

A brief review on the lessons learned from COVID-19 on drug discovery and research



PHARMACOLOGY

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Abstract

COVID-19 pandemic has taught many lessons regarding drug discovery and development. This review covers these aspects of drug discovery and research for COVID-19 which might be used as a tool for future. It summarizes the positives such as progresses in antiviral drug discovery, drug repurposing, adaptations of clinical trial and its regulations, as well as the negative points such as the need to develop more collaboration among stakeholders and future directions. It also discusses the benefits and limitations of finding new indications for existing drugs, and the lessons learned regarding rigorous and robust clinical trials, pharmacokinetic/pharmacodynamic modelling, as well as combination therapy. The pandemic has also revealed some gaps regarding global collaboration and coordination, data sharing and transparency and equitable distribution. Finally, the review enumerates the future directions and implications of drug discovery and research for COVID-19 and other infectious diseases such as preparedness and resilience, interdisciplinary and integrative approaches, diversity and inclusion, and personalized and precision medicine.

Keywords: COVID-19, drug discovery, drug development, anti-viral drugs and drug repurposing

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed unprecedented challenges and opportunities for the biomedical community to develop effective therapeutics and vaccines. The pandemic necessitated urgent need of effective and safe drugs to combat the morbidly and mortality entailed by the disease, as well as an effective vaccine to control the spread. There were many anti-viral drugs and vaccine which were tested and some were recommended in very short period. This has been largely due to innovative strategies for drug development, drug repurposing and collaboration of various stakeholders [1-3]. This lesson must be continued to be used for other diseases for the benefit of society. In this review, we summarize the progress and lessons

learned from COVID-19 on drug discovery and research, covering the following aspects:

- The importance of antiviral drug discovery and the strategies to accelerate it
- The benefits and challenges of drug repurposing for COVID-19
- The role of biomarkers in drug development and clinical practice
- The innovations and limitations of clinical trials during the pandemic
- The need for collaboration at various levels especially for drug distribution
- The future directions and implications for drug discovery and research

Antiviral drug discovery

Antiviral drugs are essential to prevent, treat, and control viral infections, especially in the absence of vaccines or in the presence of variants that may

DOI: 10.15386/mpr-2641

Manuscript received: 28.05.2023
Received in revised form: 03.11.2023
Accepted: 15.11.2023

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Pharmacology

escape vaccine-induced immunity. However, antiviral drug discovery is a complex and lengthy process that faces many scientific, technical, regulatory, and economic hurdles [4]. The COVID-19 pandemic has stimulated tremendous efforts to accelerate antiviral drug discovery by leveraging various approaches, such as:

- Targeting viral proteins: Several viral proteins have been identified as potential drug targets, such as the spike protein, the main protease (Mpro), the RNA-dependent RNA polymerase (RdRp), the papain-like protease (PLpro), the helicase (Hel), Transmembrane protease, serine 2 (TMPRSS2) and the nonstructural protein 15 (nsp15) [5-8]. These proteins are involved in key steps of the viral life cycle, such as entry, replication, transcription, translation, assembly, and release (Table I).

- Targeting host factors: Several host factors have been implicated in facilitating or modulating viral infection, such as angiotensin-converting enzyme 2 (ACE2), transmembrane protease serine 2 (TMPRSS2), Janus Kinase (JAK), CD147, neuropilin-1 (NRP1), importin (α/β 1), interferons (IFNs), cytokines, chemokines, and immune cells. These factors can be targeted by drugs that either inhibit their interaction with viral proteins, or modulate their expression or function (Table II).

Some of the lessons learned from antiviral drug discovery for COVID-19 are:

- The need for pan-coronavirus drug targets that can inhibit a broad range of coronaviruses and prevent the emergence of resistant variants.

- The value of structure-based drug design and fragment screening to identify novel inhibitors of viral proteins with high potency and specificity.

- The importance of *in vitro* assays and animal models that can faithfully recapitulate the viral infection and pathogenesis in humans.

- The potential of artificial intelligence and machine learning to accelerate antiviral drug discovery by mining large-scale data, predicting drug properties, optimizing drug candidates, and designing clinical trials.

Drug repurposing

Drug repurposing is the process of finding new indications for existing drugs that have already been approved or tested for other diseases. It is a promising strategy to rapidly identify safe and effective therapeutics for COVID-19, as it can bypass or shorten the preclinical development and regulatory approval stages. Several drugs have been repurposed for COVID-19 based on their known mechanisms of action or their observed activity against SARS-CoV-2 or related coronaviruses *in vitro* or *in vivo* (Table III).

