Drugs Shown to Inhibit SARS-CoV-2 in COVID-19 Disease: Comparative Basic and Clinical Pharmacology of Molnupiravir and Ivermectin

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Abstract

The pharmacology of anti-SARS-CoV-2 drugs, Molnupiravir (M) and repurposed Ivermectin (IV) were compared. The IC_{50} for the inhibition of viral replication were 0.3µM for M and 2.8µM for IV. Both drugs have good oral absorption, with M achieving peak plasma concentrations by 2 hours and IV by 5 hours. The plasma half life were 7 hours for M and 81-91 hours for IV. M inhibits viral replication inducing viral mutagenesis in RdRp, causing viral error catastrophe and viral extinction. IV affects viral cell entry, nuclear transport and inhibits replication *via* RdRp. IV has additional effect to suppress cytokine production through STAT-3 inhibition. M is a more potent antiviral drug and IV has a longer residence in the body. Their effects on RdRp and cytokine inhibition are potentially complimentary for anti-COVID-19 activity. Both IV and M should be compared in randomized controlled clinical trials, and the possibility of their combination for anti-SARS-CoV-2 antiviral actions, explored further.

Keywords: COVID-19; Antiviral therapeutics; Molnupiravir; Ivermectin; Combination

Introduction

The COVID-19 pandemic caused by SARS-CoV-2, has affected more than 120 million people and resulted in nearly 3 million deaths worldwide. Although vaccine roll out is mitigating the community transmission and enabling a reopening of global economy piecemeal, there are still many nations where vaccines are not yet widely available, and new viral variants are emerging. There is a gradual shift in focus, to antiviral drugs, both for possible adjunctive chemoprophylaxis, as well as for active treatment of patients with new SARS-CoV-2 infections, or post -vaccination breakthrough COVID-19 cases. There have been purposive efforts, to develop novel and specific antiviral drugs for SARS-CoV-2, and to repurpose existing FDA -approved drugs to treat COVID-19. Molnupiravir is the most advanced of the novel antiviral drugs undergoing clinical development and trials, whilst Ivermectin is the most studied "repurposed" medication globally, in randomized clinical trials, retrospective studies and meta-analyses. This mini- review examines and compares their basic and clinical pharmacology and the possible utility of their combination, in treating COVID-19 and future corona virus diseases.

Molnupiravir and Ivermectin Anti-SARS-CoV-2 Mechanisms, Pharmacokinetics and Pharmacodynamics

Molnupiravir (EIDD2801/MK-4482) is a pro-drug of the novel active antiviral nucleoside analogue β-d-N4-hydroxycytidine (NHC, EIDD1931) [1]. It's a broad spectrum antiviral agent against SARS-CoV-2, SARS-CoV,seasonal or pandemic influenza and MERS corona virus [1]. The basic and clinical pharmacological properties are shown on Table 1. Ivermectin is an FDA-approved, WHO essential drug used as broad spectrum antiparasitic, antibiotic and

which has demonstrated broad spectrum antiviral activity against RNA viruses, including HIV, Zika, MERS corona virus. It is being repurposed as a therapeutic agent for COVID-19, after *in vitro* studies in Vero/hSLAM cells, showed that it caused a 5000-fold inhibition of SARS-CoV-2, (99.98% at 48 hours) with an IC50 of 2.8µM [2]. The corresponding *in vitro* IC_{50} of molnupiravir for SARS-CoV-2 is 0.3µM in Vero cells and 0.08µM in Calu-3 Cells [3]. The IC_{50} of Molnupiravir shows it to be a more potent anti-SARS-CoV-2 agent, compared to Ivermectin *in vitro*. Both molnupiravir and ivermectin are well absorbed after oral dosing, the Tmax of molnupiravir being 1-1.75 hours , with a half life of 7 hours, 1 whilst the Tmax of ivermectin is 4-6 hours, and a very long half life of 81-91 hours [4]. Ivermectin, being lipophilic has a large volume of distribution (V_d) and the ability to accumulate in the lungs [5], the major target organ of COVID-19. Molnupiravir is given twice daily, and doses of 400 and 800 mg showed viral clearance by RT-PCR [1]. By contrast, the dosing regimen of ivermectin in randomized clinical trials with RCT-PCR SARS-CoV-2 clearance, varied from 12mg daily [6], to 12mg twice a week [7]. The anti-SARS-CoV-2 actions, both of molnupiravir and ivermectin, are dose and concentration dependent [1,7]. Pharmacodynamically, the mechanisms of anti-SARS-CoV-2 action, both of molnupiravir and ivermectin are overlapping and complimentary (Table 1). Molnupiravir active metabolite (NHC-5' Triphosphate), acts as a competitive alternative substrate for the viral RNA dependent RNA polymerase (RdRp), causing viral mutagenesis or transition mutations, which leads to viral error catastrophe and extinction of replication [8]. There is some concern about the safety of NHC -nucleoside triphosphate, which is also mutagenic to mammalian cells [9]. Ivermectin (Table 1) exhibits multifarious actions, ranging from binding to SARS-CoV-2 spike protein S, reducing cell entry *via* human ACE2 receptors, inhibition of the

