Quest Journals
Journal of Research in Pharmaceutical Science
Volume 7 ~ Issue 10 (2021) pp: 01-04
ISSN(Online) : 2347-2995
www.questjournals.org

Research Paper

Repurposing of Drugs for COVID-19: The Way Forward

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Abstract
Drug repurposing/ repositioning is an unconventional drug discovery approach to explore new therapeutic benefits of existing drugs and many abandoned compounds. It helps to accelerate the drug discovery process through the identification of a novel clinical use for an existing drug. The repositioning or "repurposing" of existing therapies for alternative disease indications is an attractive approach that can save significant investments of time and money during drug development. With the rise in COVID-19 cases globally, the scientific community made enormous efforts in order to rapidly develop vaccines that prevent the spread of COVID-19 infection. Due to the urgent need for development of drugs, repurposing of drugs was one of the most important strategies for COVID-19.

Received 04 October, 2021; Revised: 16 October, 2021; Accepted 18 October, 2021 © The author(s) 2021. Published with open access at www.questjournals.org

I. INTRODUCTION

The repurposing of drugs is defined as a process of identifying new pharmacological indications from old/existing/failed/investigational/already marketed/approved drugs/ for the treatment of diseases other than the drug's original therapeutic use. The traditional drug discovery method is strenuous, highly expensive and risky. Thisinnovative approach of drug repurposing has the potential to overcome the challenges imposed by traditional drug discovery by easing the longer duration of development, high monetary cost and the increased risk of failure.[1]

Technologies like bioinformatics/cheminformatics tools have made drug repositioning significantly easier by decreasing the time and cost of the drug development and also increasing the success rate. Recently, the use of artificial intelligence (AI) technology has further accelerated the drug purposing process.[2]

The rapid emergence in December 2019 of cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in China rapidly expanded to other countries. World Health Organization (WHO) declared COVID-19 as a Public Health Emergency of International Concern (PHEIC) on January 30, 2020; and a pandemic on March 11, 2020.[3,4]

[1]MithunRudrapal, Shubham J. Khairnar and Anil G. Jadhav (July 13th 2020). Drug Repurposing (DR): An Emerging Approach in Drug Discovery, Drug Repurposing - Hypothesis, Molecular Aspects and Therapeutic Applications, Farid A. Badria, IntechOpen, DOI: 10.5772/intechopen.93193. Available from: https://www.intechopen.com/chapters/72744. https://www.intechopen.com/chapters/72744

[2] Agrawal P (2018) Artificial Intelligence in Drug Discovery and Development. J Pharmacovigil 6: e173. doi:10.4172/2329-6887.1000e173. https://www.researchgate.net/profile/Prashansa-Agrawal-5/publication/324986571_Artificial_Intelligence_in_Drug_Discovery_and_Development/links/5c1f9d23a6fdccfc7064a671/Artificial-Intelligence-in-Drug-Discovery-and-Development.pdf

[3] https://www.who.int/director-general/speeches/detail/who-director-general-s-statement-on-ihr-emergency-committee-on-novel-coronavirus-(2019-ncov)

[4] https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

Scientistsworld over also made attempts to identify effective and safe pharmacological treatments against the virus.As there was no approved treatment for COVID-19, WHO recommended evaluation of four repurposed drugs Remdesivir, Lopinavir, Interferon (β1a), and chloroquine or hydroxychloroquine in an international solidarity trial in patients hospitalized with coronavirus disease 2019. This large Solidarity trial was an international clinical trial conducted in over 30 countries to help find an effective treatment for COVID-19.This trial showed little or no effect on hospitalized patients with Covid-19 on mortality, initiation of ventilation, and duration of hospital stay.[5]Further the next phase of WHO Solidarity Trial; Solidarity PLUS is ongoing where it aims to test three new drugs, artesunate, imatinib and infliximab for their potential in reducing the risk of death in hospitalized COVID-19 patients.[6]