Table I. List of drugs targeting viral proteins and their status [5-8].

| Drug | Target | Mechanism | Status (FDA) |
|-------------------|---------|---|--|
| Remdesivir | RdRp | Nucleoside analogue that inhibits viral RNA synthesis | First treatment for COVID-19 to be approved for the treatment of COVID-19 (2020) |
| Molnupiravir | RdRp | Nucleoside analogue that induces lethal mutagenesis of viral RNA | Emergency use authorization (2021) for use in certain populations where other treatments are not feasible |
| Nirmatrelvir | Mpro | Peptidomimetic inhibitor that blocks viral polyprotein processing | First oral antiviral (nirmatrelvir tablets and ritonavir tablet) for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19 (2023) |
| Camostat mesylate | TMPRSS2 | Serine protease inhibitor that prevents viral entry via membrane fusion | A phase 3 trial did not find beneficial effect in terms of time to viral clearance for patients with COVID-19 |

Table II. List of drugs targeting host factors and their status [9-12].

| Drug | Target | Mechanism | Status |
|-------------|----------------------|--|---|
| Baricitinib | JAK1/JAK2 | Janus kinase inhibitor that blocks cytokine signalling and reduces inflammation | Approved in combination with remdesivir for hospitalized patients with severe COVID-19 (FDA-2020) |
| Tocilizumab | IL-6R | Monoclonal antibody that blocks interleukin-6 receptor and reduces cytokine storm | Approved for hospitalized patients with severe or critical COVID-19 (European Medicines Agency -2021, FDA-2022) |
| Ivermectin | IMP α/β 1 | Antiparasitic agent that inhibits importin α/β 1-mediated nuclear transport of viral proteins | Under investigation for mild-to-moderate COVID-19 |
| Vilobelimab | Human C5a | human-mouse chimeric IgG4 kappa antibody that targets human C5a in plasma | Emergency use authorization (EUA) by FDA for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (2023) |

Table III. List of repurposed drugs and their current status [13-15].

| Drug | Original indication | Mechanism for COVID-19 | Status |
|------------------------------------|--|---|---|
| Hydroxychloroquine/ chloroquine | Malaria/rheumatoid arthritis/lupus erythematosus | Antimalarial/immunomodulatory agent that interferes with viral entry via endocytosis and modulates immune response | Not recommended for COVID-19 due to lack of efficacy and safety concerns |
| Ritonavir/lopinavir | HIV infection | Protease inhibitors that block viral polyprotein processing | Not effective for COVID-19 as monotherapy or in combination with other drugs |
| Favipiravir | Influenza infection | Nucleoside analogue that inhibits viral RNA synthesis | For mild-to-moderate COVID-19 with mixed results, not approved by FDA but was approved in several countries including Japan and India |
| Dexamethasone | Various inflammatory and autoimmune conditions | Glucocorticoid that suppresses inflammation and immune response | Recommended for hospitalized patients with severe or critical COVID-19 requiring oxygen therapy or mechanical ventilation |

Table IV. List of biomarkers and their role in diagnosing COVID-19 [16-18].

| Biomarker | Type | Role |
|---------------------------------------|-----------------|--|
| SAR- CoV-2 RNA | Molecular | Detects active viral infection by RT-PCR or antigen tests |
| SARS-CoV-2 antibodies (IgM, IgG, IgA) | Serological | Detects past or recent viral infection by ELISA or lateral flow tests |
| Neutralizing antibodies | Functional | Measures the ability of antibodies to block viral entry by pseudovirus or live virus assays |
| C-reactive protein (CRP) | Inflammatory | Indicates systemic inflammation and disease severity |
| D-dimer | Coagulation | Indicates thrombotic risk and disease severity |
| Lactate dehydrogenase (LDH) | Cellular damage | Indicates tissue damage and disease severity |
| Interleukin-6 (IL-6) | Cytokine | Indicates cytokine storm and disease severity |

Some of the lessons learned from drug repurposing for COVID-19 are:

- The need for rigorous and robust clinical trials to evaluate the efficacy and safety of repurposed drugs, as well as to avoid premature conclusions based on anecdotal evidence or low-quality studies.
- The value of large-scale screening platforms and open-access databases to identify potential repurposed drugs from existing libraries of approved or investigational drugs.
- The importance of pharmacokinetic/pharmacodynamic (PK/PD) modelling and physiologically based pharmacokinetic (PBPK) modelling to predict the optimal dose, exposure, and response of repurposed drugs for COVID-19.
- The potential of combination therapy to enhance the antiviral activity, reduce the viral load, and prevent the emergence of resistance of repurposed drugs.

Biomarkers

Biomarkers are measurable indicators of a biological state or condition, such as viral DNA, antibodies, or cytokines. They can help to diagnose diseases, monitor disease progression, predict treatment response, and assess drug safety and efficacy. During the

COVID-19 pandemic, biomarkers played a crucial role in identifying and testing patients for SARS-CoV-2 infection, as well as evaluating the immunogenicity and protection of vaccines. Biomarkers can also help identify novel drug targets, stratify patient populations, and optimize drug dosing for different diseases (Table IV).

