SM Virology

Short Communication

Why Multi-Drug Antiviral Therapy is Needed for COVID-19

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Abstract

In response to the escalating threat of COVID-19 antimicrobial resistance, we emphasize the potential of multi-drug combinations to counteract this trend. We examine the controversy surrounding the use of ivermectin, antibiotics, and zinc, and conclude that their repurposing in COVID-19 therapies, in principle, may enhance treatment outcomes.

Keywords: COVID-19; Antimicrobial resistance; Ivermectin; Antibiotics; Zinc; Chronic infection; Avermectins.

Abbreviations: COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TB: Tuberculosis; RNA: Ribonucleic Acid; HIV: Human Immunodeficiency Virus; RCT: Randomized Controlled Trials; IVM: Ivermectin

Introduction

Our 80-year history of antimicrobial therapy evolution provides a framework for how best to treat COVID-19 and address efficacy and resistance. Introduction, in 1941, of penicillin led quickly to the spread of resistant strains of staphylococcus, and over the next 20 years bacteria adapted, and resisted eradication by new antibiotics [1]. Similarly, it has been observed that variants of the SARS-COV-2 virus have also evolved and adapted in response to our management strategies [2]. By revisiting these lessons from antibiotics, modern solutions can be gleaned to eradicate COVID-19 and its strain variants.

Multi-drug therapy becomes effective in tackling antibacterial resistance

Treatment of Tuberculosis (TB) has taught us the value of multi-drug combinations. While penicillin and sulphonamides proved effective in treating "single cavity" systemic infections, neither class was effective in treating intracellular tuberculosis. The introduction of streptomycin, developed in 1944, saw effective killing of M. tuberculosis by binding to the 16S RNA of the 30S ribosomal subunit causing codon mis-read and consequent inhibition of protein synthesis. However, clinical relapse was observed within six months of monotherapy due to TB developing resistance to streptomycin.

The application of multi-drug therapy became established in 1950 when streptomycin combined with bacteriostatic PAS was used for TB [3]. Addition of a third drug, Isoniazid (INH), offered additional efficacy. Altogether all three drugs became standard therapy for tuberculosis with a two-year course of which led to complete remission in 96%, and relapse in only 1-2%. The resulting combination was not only highly effective in returning bacteriologically negative tests in treated groups, but also prevented the evolution of antibiotic resistant variants of tuberculosis [4]. While antimicrobial resistance through mutation was well known in tuberculosis, the success of multi-drug therapy in TB establishes the principles that apply to the treatment of COVID-19, another intracellular infection.

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Multi-drug therapy is effective in tackling stubborn intracellular chronic infections

While intracellular chronic infections represent a formidable challenge in public health, multi-drug therapy may prove to be an effective solution. As referenced earlier, intracellular pathogens such as Human Immunodeficiency Virus (HIV), *Mycobacterium leprae* (Leprosy), and TB take refuge within host cells which enables the evasion of the immune system's surveillance and persistence over long periods. In all three infections, multi-drug combinations have become the standard after demonstrable effects in eradicating pathogens.

Both the application of intracellular and extracellular distributed antibiotics is therefore crucial in the strategy for long term clearance of such pathogens. Rifabutin, for example, is highly lipophilic and concentrates itself within tissues and intracellular compartments at concentrations ~10 times greater than in plasma concentrations [5]. Amoxicillin, an extracellular antibiotic, is distributed almost exclusively in extracellular spaces and is completely ineffective when transported intracellularly [6]. Antibiotics like rifabutin, with excellent intracellular penetration, may therefore complement amoxicillin's effectiveness against extracellular forms to encourage full pathogen clearance.

Drug Resistance in Viral Infections

An important discovery was made in the 1980's when viruses began to develop drug resistance [7]. Amantadine, an adamantanes derivative, was first used for the treatment of influenza A in 1963, however by 2015, 45% of influenza A viruses became resistant to adamantanes based compounds. Monotherapy, in the treatment of HIV and Hepatitis C, also showed similar cases of resistance.

Multi-drug therapy becomes effective in tackling intracellular viral infections

While combination anti-HIV 1 therapy was readily adopted and proved highly effective for infected individuals, it was observed that drug efficacy relied on early simultaneous delivery before viral load and replication increased. Of note, HIV clinical outcomes changed dramatically when anti-viral drugs targeting reverse transcriptase were combined with protease inhibitors in the 1990s [8].