Table 1: Comparison of Anti-SARS-CoV-2 pharmacology of Molnupiravir and Ivermectin.

	Molnupiravir	Ivermectin
Chemical structure/Name	RiboNucleoside analogue. Pro-drug of β-d-N^4 Hydroxycytidine (NHC), EIDD 2801	22,23 dihydroavermectin B1a + B1b (80:20) mixture

Pharmacokinetics
  Absorption and F
  Distribution (V_d)
  Metabolism
  Excretion routes
  T ½ (hours)
  Mean Residence Time (hours)
  Tmax (hours)
 	
Daily doses
 	
SARS-CoV2 IC$_{50}$
	Rapid
	
	Prodrug > EIDD1931 (plasma esterases) > active 5'ATP EIDD (tissue kinases).
	
	7 hours
	?
	
	1-1.75 hours
	
	2
	
	0.3μM (Vero cells) 0.08μM (Calu cells)
	414.6 nM (Syrian Hamster)
		Good
		9-12L/Kg
		Hepatic CYP3A4 mainly, 3A5, 2C9, 2D6
		Fecal >99%
		81-91 hours
		84 hours
		
		5 hours
		1
		
		2.5-2-8 μM (E, RdRP cell associated virus genes)
		Vero-h/SLAB

Pharmacodynamics *Antiviral mechanisms* • Cell viral entry-hACE2 receptor. • Nuclear transport -importin α/β1 • RNA dependent, RNA polymerase (RdRp)* Viral mutagenesis Dose/Concentration-anti SARS-CoV-2 response	 ? ? Competitive alternative substrate for SARS-CoV-2 RdRP viral genome >excessive mutations > viral error catastrophe > viral extinction. Yes Dose -Dependent Viral RNA clearance in human phase 2A study.	 Binds to active sites of spike protein S. Inhibits human cell entrance of virus via h-ACE2. Binds Importin α to prevent link with β1 and nuclear transport of viral and host proteins. Binds to and inhibits viral RdRp replication and transcription complex with -9.7Kcal/mol energy No Significant dose and concentration dependent virucidal response seen in humans.
Effects on Cytokines & interleukins (IL)	?	Inhibits Janus Kinase (JAK) Signal transduction Activator of Transcription (STAT-3) and IL-6/10
Clinical Trials and Real World Efficacy **RT-PCR Cases**	Phase 2A shows dose dependent high anti-SARS-CoV-2 efficacy in COVID-19.	Mixed outcomes. Meta-analyses show clinical and laboratory benefits and mortality reduction.
Adverse effects and Drug-Drug Interactions	No Serious Adverse effects compared to placebo.	No Serious Adverse Effects. Dizziness

nuclear transport of viral proteins, which prevents interference with replication, to binding to RdRP, reducing the activity of the viral transcription -replication complex [10]. Ivermectin has additional effects on Signal Transduction Activation of Transcription (STAT-3) and inhibition of cytokine production and inflammation, which has not yet been shown for molnupiravir.

As most but not all double blind studies, and meta-analyses, have shown benefits of ivermectin in COVID19 including 56% mortality reduction [11], and given the complimentary pharmacokinetics and pharmacodynamics of the drugs, direct head -to -head comparison of molnupiravir and ivermectin, in blinded randomized clinical trials are needed. A combination of molnupiravir with Ivermectin putatively, may be at least additive or synergistic in effects on RdRP or cytokine release. This should be further investigated in anti-SARS-CoV-2 antiviral combination therapy.

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