The Need for Combination Antiviral Therapy for Effective Treatment of COVID-19

Misaki Wayengera

Department of Immunology, Molecular Biology and Pathology, College of Health Sciences, Makerere University Kampala, Uganda

INTRODUCTION

The World Health Organization (WHO) declared coronavirus diseases 2019 (COVID-19) on 30th January 2020. To date, infections with Severe Acute Respiratory Syndrome Coronavirus type II (SARS-CoV2) have reached pandemic levels. Despite several clinical trials, there is no specific effective treatment for COVID-19. Among the many trialed drugs with demonstrated in vitro antiSARS-CoV2 effects, include Hydroxyl-Chloroquine (HCQ), Azithromycin (AZ), Antivirals (remdesivir-RDV and lopinavir-ritonavir-LPV/r), and Ivermectin-IVM. Many of these have only been trialed as monotherapies. Considering the low antiviral efficacy of each monotherapy and promiscuous vulnerability of the Replication Transcription Complex (RTC) of SARS-CoV2, it becomes necessary consider combinational therapies. We propose a new combinatorial regimen comprising of HCQ/RDV/LPV-r/IVM for clinical testing in the treatment of COVID-19. Other combinational therapy regimens need to be considered to optimize the desired combined in vitro virocidal and virostatic.

The world is to-date held-hostage to the pandemic of Coronavirus Disease (Covid-19). Covid19 is caused by Severe Acute Respiratory Syndrome Coronavirus type II (SARS-CoV2). Coronavirus (CoV) are enveloped, positive-stranded RNA viruses with a nucleocapsid [2]. SARS-CoV2 belongs to the beta category (betaCoV) of the Orthorcoronavirinae subfamily of the family Coronaviridae [2,3]. In genetic terms, Chan et al. have proven that the genome of SARS-CoV2 has 82% nucleotide identity with that of human SARS-CoV-1 [4].

CoVs generally replicate via a Replication-Transcription Complex (RTC) formed by virus RNA and the replicate-transcriptase (RdRp) complex. Unlike polymerases III, RdRp-like HIV-1’s reverse transcriptase, lacks the proof reading mechanisms bestowed by the small polymerases (alpha, beta, gamma, Delta, Epsilon) and apurinic/apyrimidinic endonuclease (APE). As a result, CoVs are prone to high mutational rates in course of several cycles [5].

In light of our longstanding experience with the treatment for HIV-1/AIDS, in which we evolved from absence of drugs, through monotherapy and finally several options of optimized Highly Active Antiretroviral Combinatorial Therapy (HAART) regimens, it suffices to consider combination antiviral therapy for SARS-CoV2/Covid19 as well [6,7].

This especially in light of repeated reports of resurgence of viraemia among COVID patients who had successfully been treated on monotherapy. It remains too early to determine whether resurgence issues from re-infection with a different strain of virus (which would suggest that protective immunity is very short lived or not ever attained among infected and recovered persons) or reactivation of virus concealed within sites inaccessible by monotherapy [8]. Regardless, the concept of combination SARS-CoV2 Antiviral Therapy (SARS-CoV2-ART) is to attain complete viral replication cycle inhibition and elimination, early in course of the infection before a potential reservoir if present, is established.

Despite several clinical trials, there is no specific effective treatment for COVID19. Among the many trialed drug with demonstrated in vivo antiviral effects, include: Hydroxy-Chloroquine (HCQ), antivirals (remdesivir-RDV and lopinavir-ritonavir-LPV/r), and Ivermectin-IVM (Table 1) [9-12].

Table 1: List of drugs with demonstrated antiviral activity against SARS-CoV2 and benefit for treating COVID19.

<table>
<thead>
<tr>
<th>Class</th>
<th>COVID19 therapeutic agent</th>
<th>Site of action</th>
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<tbody>
<tr>
<td>Antimalarial, Quinolone</td>
<td>Hydroxychloroquine (HCQ)</td>
<td>pH mediated endocytosis</td>
</tr>
<tr>
<td>Antiviral (nucleotide analogue)</td>
<td>Lopinovir/Ritonavir (LPV/r)</td>
<td>RTC competitive inhibitor</td>
</tr>
<tr>
<td>Antiviral (virostatic)</td>
<td>Favipiravir, Peniclovir (FVP, PCV)</td>
<td>RdRp inhibitor</td>
</tr>
<tr>
<td>Antiparasitic</td>
<td>Ivermectin (IVM)</td>
<td>Non-specific innate system</td>
</tr>
</tbody>
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Several other highly-priced agents that are not readily available to all, but are known to inhibit various stages of the SARS-CoV2 replication cycle, can makethislist.

Many of these have only been trialed as mono-therapies. Considering the low antiviral efficacy of each monotherapy and promiscuous vulnerability of the Replication Transcription Complex (RTC) of SARS-CoV2, it becomes necessary consider combinational therapies. We propose a new combinatorial regimen comprising of HCQ/RDV/LPV-r/IVM for clinical testing in the treatment of COVID19. Other combinational therapy regimens need to be considered to optimize the desired combined in vitro virocidal and virostatic.
CONCLUSION

In conclusion, we propose the use of at least a 3-drug combination regimen for the effective treatment of SARS-CoV2/COVID19. Several options are possible from the existing agents, which might enable us define a 1st line, 2nd line and 3rd line option of therapy.

REFERENCES