs for emerging or (re)emerging diseases, as is the case for COVID-19, is a very unlikely option. In this sense, repurposing of drugs already approved seems an excellent opportunity to find an effective treatment against COVID-19 (6).

Drug repurposing is a recent technique that refers to the process of reusing existing drugs for new therapeutic purposes (7,8), thus generating a promising treatment option in a remarkably shorter time (9,10). The main advantages of drug repositioning include the availability of information on the pharmacokinetics, pharmacodynamics and toxicity of a given drug of interest (10,11). This translates into lower risks of adverse side effects, drug-drug interactions and drug development time and costs, therefore, the risks in the development of the drug are considerably reduced.

There are two main approaches in the drug repurposing process: target- and disease-based approaches. The former allows the drug and target to interact with each other, thus allowing drug-target interactions to be established. The second uses datasets to determine new indications for already approved drugs based on comparisons of disease characteristics.

Since the beginning of the pandemic, several potential drugs against SARS-CoV-2 have been investigated in clinical trials, among these: chloroquine and hydroxychloroquine (malaria treatment), favipiravir (influenza treatment), the combination of lopinavir and ritonavir (HIV treatment), and, more recently, masitinib (mast cell tumors treatment) (https://clinicaltrials.gov/ct2/results?cond=COVID-19, accessed on June 2022). An example of successful repurposing is the FDA approval of remdesivir for the treatment of COVID-19 (initially developed for the treatment of Ebola virus infection (12)), which has paved the way for many approved and investigational drugs with potential for reuse in clinical trials for COVID-19, such as dexamethasone (13) and tocilizumab (treatment of rheumatoid arthritis) (14). More recently, the EU approved the emergency use of molnupiravir and the combination of nirmatrelvir and ritonavir to treat adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of developing severe COVID-19 (15). In this work we review these and some of the other drugs that have been postulated to have antiviral potential against SARS-CoV-2 as a drug repositioning strategy to provide a rapid and effective solution to the treatment of COVID19.

1. Treatments for COVID-19 disease and vaccine administration

The development of efficient and safe vaccines against COVID-19 was achieved through international scientific collaboration. Thus, vaccination was installed as a preventive strategy prior to exposure to the virus, together with the use of masks, hand washing and physical distancing.

Several medicinal products have been studied to assess their safety and efficacy as potential agents for pharmaceutical prophylaxis or treatment of COVID-19. These include corticosteroids (16–19), antivirals (20), systemic interferons (21), monoclonal antibodies against components of the immune system such as interleukin-6 (IL-6) (22), other immune modulators, and monoclonal antibodies against components of SARS-CoV-2. Here, the possible effect of immunization against SARS-CoV-2 on pharmacological treatment for COVID-19 is reviewed.

1.1. Steroids

Glucocorticoids are known to have profound effects on the immune system (23). These can decrease the neutrophils migration, which leads to neutrophilia, without affect the phagocytic response. These effects do not carry over to the circulating levels of B cells in the acute setting, but with prolonged administration, the number of B cells may be reduced. IgG and IgA levels may decrease by 10–20 percent in the first few weeks of treatment with regular

moderate-to-high dose (≥40 mg per day) steroid administration (24).

Glucocorticoids have variable effects on T lymphocytes. At low doses, the effects are primarily on naive CD4 T cells rather than effector and memory T cells (19). Steroids can be reduce Th1 and Th2 derived cytokines in activated T cells (25). Because the COVID vaccine helps proliferate the antigen specific Th1-type CD4+ T-cell responses, there can be a theoretical link between steroid administration and reduced efficacy of vaccination.

Steroid treatments such as dexamethasone may be given to patients experiencing severe COVID-19 symptoms to suppress the immune response and reduce inflammation (17,18,26).

Based on current evidence, the NIH recommends the use of dexamethasone 6 mg per day for up to 10 days or until discharge for patients hospitalized with COVID-19 requiring supplemental oxygenation (16,26). It should be noted that in milder COVID-19 there remains a possible risk that steroids might worsen the disease course, as steroids increase the risk of infection(27). Certainly, it should not be assumed that patients on chronic steroid therapy are immune from developing severe COVID-19 or that they are at a lesser risk of becoming infected by SARS-CoV-2.

