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A comprehensive narrative review of the organic evolution of global initiatives and developments in Covid 19 drugs and therapeutics repurposing research with regard to Monoclonal antibodies and Antivirals.

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Abstract

Introduction: Drug repositioning is being actively pursued for Covid 19. Drug repositioning is also known as therapeutic switching, drug re purposing, drug re tasking or drug re profiling. This is the re tasking of a previously tested and approved drug to attempt to address the treatment requirements of a different disease or medical condition. **Methods:** A systematic search of Scopus, Web of science, PubMed and Google scholar was conducted to identify articles that involved studies on repurposing of drugs for clinical management of COVID-19 disease. The following 'Medical Subject Headings' (MeSH) terms and text words were used in the search in Scopus: (Drug Repurposing or Drug Re-profiling or Drug re-positioning) AND (Coronavirus disease) OR (COVID 19) OR (SARS-coronavirus-2 diseases.) The following 'Medical Subject Headings' (MeSH) terms and text words were used in the search in Web of Science: (Drug Repurposing or Drug Re-profiling or Drug re-positioning) AND (Coronavirus disease) OR (COVID 19) OR (SARS-coronavirus-2 diseases.) The following 'Medical Subject Headings' (MeSH) terms and text words were used in the search in Pubmed: (Drug Repurposing or Drug Re-profiling or Drug re-positioning) AND (Coronavirus disease) OR (COVID 19) OR (SARS-

coronavirus-2 diseases.) The following 'Medical Subject Headings' (MeSH) terms and text words were used in the search in Google scholar: (Drug Repurposing or Drug Re-profiling or Drug re-positioning) AND (Coronavirus disease) OR (COVID 19) OR (SARS-coronavirus-2 diseases.) **Results and Discussion:** The Monoclonal antibodies space is seeing repositioning as well as development of new therapeutic alternatives specifically for Covid 19. The antibodies being investigated for repositioning are anti-IL-8 (BMS-986253) and anti-IL-6 agents (Tocilizumab). The antiviral therapeutic space is seeing significant research activity in re positioning previously developed and approved anti viral agents. These anti viral agents had been therapeutically weaponised against SARS-CoV, MERS-CoV and the West Nile virus. The antivirals currently being repurposed are Favipiravir, Remdesivir, Umifenovir, Triazavarin and Ribavirin.

Keywords

Covid 19, drug repurposing, drug repositioning, therapeutic switching, drug retasking, drug re profiling

Introduction

COVID-19 drug development includes all research that works towards developing therapeutic and preventative pharmaceutical interventions for the alleviation of the severity of the Covid 19 disease. Health organisations, hundreds of pharmaceutical companies, university researchers and firms working in biotechnology have been, from the beginning of the pandemic in early 2020, all through 2021, working towards the development of these interventions. These therapeutic and preventative pharmaceutical candidates are in different stages of research: clinical and preclinical. As of April 2021, the total number of candidates was 506 and the number of potential Covid 19 drugs in clinical trials was 419.[1] Concerted efforts for the development of vaccines, post infection therapies and antiviral drugs had begun in March 2020 with the US Food and Drug Administration (USFDA), WHO, European Medicines Agency (EMA), the government of China and pharmaceutical companies[2,3,4,5,6] coordinating closely with researchers in industry and academia to hasten the pace of development.[7,8,9,10] 536 clinical studies with the objective of coming out with covid 19 post infection treatments are registered with the WHO's Registry platform for International Clinical Trials.[11,12] The Solidarity trial was run by the WHO in 10 countries, starting from March 2020. Thousands of Covid 19 positive patients were enrolled. The clinical objective was to ascertain the efficacy of four antivirals used in the trial.[13,14,15] In April 2020, a dynamic systematic review was set in motion. The purpose of this review was to track the progress of covid 19 related registered clinical trials for treatment drugs and vaccines.[16] With drug development being a time intensive process, typically taking above five years to meet all standard safety requirements[17], U.S. and European regulatory bodies moved quickly to bring down barriers and speed up clinical testing.[18] In June 2021, the final stage of human testing for phase 3 and phase 4 clinical trials had been reached by several potential candidates for post covid infection pharmaceutical therapy.[19]