The modern use of multi-drug therapy has converted HIV infection from a terminal illness into a chronic condition. Since the development of combination anti-viral therapy, 60-80% reduction in rates of AIDS (Acquired Immunodeficiency Syndrome) has been recorded, as well as major declines in hospitalization, and death rates for those infected. The principles of multi-drug therapy developed through the study of tuberculosis are paralleled in HIV infections. Multi-drug therapies for other viral infections such as Hepatitis B, C and HSV have followed suit, demonstrating improved viral clearance and lower viral resistance. Could combination anti-viral therapy be conceivably applicable to COVID-19?

Plant Derived Compounds with Antiparasitic and Anti-Viral Activity (Allelochemicals)

The next major advance could come from the recognition that natural products bring a different approach to inhibiting microbial activity. Plant compounds possess an enormous capacity to synthesise aromatic substances such as phenolic compounds. Plant secondary metabolites also include tannins, terpenoids, alkaloids and flavonoids, many of which have potent therapeutic activity.

An added benefit also came from the fact that plant compounds coevolved with pathogenic viruses, eventually developing the ability to target multiple active sites in both the pathogen and host to prevent viral replication. Many of these 'phytochemicals' were recognised in ancient cultures, and more recently have been rediscovered in western medicine and rebranded as colchicine, hydroxychloroquine, quercetin, and avermectins [9].

Several of these phytochemicals are effective in COVID-19 treatment and include colchicine (22% improvement in 17 randomised controlled trials); quercetin (57% improvement in 8 RCT's); hydroxychloroquine (62% improvement in 36 early treatment studies), and ivermectin (53% improvement in 42 RCT's) [10]. Each of these phytochemicals have also been extensively studied and shown to have wide-ranging antimicrobial activity consistent with their protective role in nature.

Amongst these plant-derived compounds, quinine and its derivatives have shown inhibitory activity against malaria by preventing molecular synthesis in Plasmodium schizonts and alkalisation of intracellular vesicle compartments [11]. Quercetin, demonstrates antiviral activity on multiple levels [12] by blocking virus proliferation through the inhibition of protein mediated translation and the induction of Heat-Shock-Protein-70. Similarly, colchicine demonstrates anti-inflammatory activity that may be beneficial in reducing clinical symptoms of COVID-19 infection [13]. The demonstrated anti-pathogenic effects of the above plant-derived medications support the investigation of ivermectin as a potential therapeutic agent for COVID-19 infection.

Anti-viral activity of ivermectin

Ivermectin (IVM) is a well-established and safe antiparasitic drug derived from plants (soil streptomyces). It has a manifold wide spectrum of action with minimal side-effects. Importantly, it interacts with both viral and host targets meaning it can be effectively repurposed in resource constrained healthcare settings. While its monotherapy effectiveness in COVID-19 is still being debated, a number of clinical trials are ongoing and meta-analysis is being conducted in real-time [14]. Multi-drug IVM therapy is well established.

In COVID-19, ivermectin has multiple mechanisms of action: it inhibits the import of alpha/beta receptors, thereby blocking the transport of viral proteins into the nucleus; it acts as an ionophore, inducing ionic imbalance and osmotic lysis; and it also hinders the virus from docking at the cell receptor site, preventing viral entry [15]. These interactions make ivermectin a more effective anti-viral compound.

Anti-inflammatory activity of ivermectin

Ivermectin's anti-inflammatory effects can also lead to improved clinical outcomes. This includes: the blocking of NF-KB (to inhibit cytokine secretion); inhibition of Toll-Like receptor 4 (a major Pattern Recognising Receptor for pathogens); and inhibition of mitogen activated kinases (modulators of the host response). Altogether, ivermectin's advantage in accessing both viral targets and modulating inflammation provides stable and robust efficacy against infectious diseases.

Adding ivermectin to multi-drug therapies

Ivermectin has demonstrated marked efficacy when used in multi-drug therapies, especially in trials and observational studies. In physician-led clinical studies using contemporary matched controls, a total of 220,000 subjects have been analysed over 35 studies [14]. Protection as monotherapy against hospitalization was 33%, and improvements against mortality was 51% [14]. Impressive clinical results in two studies combining ivermectin with doxycycline and zinc observed reversal of oxygen desaturation in most subjects within 24 hours [16]. A second study by Stone et al., demonstrated significantly improved efficacy with ivermectin when comparing both ivermectin treated and non-ivermectin treated cohorts in both the mentioned studies. When saturated oxygen levels of the two groups were compared, a mean absolute increase of 5% in SpO2 at 24 hours was observed with ivermectin, tetracycline and zinc. In contrast, the study using anti-viral drugs alone only saw an improvement of 5% SpO2 at day 10 of treatment [17]. Thus, ivermectin in combination appears to increase recovery despite mixed results in monotherapy trials. In a third study of IVM zinc and doxycycline in 600 patients there were no deaths and rare hospitalisations generally unrelated to COVID-19.