As the currently authorised COVID-19 vaccines are non-live vaccines, the response to these vaccines should not be affected by short-term steroid treatment. In addition, by the time a person who has received steroid treatment for COVID-19 infection is well enough to receive a COVID-19 vaccination, the suppressant effect of the steroid treatment should be gone. On the other hand, given that the Pfizer and Moderna vaccines in the United States are novel mRNA-based immunizations, and there is no literature to evaluate antibody response to these vaccines after injected or systemic steroids, this conclusion should be interpreted within the context of this limitation.

1.2. Monoclonal antibodies

Monoclonal antibodies (mAbs) are a type of therapeutic agent under investigation for the treatment of COVID-19. The majority of direct antiviral monoclonal antibody products under development for SARS-CoV-2 target the spike protein, which the virus utilizes to enter host cells (28,29).

As a response to the pandemic, AstraZeneca is developing mAbs to the SARS-CoV-2 S protein. The SARS-CoV-2 spike protein contains the virus's RBD, which enables the virus to bind to receptors on human cells. By targeting this region of the virus's spike protein, antibodies can block the virus's attachment to human cells, and, therefore, is expected to block infection (30). AZD7442, a combination of 2 of these mAbs (AZD8895 and AZD1061), is being evaluated for administration to prevent and/or treat COVID-19 (Clinicaltrials.gov. Phase III study of AZD7442 for treatment of COVID-19 in outpatient adults (TACKLE). Available at: https://clinicaltrials.gov/ct2/show//NCT04723394).

Monoclonal antibody preparations containing specific man-made antibodies which bind to the surface of the SARS-CoV-2 virus and stop it from attaching to the body's cells and replicating further have been licensed for the treatment and prophylaxis of COVID-19 infection. Primate data suggests that administration of the AstraZeneca combination monoclonal antibody product does not interfere with the subsequent response to active vaccination. Based on this limited evidence, therefore, no specific interval is required between receipt of these products and COVID-19 vaccination, or vice versa. As the use of these products is likely to be prioritised to those who are less able to respond to vaccination, for example immunosuppressed individuals, additional doses of vaccine may be required.

However, the Centers for Disease Control and Prevention recommends that the COVID-19 vaccines should be delayed for at least 90 days after the receipt of SARS-CoV-2 monoclonal antibodies or convalescent plasma provided for treatment of COVID-19 infection. A deferral for at least 90 days is based on the estimated half-life of such therapies and evidence suggesting that reinfection is uncommon within the 90 days after initial infection. This is a precautionary measure until additional information becomes available, to avoid potential

interference of the antibody therapy with vaccine-induced immune responses (Centers for Disease Control and Prevention. (2021, September). Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States (https://www.cdc.gov/vaccines/covid-19/clinicalconsiderations/covid-19-vaccines us.html#CoV-19-vaccination).

1.3. Antivirals

Antiviral medicines prevent further replication of viruses. As none of the currently authorised COVID-19 vaccines contain live replicating virus, response to COVID-19 vaccine will not be affected by prior or recent receipt of anti-viral medication.

Another issue that has been important at the social level is the acceptance of vaccines by the population, since there are still groups of people who are not willing to undergo the vaccination process, despite the social and/or legal sanctions that this entails. For various anti-vaccination groups, there is little relationship between vaccination and the degree of protection they confer against the virus. Moreover, there is still fear of the adverse reactions that this new type of vaccines may cause in the short, medium, and long term. For example, for vaccines against COVID-19, it is estimated that the acceptance rate fluctuates between 55% and 90% worldwide (31), while in a developed country such as the United States the acceptance rate does not exceed 75%, which may result in low herd immunity against SARS-CoV-2 (32).

2. Drug repurposing after COVID-19 strikes

The SARS-CoV-2 coronavirus outbreak has caused a major public health problem worldwide, so using drugs intended to treat other diseases became a suitable approach to combat COVID-19. Among the groups of drugs that have been tested to treat COVID-19 are *i*) drugs that act on viral replication, *ii*) drugs that act on viral entry, *iii*) drugs that act on cytokine release, and *iv*) miscellaneous. Some of them are described below.