The process of drug development has the following components: animal and microorganism laboratory research and fulfilment of regulatory requirements.[20,21] Typically, the whole process from concept to approved drug / vaccine takes at least 10 years. The intervening stages are those of laboratory based preclinical testing and development of clinical trials including phase 1, phase 2 and phase 3 trials.[17,20,21] Typically, the preclinical stage for Covid 19 treatments requires 1 to 2 years.[22,23,24,25] This includes testing for safety and efficacy in a statistically significant sample size of Covid 19 patients. In different countries, the statistically significant size can vary from hundreds to thousands. The success

rate to attain eventual regulatory approval is only 19 percent.[26] Phase 1 trials assess mainly initial dosing and safety. The testing is done in a cohort size of a few dozen. After success in Phase 1 trials, Phase 2 trials begin. These trials assess efficacy of increasing dosage levels on Covid 19 disease. Efficacy is measured by biomarkers. The cohort size in phase 2 trials is in the hundreds. Close monitoring is done for adverse events. Phase 2 trials of Covid 19 therapeutic candidates have typically been blinded, randomised, placebo controlled and operationally executed at multiple sites.[27] The strike rate for Phase 2 trials to move to Phase 3 (for all conditions) is 31 percent. The strike rate for Phase 2 trials to move to Phase 3 (for infectious diseases only) is 43 percent.[26] Phase 2 trial lengths can extend from many months to 2 years. The longer the duration, the more expensive it is.[27] In literature, the available estimates of the cost for an average length Phase 2 trial inclusive of the costs of the preclinical and Phase 1 stages is 57 million dollars (in 2013 dollars).[28] Successful execution of a Phase 2 trial does not necessarily translate into success in Phase 3 research.[29] Phase 3 trials have a sample size that can range from a few hundreds to thousands. The cohort consists of hospitalised patients. The variable tested is the efficacy of the drug in reducing disease effects. It includes continuous monitoring for adverse events following drug administration.[2,17,30]

Drug repositioning is being actively pursued for Covid 19. Drug repositioning is also known as therapeutic switching, drug re purposing, drug re tasking or drug re profiling. This is the re tasking of a previously tested and approved drug to attempt to address the treatment requirements of a different disease or medical condition.[1] Many antiviral medications currently in use or that have been used previously as treatments for Malaria, Severe acute respiratory syndrome(SARS), HIV and Middle east respiratory syndrome (MERS) are potential drug repurposing candidates. There exists a significant similarity in the genomic layout, replication characteristics and biology of the SARS Cov 2, SARS and MERS viruses. Therefore it is a logical step to test therapeutic options across these viruses.[2]

Methods

A systematic search of Scopus, Web of science, PubMed and Google scholar was conducted to identify articles that involved studies on repurposing of drugs for clinical management of COVID-19 disease. The following ‘Medical Subject Headings’ (MeSH) terms and text words were used in the search in Scopus: (Drug Repurposing or Drug Re-profiling or Drug re-positioning) AND (Coronavirus disease) OR (COVID 19) OR (SARS-coronavirus-2 diseases.) The following ‘Medical Subject Headings’ (MeSH) terms and text words were used in the search in Web of Science: (Drug Repurposing or Drug Re-profiling or Drug re-positioning) AND (Coronavirus disease) OR (COVID 19) OR (SARS-coronavirus-2 diseases.) The following ‘Medical Subject Headings’ (MeSH) terms and text words were used in the search in Pubmed: (Drug Repurposing or Drug Re-profiling or Drug re-positioning) AND (Coronavirus disease) OR (COVID 19) OR (SARS-coronavirus-2 diseases.) The following ‘Medical Subject Headings’ (MeSH) terms and text words were used in the search in Google scholar: (Drug Repurposing or Drug Re-profiling or Drug re-positioning) AND (Coronavirus disease) OR (COVID 19) OR (SARS-coronavirus-2 diseases.)