Adding antibiotics to COVID-19 therapies

Improved efficacy is observed when adding an antibiotic to multi-drug therapy, and this result is consistent with several large studies in Brazil, Mexico, and France. Two such antibiotics, doxycycline and azithromycin, have been used with demonstrated efficacy to reduce bacterial abundance in virus infected airways [18]. Furthermore, the role of the bacterial microbiome in exacerbating clinical symptoms in COVID19 infection also supports the inclusion of antibiotics.

Adding zinc to COVID-19 therapies

Zinc similarly has potent antiviral and antimicrobial effects. Its entry into cells is promoted by ionophores especially by ivermectin which may explain its improved efficacy in combination [19]. It has been proposed that ivermectin and other ionophores can enhance zinc thereby impact various stages of the viral life cycle, including viral entry, replication, and maturation. By promoting the influx of calcium and zinc ions into host cells, ionophores disrupt essential processes required by the virus for its propagation [20]. Moreover, they may help mitigate the dysregulation of the immune response observed in severe cases of COVID-19. While the effectiveness of ionophores in COVID-19 treatment remains a subject of ongoing research and debate, their unique mechanism of action underscores their importance for further research. Nevertheless the meta-analysis of over 1506 subjects who used zinc in either a single supplement or in combination (Ziverdox) with other supplements has demonstrated reductions in mortality when zinc was used [21].

Rationale for Multi-Drug Therapy in COVID-19

Empirical experience from treating both bacterial infections and viral infections suggests combination multi-drug therapy minimizes viral loads more effectively than monotherapy. This has several flow-on effects including faster clinical recovery, preventing the development of anti-viral resistance, and inhibition of newer SARS-COV-2 mutants. As there have been over 770-million confirmed cases of COVID-19 and the development of five major variants Alpha, Beta, Delta, Delta AY4.2, Omicron [22]. Both the large-scale nature of the pandemic and the formation of new variants

requires a multi-pronged approach combining vaccines and effective multi-drug therapies.

An added benefit of multi-drug combinations is that lower individual drug doses can be used to treat diseases effectively without increasing the adverse effects commonly observed in anti-viral medications. In HIV therapy for instance, an intentional pooled screening approach to measure the effectiveness of two-drug combinations for HIV infection from 1000 compounds, uncovered a number of drug combinations within the glucocorticoid drug group and nitazoxanide group that reduced viral infection by more than 50% [23] with synergistic effects at lower doses. In a recent example we compared Monotherapy (Molnupiravir), dual therapy (Paxlovid) and the Triple Therapy (Ziverdox) in COVID-19 patients (Table 1). Accordingly, a multi-drug approach serves to both eradicate viral infection and minimise side-effects.

Table 1: Triple-therapy outperforms monotherapy and dual-therapy [24-26].

Properties	Ziverdox [25]	Paxlovid [24]	Molnupiravir [26]
Efficacy	>96%	89%	34%
Approved ingredients	Yes	No	No
No/Low side effects	Yes	Yes	No
Unbiased patient selection	Yes	No	No
Low/Nil drug interactions	Yes	No	Yes
Extended half-life	Yes	No	No
Resistant to microbial drug resistance	Yes	Yes	No

Conclusion

The continued threat of SARS-COV-2 variants demands rapid treatment of COVID-19. While more directed biological treatments for COVID-19 may become effective, traditional development processes for novel drugs require a significant period of development of over a decade prior to FDA approval. Moreover, when effective antiviral monotherapies are approved, historical experience has shown that drug resistance develops.

Given the significance for halting progression of COVID-19 in current times, and considering the above limitations, repurposed multi-drug therapies may be a new way forward for controlling the global pandemic. Multi-drug combinations such as ivermectin, doxycycline and zinc have synergistic, anti-viral and anti-inflammatory activity with demonstrated efficacy, and safety observed with minimal side effects. Effective repurposed multi-drug combinations in concert with vaccines and future monotherapies can form the basis of a coordinated and effective health policy to combat COVID-19 and its evolution.

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Conflicts of Interest

Thomas Julius Borody has a pecuniary interest in the Centre for Digestive Diseases, Finch Therapeutics, Topelia Aust. Ltd, and Giaconda Ltd, and holds patents in the use of antibiotics for treatment of Crohn's disease and in the field of FMT, and inflammatory bowel disease treatment and antivirals in Covid-19. Sabine Hazan holds patents on microbiome technology, covid therapies and covid diagnostics. CEO of Progenabiome, Ventura clinical trials and Topelia Us. Founder of microbiome research foundation. NIL other authors.

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