Remdesivir is a nucleotide analog developed initially against the Ebola virus (2). When evaluating this drug against COVID-19 in macaques, 12h after the first dose, no signs of respiratory disease were observed in these animals. Also, radiographs showed lower pulmonary infiltrates and bronchoalveolar lavages had low virus titers (3). On the other hand, in a posthoc analysis of patients with severe COVID-19, it was found that when receiving treatment with Remdesivir, the median recovery time was shorter (11 days), and the need for mechanical ventilation was lower (4). Arbidol is a potent broad-spectrum antiviral agent commonly used to treat Influenza in Russia and China. It is one of the drugs in phase 4 clinical trials for treating patients with COVID-19. With Arbidol, a reduction in the mortality rate and an increase in the recovery rate was observed (5, 6). In addition, treatment with Arbidol and lopinavir/ritonavir has been shown to delay the development of lung lesions while reducing the respiratory and gastrointestinal viral load of COVID-19, thereby reducing transmission (7).

Chloroquine and its analog hydroxychloroquine are potent inhibitors of most coronaviruses (8). They are used for the treatment or prevention of malaria and certain autoimmune diseases. Studies in African green monkey Vero E6 cells showed significantly higher potency for chloroquine than hydroxychloroquine (9). Chloroquine has an EC90 value of 6.90 µM against SARS-CoV2 in Vero E6 cells, which can be clinically achieved after administration of 500 mg, as shown in patients with rheumatoid arthritis (10). A safe dose of 6 to 6.5 mg/kg per day of hydroxychloroquine could produce serum levels of 1.4 to 1.5 µM in humans (11). It is speculated that hydroxychloroquine could reach the concentration in the above tissues at a safe dose to inhibit SARS-CoV2 infection.

The randomized clinical trial RECOVERY (Randomised Evaluation of COVid-19 theERapY) evaluates several possible therapeutic alternatives for hospitalized patients with COVID-19; high dose corticosteroids vs. standard dose (26,33), empagliflozin, used in the treatment of diabetes and heart and kidney disease; sotrovimab, monoclonal antibodies against