Results and Discussion

1. Monoclonal antibodies

The Monoclonal antibodies space is seeing repositioning as well as development of new therapeutic alternatives specifically for Covid 19.[31] The antibodies being investigated for repositioning are anti-IL-8 (BMS-986253) and anti-IL-6 agents (Tocilizumab).[10] Mavrilimumab is a monoclonal antibody. It suppresses granulocyte macrophage colony-stimulating factor receptor (GM-CSF-R).[11][12] Its efficacy in bettering the prognosis of Covid 19 pneumonia and systemic hyperinflammation has been studied. Some beneficial effects have been reported.[13] Sarilumab and Tocilizumab have been declared fit for Covid 19 use by the UK NHS in January 2021. The indication is ICU admissions. The evidence points to a decrease in risk of death by 24 percent.[14] Tocilizumab is an interleukin 6 inhibitor. Tocilizumab use has been assessed in multiple trials. It is authorised for clinical use in severe cytokine release syndrome, rheumatoid arthritis, systemic juvenile idiopathic arthritis and giant cell arteritis.[15] WHO and Hoffmann-La Roche have conducted exclusive clinical trials on cohorts of clinically severely ill patients.[16] On July 29,2020, Roche announced that there was no evidence of clinical benefits in the double blind randomised trial of tocilizumab in treatment of Covid 19 pneumonia.[17] In contrast, the UK based REMAP-CAP trials came up with data that strongly suggested that tocilizumab provided significant therapeutic benefits. These therapeutic benefits were seen in adults when the administration was started within 24 hours of the beginning of indications for organ support in patients who were critically ill with Covid 19. The patients in the trial cohort were in an ICU setting, receiving cardiovascular and/or respiratory support.[15] In January 2021, the UK National Institute for Health and Care Excellence (UK NICE) updated its therapeutic guidelines for Tocilizumab therapy.[15] Tocilizumab has been tested in the large scale RECOVERY trial in the UK.[9] The proponents of Tocilizumab have held up the results of this trial as clinching proof of the efficacy of Tocilizumab in the treatment of severe cases of Covid 19.[18] The RECOVERY trial had a cohort of 4000 adults. This cohort size was substantially more than the combined cohorts of all previous randomised control trials. It was in fact several times more. This cohort was randomly assigned to either the standard protocol treatment of the time or to Tocilizumab.[32] In patients on Tocilizumab, mortality rate was 31 percent as compared to 35 percent in patients receiving standard protocol treatment of the time. Deaths within 28 days were considered for the purpose of calculation. Hospital discharge within 28 days was also seen to be significantly more probable in patients on Tocilizumab than in patients receiving standard protocol treatment of the time.[18] Tocilizumab was authorised for emergency use in the U.S. in June 2021. The indications for emergency use were Covid positive patients older than two years of age and receiving inpatient treatment with systemic steroids, oxygen supplementation, mechanical ventilation (non invasive or invasive) or extracorporeal membrane oxygenation (ECMO).[19]

2. Antivirals

The antiviral therapeutic space is seeing significant research activity in re positioning previously developed and approved anti viral agents. These anti viral agents had been therapeutically weaponised against SARS-CoV, MERS-CoV and the West Nile virus.[20] The antivirals currently being repurposed are Favipiravir, Remdesivir, Umifenovir, Triazavarin and Ribavirin.[20,21,22,23,24] There is evidence of the

artesunate-pyronaridine combination inhibiting the activity of SARS-CoV-2 in in vitro tests utilising Hela cells. Post twenty four hours, this combination had a virus titre inhibition rate of more than 99 percent. Evidence of significant reductions in Cytotoxicity were also observed.[25] A peer reviewed pre print published in July 2020 gave evidence of this combination using human lung epithelial cells to display antiviral actions against influenza and SARS-CoV-2 viruses.[26] The artesunate-pyronaridine combination is undergoing phase 2 clinical trials in South Africa and South Korea.[27,28,29,30] ProTide Remdesivir contains the nucleoside GS-441524. ProTide Remdesivir has shown a 96 percent success rate in the treatment of Feline infectious peritonitis (FIP) which is caused by a feline coronavirus.[31,32] After administration, Remdesivir is subjected to rapid hydrolysis and dephosphorylation with the result that GS-441524 is the active metabolite in circulation.[33,34,35,36] These findings have pushed it as a therapeutic option for Covid 19.[33,37,38,39,40] Factors favouring ProTide Remdesivir are faster synthesis, absence of liver first pass metabolism and enhanced production of triphosphate and increased hydrophilicity independent of the enzymes needed for the bioactivation of Remdesivir: CTSA and CESI. Molnupiravir is used in influenza treatment. Researchers have presented evidence for the complete suppression of Covid 19 transmission within 24 hours by Molnupiravir. This evidence comes from research in ferrets. Covid 19 transmission in ferrets is very similar to Covid 19 transmission in humans.[41,42,43,44] An in vitro screening assay of drugs carried out in South Korea has come up with Niclosamide as a potential antiviral candidate.[45] Rupintrivir, CLpro 1 and GC376 are protease inhibitors that are seeing substantial laboratory research and development. These protease inhibitors have a defined target: the protease 3CLpro.[46,47,48]