Some of the lessons learned from biomarkers for COVID-19 are:

- The need for standardization and validation of biomarker assays to ensure their accuracy, reliability, reproducibility, and comparability across different settings and populations.
- The value of multiplex platforms and point-of-care devices to enable rapid, simultaneous, and convenient measurement of multiple biomarkers at low cost and high throughput.
- The importance of biomarker discovery and biomarker-based trials to identify novel biomarkers that can improve the diagnosis, prognosis, stratification, and treatment of COVID-19.
- The potential of artificial intelligence and machine learning to integrate and analyze multiple types and sources of biomarker data to generate actionable insights and predictions for COVID-19.

Table V. Examples of trial and their innovations [19-21].

| Trial types | Innovation |
|------------------------|---|
| Platform trials | Trials that test multiple interventions in parallel using a common protocol and a shared control group |
| Adaptive trials | Trials that allow modifications in design or conduct based on interim data analysis |
| Master protocols | Protocols that coordinate multiple trials under a single overarching structure |
| Decentralized trials | Trials that use remote technologies such as telemedicine, mobile apps, wearable devices, or home visits to reduce site visits |
| Patient-centric trials | Trials that involve patients in the design, conduct, and dissemination of trials to improve recruitment, retention, and relevance |

Clinical trials

Clinical trials are essential to evaluate the efficacy and safety of new drugs or vaccines in human subjects. They are usually conducted in four phases: phase I (safety), phase II (efficacy), phase III (effectiveness), and phase IV (post-marketing surveillance). During the COVID-19 pandemic, clinical trials faced many challenges due to the urgency, uncertainty, complexity, and variability of the situation. However, clinical trials also witnessed many innovations and adaptations to overcome these challenges (Table V).

Some of the lessons learned from clinical trials for COVID-19 are:

- The need for global collaboration and coordination among stakeholders such as researchers, regulators, funders, sponsors, ethics committees, health authorities, and patients to facilitate the design, conduct, and dissemination of trials.
- The value of data sharing and transparency to enable rapid dissemination of trial results, avoid duplication of efforts, and ensure scientific rigor and public trust.
- The importance of ethical principles and standards to protect the rights, safety, and well-being of trial participants and ensure the quality and validity of trial data.
- The potential of digital technologies to enable remote data collection, monitoring, and analysis, as well as to enhance patient engagement and empowerment.

Need for collaboration

Collaboration for drug distribution for COVID-19 was essential to fight the pandemic and to ensure global health security. Collaboration can involve partnerships between private and public entities, data-sharing, knowledge-sharing, and technology-sharing [22-25]. However, collaboration also faces challenges such as vaccine nationalism, export bans, intellectual property rights, and insufficient manufacturing capacity [22,26-28]. One of the main challenges is the gap in equitable distribution of vaccines. This gap means that many low-income countries have not been able to vaccinate their

high-risk populations, such as health-care workers, older adults, and people with co-morbidities [29]. This gap also poses a threat to global health security, as it increases the risk of new variants emerging and spreading. Some of the factors that contribute to this gap are the lack of local production capacity in LICs, the unequal access to vaccine doses and supplies, the weak health system infrastructure, and the low demand and trust in vaccines [30].

To close this gap, some possible solutions are to increase the global supply and availability of vaccines, to support local manufacturing and technology transfer in LICs, to strengthen the health system capacity and delivery mechanisms, to enhance the risk communication and community engagement strategies, and to coordinate the domestic and international funding and support [31,32]. These solutions require strong leadership, commitment, and collaboration from all stakeholders involved.

Future directions and implications

The COVID-19 pandemic has highlighted the strengths and weaknesses of the current drug discovery and research landscape. It has also provided valuable insights and lessons for future drug discovery and research endeavors. Some of the future directions and implications are:

- The need for preparedness and resilience to anticipate and respond to emerging infectious diseases and other public health threats by developing rapid diagnostics, therapeutics, and vaccines.
- The value of interdisciplinary and integrative approaches to drug discovery and research that combine biological, chemical, physical, computational, social, and behavioral sciences.
- The importance of diversity and inclusion in drug discovery and research to ensure that drugs are safe and effective for different populations across age, gender, ethnicity, geography, and comorbidity.
- The potential of personalized and precision medicine to tailor drugs to individual patients based on their genetic, molecular, physiological, environmental, and lifestyle factors.

Conclusion

The COVID-19 pandemic has been a catalyst for innovation and collaboration in drug discovery and research. It has also revealed the gaps and challenges that need to be addressed to improve the efficiency, effectiveness, and equity of drug discovery and research. By learning from the COVID-19 experience and applying the lessons learned to future drug discovery and research endeavors, we can hope to achieve better health outcomes for all.

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