FIGURE 1

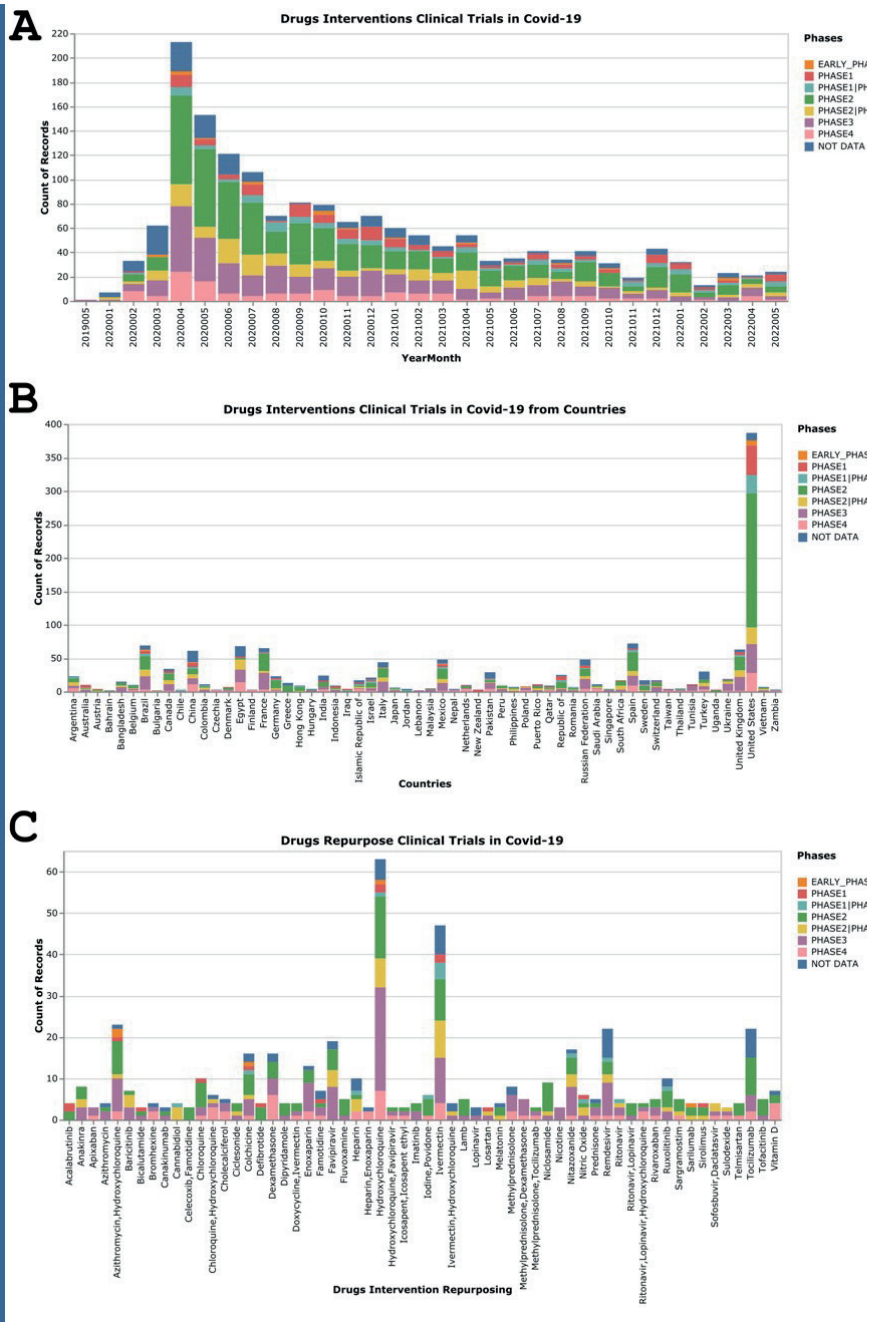

Figure 1. Covid-19 Drugs Repurposing Analysis from ClinicalTrials.gov. A. Drugs Interventions of Clinical Trials in Covid-19. From ClinicalTrials.gov (https://beta.clinicaltrials.gov) we download a total of 6231 Clinical Trials (CT) related to keyword "Covid-19", then filters from Jan 2019 to May 2022, and the intervention type by 'DRUG' with a remain of 1664 CT. The progression in plot for months and years and the Clinical phases is colored from the legend. The peak CT is observed in April 2020 with more of 200 CT from repurposing and main from phase 2. **B.** Drugs Interventions of Clinical Trials in Covid-19 from Countries. The 1664 CT countries are in bar plot, the bar is colored from the legend. United States have 350 CT, and a dozen in several places, the main cities are New York and California. Other countries with more of 50 CTs are Brazil, China, Egypt, Mexico, Russian Federation, Spain, and United Kingdom. **C.** Drugs Repurposing Clinical Trials in Covid-19. The 1664 initial CTs from drugs, 864 are repurposing drugs (FDA approved). The drugs with more CTs are hydroxychloroquine (63), ivermectin (47), azithromycin/ Hydroxychloroquine (23), remdesivir (22), tocilizumab (22), favipiravir (19), nitazoxanide (17), colchicine (16), Dexamethasone 16), and Enoxaparin (13). In brief, we found the antiparasitic drugs hydroxychloroquine, ivermectin, and nitazoxanide; the antibiotic azithromycin; the antivirals remdesivir and favipiravir; the corticoids dexamethasone and prednisone, the antibodies tocilizumab, sarilumab, and canakinumab; and the vitamin D.

the spike protein and the antivirals molnupiravir and paxlovid. Another clinical trial is SOLIDARITY, which is determining the effectiveness and safety of lopinavir, hydroxychloroquine, interferon (IFN)-β1 and remdesivir (34,35). In both studies the results are not yet conclusive for their use in the treatment of patients with COVID-19. If we consider all the available laboratory and clinical trial results on drug repositioning to treat COVID-19, no substantial evidence supports the efficacy of the drugs mentioned above. Further studies are required to define their effectiveness as well as their safety.