Favipiravir is approved for Influenza treatment in Japan.[49,20] With regard to favipiravir efficacy in Covid 19 treatment, it is safe to say that more evidence is required.[50] Clinical trials on Favipiravir in the Chinese research centres in Shenzhen and Wuhan reported significant efficacy in Covid 19 treatment.[51] The Wuhan study had a cohort size of 240 patients with Covid 19 pneumonia. The cohort was divided into two batches. One batch was administered Favipiravir. The other batch received Umifenovir.[52] Clinical recovery from fever and cough was quicker in the favipiravir cohort. There was no significant difference in the probability of progression to more serious illness that required ventilator support.[53] Favipiravir was approved by the Italian administration for experimental treatment in Covid 19 in March 2020. Three high Covid 19 disease burden regions in Italy were chosen for the conduct of clinical trials.[54] Public announcements were made by the Italian pharmaceutical agency that the then levels of evidence in favour of the efficacy of Favipiravir in Covid 19 treatment were at best patchy and insufficient.[55] In May 2020, Avifavir, a generic version of Favipiravir was granted approval by the health ministry of the Russian government for treatment of Covid 19. The phase 1 clinical trials of Avifavir had shown very encouraging results.[56,57,58] The use of Fabiflu, a generic version of Favipiravir developed by Glenmark pharmaceuticals was approved in June 2020 by the Indian government for the management of mild and moderate cases of Covid 19.[59] A systematic review published in May 2021 shared the following results: Patients who received Favipiravir in the first seven days of inpatient treatment had a 24 percent higher chance of improvement in clinical status. With regard to mortality reduction, there was no statistically significant impact in any of the groups including inpatients and those without serious symptoms.[60,61]

Lopinavir and Ritonavir

In March of 2020, it was identified that post infection drugs could target 3CLpro, which is the main protease of the SARS-Cov-2 virus. This protease is an enzyme that is required in the processing of polyproteins related to replication. The identification of the protease enzyme was facilitated significantly by the publication of the genome by Chinese researchers in January of 2020.[62] Lopinavir and Ritonavir are protease inhibitors that are currently being used in the treatment of Human Immunodeficiency Viruses (HIV). There is evidence of their antimicrobial activity against coronaviruses, MERS and SARS.[6,63] Their efficacy as a potential combination therapy has been studied in 2 arms of Phase 3 of the 2020 global solidarity Covid 19 project.[63,64] There was no effect of this combination on Covid 19 inpatients in a preliminary study conducted in China.[65] University of Colorado researchers are trying to modify these drugs into something that will bind with the SARS-CoV-2 protease.[66,67] There has been academic criticism from within the peer scientific community regarding the logic of directing research funding towards the repurposing of drugs that have been developed very specifically for HIV/AIDS. There is scepticism regarding whether such drugs will have any efficacy against a virus that does not have the particular HIV-1 protease that these drugs target.[2] Lopinavir and Ritonavir were included in the International solidarity trial by the WHO.[68] In June 2020, the UK RECOVERY trial investigators released their report: the administration of Lopinavir and Ritonavir over a treatment duration of 28 days in a cohort of 1596 inpatients with severe Covid 19 infection did not yield any significant therapeutic benefits.[69,70] In October 2020, a study of FDA approved therapeutic agents that targeted the SARS-CoV-2 spike (S) protein was published. It suggested that the combination of Lopinavir and Ritonavir was unbalanced, resulting in Lopinavir interfering with Ritonavir's action and significantly negatively impacting its therapeutic benefits. Ritonavir's action is blocking activity on the RBD-hACE2 interaction (Receptor Binding Domain-human Angiotensin Converting Enzyme-2).