Advantage of Drug Repurposing

Repositioned drugs have the advantage of decreased development costs and decreased time to market than traditional discovery efforts, due to availability of previously collected pharmacokinetic toxicology, and safety data. In fact, this strategy of using existing therapeutics for new indications has demonstrated success through previous observational studies such as sildenafil (Viagra), a phosphodiesterase inhibitor initially developed to treat angina and now repurposed as a medication for erectile dysfunction, as well as metformin (Glucophage), a common diabetes medication that is now the active chemical in 100+ ongoing Phase II and Phase III clinical trials as a cancer therapeutic. Owing to massive failures in unearthing novel chemical entities and lack of financial support for the traditional drug discovery and development pipeline, pharma industries diverted their focus towards drug repositioning . With advancement in the technologies and computational methods, screening of drugs for off-label indication has become much easier.

National Institute of Health Model

The National Center for Advancing Translational Sciences (NCATS) Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) program at the National Institutes of Health (NIH) essentially serves as a "matchmaker" to provide academic investigators an opportunity to access pharmaceutical industry agents and explore new ways to treat disease. Through its Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) program, NCATS aims to improve the process of developing new treatments and cures for disease by finding new uses for existing therapies that already have cleared several key steps along the development path.

Recent pandemic of COVID 19 has led to research across global for getting treatment against COVID-19 with major emphasis on repurposed drugs as they can be quickly deployed for treatment as opposed to new drugs which need almost a decade of development. In India CSIR has partnered with the some of the major Pharmaceutical companies for repurposing drugs and attempts to find new molecules. It has been identified that drugs such as paracetamol, Remdesivir, hydroxychloroquine, Azithromycin, Flaviparavir, LupinivirRemdesivir,

[5]https://www.nejm.org/doi/10.1056/NEJMoa2023184
[6] https://www.who.int/news/item/11-08-2021-who-s-solidarity-clinical-trial-enters-a-new-phase-with-three-new-candidate-drugs

Arbidol, Baloxavir, Baricitinib, Camostat mesylate, Galidesivir, Ruxolitinib, Teicoplanin, Niclosamide and Rivavirin. etc. can be helpful for coronavirus treatment.

II. REMDESIVIR

Remdesivir is an in vitro inhibitor of the viral RNA-dependent, RNA polymerase and has shown proven results against SARS-CoV-1 and the Middle East respiratory syndrome (MERS-CoV) in reducing lung virus levels and lung damage. A phase 3, randomized, double-blind, placebo-controlled trial of intravenous remdesivir was conducted in hospitalized adults with Covid-19 and had evidence of lower respiratory tract infection. The findings from this Adaptive COVID-19 Treatment Trial (ACTT-1) in 1062 patients reported shortened time to recovery in hospitalised COVID-19 patients compared to standard care.[7]

Thereafterremdesivir was first given emergency use authorization by United StatesFood and Drug Administration on May 1, 2020, for treatment in adults and children hospitalized with suspected or laboratory-confirmed Covid-19 and later also received full or conditional approval in several other countries.

Another randomised clinical study in patients with moderate to severe COVID-19 reported results in line with the WHO Solidarity Trial. This study evaluated the effects of treatment with remdesivir for 5 days in patients with moderate to severe coronavirus infection.The findings from the trial showed no significant difference in efficacy between remdesivir course and non-remdesivir course. Hence concluding that treatment using remdesivir for five days produced no improvement in clinical outcomes.[8]

III. DEXAMETHASONE

Dexamethasone is a synthetic corticosteroid produced in the adrenal cortex in healthy individuals. In view of the pandemic and the urgent need for treatment options WHO released living guidance for COVID-19 treatment with Corticosteroids in September 2020 wherein an expert panel reviewed data from 8 clinical trials of systemic corticosteroids for COVID-19. The panel gave recommendations to treat patients with severe and critical COVID-19 with systemic corticosteroid therapy in appropriate doses for 7 to 10 days and a conditional recommendation not to use corticosteroid therapy in patients with non-severe COVID-19.[9]