There are controversies about the molecules that received emergency approval to treat COVID-19 patients. At that same time, several clinical trials for drugs repurposed for the treatment of COVID-19 were observed. A recent article reported that 3,754 clinical trials had been completed (1), and to date (2022-06-15) there are 8.106 clinical trials register in the ClinicalTrials.gov database from the U.S. National Institutes of Health, these studies are distributed as follows: Africa: 505; North America: 2.179; Central America: 61; South America: 506; North Asia: 209; East Asia: 557; South Asia: 262; Southeast Asia: 210; Europe: 2.855; Middle East: 692; and Pacifica: 72. In the Figure 1, an analysis of all reported clinical trials is presented.

Table 1. Relevant clinical trials for drug repurposing against COVID19

Drug molecules	CONCLUSION	CLINICAL TRIAL Nº	REFERENCE
Hydroxychloroquine with or without azithromycin	the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care	NCT04322123	(36)
Hydroxychloroquine	Hydroxychloroquine did not considerably improvement of clinical status of Hospitalized COVID-19 patients at day 14	NCT04332991	(37)
Lopinavir-ritonavir	These findings do not support the use of lopinavir-ritonavir for treatment of patients admitted to hospital with COVID-19.	NCT04381936	(38)
Remdesivir	Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection	NCT04280705	(39)
Remdesivir	Remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies.	NCT04257656	(40)
Ivermectin	Ivermectin achieved a marked reduction in self-reported anosmia/hyposmia, a reduction in cough, and a tendency to lower viral loads and IgG titers.	NCT04390022	(41)

Some relevant examples of some of these clinical trials are showed in Table 1.

Here we also highlighted some clinical trials with meaningful results, described bellow:

2.1. Montelukast

Montelukast is a leukotriene (D4) receptor antagonist approved for treating asthma (42), Exercise-Induced Bronchoconstriction (43), and Seasonal Allergic Rhinitis (44). Montelukast is a novel agent that simultaneously targets two important drug targets of SARS-CoV-2. The investigators initially demonstrated the dual profile of Montelukast purpose inhibitor of SARS-CoV-2 infection and IL-6 production by immune cells (45).

Currently, the undergoing study is a national, multi-center, open-label, three-arm, phase ii study to investigate the effect of montelukast between emergency room visits and hospitalizations in COVID-19 pneumonia in comparison with standard treatment (Clinical trial Nº NCT047118285 from ClinicalTrials.gov).

2.2. Hydroxychloroquine in combination with sirolimus and dexamethasone

Some prospective results suggest a beneficial role for antimalarial drugs (chloroquine and hydroxychloroquine) in treating COVID-19. This effect is reinforced with the addition of azithromycin (46). Dexamethasone is a therapeutic molecule widely used to restrain inflammation (47). It is the first drug that significantly helped the recovery and survival of COVID-19 patients in a randomized controlled trial (48). Sirolimus is also referred to as Rapamune, and rapamycin is approved for clinical use to prevent organ transplant rejection (49). The benefits of sirolimus for influenza showed decreased viral titer and improved respiratory function in patients with severe H1N1 virus-induced pneumonia (50). The investigators hypothesized that the combination of sirolimus and hydroxychloroquine would improve the respiratory status. However, this work has not yet been completed and is still in progress (Clinical trial Nº NCT04374903 from ClinicalTrials.gov).

2.3. Doxycycline

Doxycycline is an antimicrobial agent with good tolerance and a broad antibacterial spectrum. In addition to their antibiotic effect, they show many non-antibiotic properties (51). It has been reported to have anti-inflammatory, anti-oxidant, neuroprotective, and immunomodulatory effects (52). These properties make it possible to use the drug in the treatment of osteoarthritis, neuropsychiatric disorders, multiple sclerosis, or COVID-19 (53).