Remdesivir

The United States approved Remdesivir for Covid 19 therapy in October 2020.[7,57,58,59] This approval was based on the U.S. FDA's data analysis of 3 RCTs: NCT04280705, NCT04292899, and NCT04292730. The cohort had inpatients with Covid 19 severity ranging from mild Covid 19 to severe Covid 19.[7,59] The cohort size was 2043. 226 sites in 17 countries including the USA participated. Gilead Sciences Inc. was granted approval and received the updated Emergency use authorisation (EUA). The U.S. National Institute of Allergy and Infectious Diseases conducted an RCT. It was double blinded and placebo controlled. It assessed recovery times from Covid 19 among patients within 29 days of the end of treatment.[7] The cohort size was 1062 inpatients with all three grades of Covid 19 (mild, moderate and severe). 541 patients received Remdesivir and 521 patients received placebo.[7] The definition of recovery for the purpose of the study included two options: either discharge from the hospital, or inpatient no longer needing supplemental oxygen and medical care.[7] Median time for recovery from Covid 19 was ten days for the Remdesivir group and fifteen days for the placebo group. This difference is statistically significant.[7] The Remdesivir cohort had a statistically significant higher probability of clinical improvement on day 15 compared to the placebo cohort.[7] A second multi centre RCT of hospitalised Covid 19 inpatients with moderate illness was conducted. Two cohorts received Remdesivir for 5 days (n=191) and 10 days (n=193) and one cohort received standard care (n=200).[7] The clinical status of patients was evaluated on Day 11.[7] The analysis showed that the probability of a

patient's clinical status improving on day 11 was statistically significantly higher in the 5 day Remdesivir group when compared to the group receiving standard care.[7] The probability of a patient's clinical status improving on day 11 was higher in the 5 day Remdesivir group when compared to the group receiving standard care, but not statistically significantly.[7] A third multi centre RCT of hospitalised Covid 19 inpatients with severe illness was conducted. Two cohorts received Remdesivir for 5 days (n=200) and 10 days (n=197).[7] The clinical status of patients was evaluated on Day 14.[7] The analysis showed that the probability of a patient's clinical status improving on day 14 was the same for both cohorts. The two cohorts did not have any statistically significant differences in their recovery rates and mortality rates.[7]

Remdesivir/baricitinib

The ACTT-2 (Adaptive COVID-19 Treatment Trial 2) to assess the impact and safety of a combination treatment of Baricitinib and Remdesivir was initiated by the US NIAID (National Institute of Allergy and Infectious Diseases) in May 2020. The study cohort was Covid 19 inpatients with lung pathology; requiring mechanical ventilation; requiring supplemental oxygen or having abnormal chest x rays.[60,61,62] Based on the results of these trials, the US FDA authorised emergency use of baricitinib in combination with remdesivir in November 2020.[23] The target population is suspected or laboratory confirmed Covid 19 inpatients older than 2 years of age requiring any of the following: ECMO (Extracorporeal membrane oxygenation), supplemental oxygen or mechanical ventilation.[23]

Remdesivir/interferon beta-1a

The ACTT-3 (Adaptive COVID-19 Treatment Trial 3) to assess the impact and safety of a combination treatment of remdesivir plus interferon beta-1a was initiated by the US NIAID (National Institute of Allergy and Infectious Diseases) in May 2020. The study cohort was laboratory confirmed Covid 19 adult inpatients with lung pathology; requiring mechanical ventilation; requiring supplemental oxygen or having abnormal chest x rays.[61,63]

Authorizations and deployment

Approximately fifty countries have authorised Remdesivir for emergency use in Covid 19.[13] India and Singapore have granted Emergency use authorisation for Remdesivir.[64,65] Australia, Japan, U.S. and the European Union have granted approvals for the use of Remdesivir in patients with severe illness.[8,9,66,67,68,69,57,58,7] An assessment of whether the usage guidelines for Remdesivir should be altered to include Covid 19 patients with no indications for supplemental oxygen was begun by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in February 2021.[70] Remdesivir is the first therapeutic intervention for Covid 19 treatment to be granted approval by the U.S. FDA.[7] The current FDA approval does not extend to the whole population that had been covered by the Emergency use authorisation granted on May 1,2020.[7] With the aim of maintaining uninterrupted access of Remdesivir to the pediatric population that had coverage previously too under

the EUA, the EUA for remdesivir was revised by the FDA to make the therapeutic option available to suspected or laboratory confirmed Covid 19 pediatric inpatients weighing between 3.5 kgs and 40 kgs.[7] Currently, the safety and impact of Remdesivir in pediatric patients is being assessed by clinical trials.[7]

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