The RECOVERY trial also worked to collect evidence for the effects of dexamethasone in hospitalized patients with Covid-19. This controlled, open-label trial evaluated the clinical outcomes in hospitalized patients with Covid-19 administered with 6 mg once daily dose of oral or intravenous dexamethasone for up to 10 days. A total of 6425 patients underwent randomization to receive either dexamethasone or usual care alone. The results from the trial showedlower 28-day mortality in patients receiving invasive mechanical ventilation and also for those on oxygen support. However, there was no evidence that dexamethasone provided any benefit among patients who were not receiving respiratory support.[10]

RECOVERY
Randomised Evaluation of COVID-19 Therapy

A subsequent prospective meta-analysis of clinical trials of critically ill patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, also confirmed the findings of from the RECOVERY trial.[11]

[7]Beigel at al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med 2020; 383:1813-1826. DOI: 10.1056/NEJMoa2007764. https://www.nejm.org/doi/full/10.1056/nejmoa2007764

[8] Mahajan L, Singh AP, Gifty. Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study. Indian J Anaesth. 2021;65(Suppl 1):S41-S46. doi:10.4103/ija.IJA_149_21. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7993042/

[9]https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1

[10] N Engl J Med 2021; 384:693-704. DOI: 10.1056/NEJMoa2021436

[11] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Oct 6;324(13):1330-1341. doi: 10.1001/jama.2020.17023. PMID: 32876694; PMCID: PMC7489434. https://jamanetwork.com/journals/jama/fullarticle/2770279

IV. HYDROXYCHLOROQUINE

Hydroxychloroquine and chloroquine, have been used to treat malaria and rheumatologic conditions for over 70 years. The drugs have shown in vitro activity against COVID-19 virus, however the exact antiviral mechanism is unclear.

As part of the controlled, open-label Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, comparison between hydroxychloroquine and usual was evaluated in patients hospitalized with Covid-19. The analysis of the this trial indicated that hydroxychloroquine is not an effective treatment for hospitalized Covid-19 patients but did not address its use as prophylaxis or in patients with less severe SARS-CoV-2 infection managed in the community.[12]

However, another small our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients when given in combination with azithromycin.[13]

V. LOPINAVIR

The drug combination Lopinavir and Ritonavir, used for treating human immunodeficiency virus infectionhas in vitro inhibitory activity against SARS-CoV, MERS and SAR-CoV-2. Lopinavir–ritonavir has been proposed as a treatment for COVID-19 on the basis of in vitro activity, preclinical studies, and observational studies.

The investigator initiated RECOVERY trial also evaluated the effects of lopinavir–ritonavir in patients admitted to hospital with COVID-19 in UK. A total of 1616 patients were randomly allocated to lopinavir–ritonavir and 3424 were randomly allocated to usual care. The data from large randomised trial reported that lopinavir–ritonavir is not an effective treatment for patients admitted to hospital with COVID-19. Additionally, allocation to lopinavir–ritonavir was not associated with reductions in the duration of hospital stay or the risk of being ventilated or dying for those not on ventilation.[14]

Another small randomized, controlled, open-label trial also confirmed the findings from RECOVERY trial and indicated that no benefit was observed with lopinavir–ritonavir treatment in confirmed cases of severe Covid-19.[15]

Way Forward

Governments should consider putting a robustframework for re-purposing to enable quicker patient access. COVID-19 is a classic example of international collaboration in research. The Government should consider increased public funding, especially for independent academic trials that are doing re-purposing research. There is also a need to encourage knowledge sharing and collaboration between all stakeholders. The international organizations could explore the potential of collaborative funding models such as, public-private partnership models specifically also for re-purposing research in life threatening and neglected disease areas.

[12] The RECOVERY Collaborative Group. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med 2020; 383:2030-2040. DOI: 10.1056/NEJMoa2022926. https://www.nejm.org/doi/full/10.1056/NEJMoa2022926

[13]Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949. doi:10.1016/j.ijantimicag.2020.105949. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102549/

[14] RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2020 Oct 24;396(10259):1345-1352. doi: 10.1016/S0140-6736(20)32013-4. Epub 2020 Oct 5. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32013-4/fulltext

[15] Cao B et al. Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 May 7;382(19):1787-1799. doi: 10.1056/NEJMoa2001282. Epub 2020 Mar 18. https://www.nejm.org/doi/full/10.1056/NEJMoa2001282