In this sense, there is a clinical trial to test if doxycycline can benefit COVID patients. The researchers propose that doxycycline inhibits virus replication and, at the same time, blocks the development of cytokine storms. Therefore, doxycycline could improve survival and reduce morbidity in patients infected with SARS-CoV-2 (Clinical trial Nº NCT04433078 from ClinicalTrials.gov).

2.4. Chlorpromazine

Chlorpromazine is one of the widely used typical antipsychotic drugs (54). The clinical trial, in course, evaluates the effects of respiratory symptoms the addition of chlorpromazine to the standard therapeutic protocol in COVID 19 patients hospitalized (Clinical trial Nº NCT04366739 from ClinicalTrials.gov). The proposal is based on studies showing that various psychotropics inhibit viral replication of MERS-CoV and SARS-CoV-1 coronaviruses in vitro.

2.5. Bromhexine as a promissory therapeutic alternative against early COVID19

Although the antiviral, anti-inflammatory and immunomodulatory drugs are targeting the virus inside the host cell, there are other mechanisms that could be a potential therapeutic target to reduce viral infection, such as preventing entry into the cell. Such is the case of compounds that target the viral Spike protein that binds to the catalytic domain of the human angiotensin-converting enzyme 2 (ACE2). Safe a wide used drug such as bromhexine, a mucolytic and antitussive agent, usually low cost and marketed without prescription, which was introduced in the market in 1963 under the brand name Bisolvon®. Bromhexine and appears to have an antiviral effect, being effective in controlling influenza infection (55,56). It is indicated both for adults and pediatric population, for the management of a wide variety of respiratory conditions in most cases involving alterations in mucus secretion. It is generally well tolerated and has few adverse effects (57,58). Bromhexine has been initially identified as a potent inhibitor (IC_{50} = 0.75 μM) of the transmembrane serine protease 2 (TMPRSS2) of SARS-CoV (59), being involved also in the binding and infection (mainly via non-endocytotic route) of SARS-CoV-2 to host cells. In 2021 much work has been developed to understand the mechanism of action of bromhexine in SARS-CoV-2 infection. Recent papers ruled out the TMPRSS2 inhibition of SARS-CoV-2 as slight antiviral activity is reported in VeroE6 cells, which lacks TMPRSS2 in their membranes (60). Thus, the antiviral activity of bromhexine may be governed by interaction of this drug with one or more other key viral/human targets. However, bromhexine reached clinical trials in the first months of pandemic for hospitalized patients showing a reduction in the mortality rate in patients with COVID-19 (61).

A randomized open-label study to test the bromhexine prophylaxis of COVID19 for medical personnel was performed, showing that bromhexine hydrochloride prophylaxis was associated with a reduced rate of symptomatic COVID-19 (62) (Clinical trial Nº NCT04405999 from ClinicalTrials.gov). Other clinical trials were bromhexine is combined with spironolactone (Nº NCT04424134), N-acetylcysteine (Nº NCT04928495), hydroxychloroquine (Nº NCT04355026 and Nº NCT04340349), Recombinant Human Interferon α2b (Nº NCT04273763), and fluvoxamine (Nº NCT05087381) are currently in process according to the ClinicalTrials.gov database. Nevertheless, new clinical studies with more patients and using placebo are needed to understand if this mucolytic and antitussive agent could be repurposed against early COVID-19 disease.

Conclusions

More than two years after its strike, the COVID-19 pandemic still represent a complex socio-health scenario, including changes in the transmission capacity of the virus and its variability in response to available pharmacological therapies, making it essential to have drugs other than vaccines that contribute to better management of the pandemic while maintaining an adequate margin of effectiveness and guaranteeing the safety of the population.

Drug repositioning strategy has several advantages with respect to the design and development of new drugs, because pre-clinical and clinical studies have already determined safety, thus reducing the time and resources required in experimentation (63). In addition, since they have lower costs, they take less time to reach the market; even more so when there are already pharmaceutical production and supply chains that support the distribution of the drug to the population, thus representing a valuable strategy to offer alternative and/or complementary treatments to vaccination against COVID-19 and future pandemics.

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