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Promoting Equitable Allocation of Medical Therapeutics in the Management of SARS-CoV-2 Patients: A Multi-Tiered Approach

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ABSTRACT

The COVID-19 global pandemic has plagued the world and crippled many economies, taking millions of lives. With the emergence of newer and more potent variants of this virus, it is imperative to remain up to date with novel treatment modalities. Medical therapeutics has been the mainstay treatment and preventive measures used by most nations to prevent widespread disease. With the discovery of oral therapeutics that can reduce the potency of the COVID-19 infection, it is important that we tackle another global health issue – inequitable distribution of healthcare resources. This article aims to address the ethical concerns of allocation of scarce drugs, and a tiered approach to prevent misuse of such oral therapeutics. Scarce resources must be protected and distributed based on a needs basis, to improve healthcare worldwide and alleviate suffering from this pandemic.

Keywords

SARS-CoV-2, COVID-19, Pandemic, Equity, Therapeutics.

Introduction

Since the discovery of SARS-CoV-2 virus in December 2019, the COVID-19 infection has rapidly become a widespread pandemic [1]. With almost half a billion infected and more that 5 million deaths worldwide to date, the COVID-19 infection has severely overwhelmed our healthcare systems and crippled the global economy. The first glimmer of hope came with the inception of the COVID-19 vaccine in December 2020. However, hopes were dashed as repeated waves of COVID-19 infection persisted, with newer and more contagious variants of concern spreading worldwide [2]. As the battle against COVID-19 intensifies, newer discoveries have surfaced, effectively equipping clinicians with alternative countermeasures to combat this pandemic. However, with newer countermeasures, it becomes paramount to ensure equitable distribution of resource on a need basis, to allow maximal benefit to the population.

Therapeutic Drugs for COVID-19 Infection

There has been increasing interest in the use of therapeutic agents to combat the SARS-CoV-2 virus. Drug repurposing has been widely used initially and remains an attractive option in the current pandemic [3]. Multiple agents including antiviral agents (eg. Remdesivir), antimalarials (eg. hydroxychloroquine), immunomodulatory agents, adjuncts (eg. Corticosteroids), and other traditional methods have been used in hopes to develop a viable method of reducing mortality in severe infection [4]. However, there has been little success in many such pharmacotherapies, where paucity of data and evidence has limited the use of such treatments.

Novel Therapeutics

The novel antivirals Molnupiravir (MK-4482) and Nirmatrelvir/ Ritonavir (Paxlovid) has garnered much interest in recent times. Clinical trials of these novel antiviral drugs have proven to be exceedingly successful in treating infections caused by multiple mRNA viruses.

The first oral therapeutic is Molnupiravir. The RNA-dependent RNA-polymerase (RdRp) is an essential component for transcription and replication for coronaviruses [5]. The active form of Molnupiravir (NHC triphosphate) is used as a substrate by SARS-CoV-2 RdRp, resulting in mutations in mRNA products and preventing viral propagation [6]. This mechanism is known as "lethal mutagenesis", where error accumulation will eventually cross a theoretical threshold and hence invoke "error catastrophe" [7].

The second oral therapeutic of interest is Paxlovid. Paxlovid is a therapeutic that has shown great potential in clinical trials, reducing hospital admissions and mortality by 89% [8]. Nirmatrelvir is a 3CL protease inhibitor that has in vitro inhibitory activity against SARS-CoV-2 [9]. Coupled with Ritonavir, its half-life in plasma is increased via the inhibition of Cytochrome P450 3A4. There are also emerging studies on the efficacy of this drug candidate against the novel Omicron strain.

Ethics of Allocation of Scarce Drugs

The initial supply of any novel treatment will be largely limited by production capacity. While beneficial for pharmaceutical companies to rapidly produce large quantities of a novel therapeutic, there remains barriers to mass production, including (1) upscaling production capacity, (2) procurement of raw ingredients and drug excipients, (3) quality control and regulation, (4) managing distribution chains and consignments. This would result in scarcity of COVID-19 countermeasures in the coming few months, which brings about the taboo topic of equitable resource allocation.

An ethical framework described in JAMA provides insights to some of the practical recommendations of scarce drug allocation [10]. This includes (1) evidence-based allocation, (2) prioritization not to be based on patient demographics, (3) allowing continued use of drug for alternate disease therapy, (4) basing clinical judgment based on rigorous evidence, (5) promoting random allocation amongst eligible individuals, (6) seeking support in difficult discussions with those who do not receive the drug [10].

A Multi-Tiered Approach

Tier 1: Departments/Ministries of Health

The government will need to perform specific roles in negotiations with pharmaceutical companies. A common practice is the use of Advanced Purchase Agreements (APAs), where an initial sum paid to pharmaceutical companies ensures that priority is given to the participating nation should the therapeutic be approved. While APAs are useful in providing pharmaceutical companies with the initial capital required for research and development of new therapeutics, it may lead to unfair practices in allocation and distribution. Nation leaders worldwide must understand the risk of "nationalism" practices, and its effect on the pharmaceutical supply chain. Steps must be taken to ensure equitable allocation of therapeutics.

World leaders should be encouraged to donate excess supply of medications to less wealthy nations, avoiding drug hoarding and nationalistic practices. The World Health Organization (WHO) has been advocating universal healthcare since its inception and has been actively urging nations to share doses of COVID-19 vaccines. However, many nations have chosen to continue employing vaccine nationalism, resulting in disproportionate vaccination rates worldwide and vaccine inequity. This must not repeat again for these COVID-19 therapeutics once approved for use.

Pharmaceutical companies can also work closely with lower income nations to ensure equitable allocation of therapeutics via the Medicines Patent Pool (MPP). Under this scheme, pharmaceutical companies can voluntarily license their therapeutics to MPP, allowing MPP to sub-license patent rights to generic companies, enabling low-cost manufacturing of these therapeutics for distribution in lower income countries.

Tier 2: Federal Agencies

Federal agencies responsible for pharmaceutical safety and regulations should provide the initial framework and policies for drug distribution. Such agencies should maintain up to date with latest evidence, conceptualizing general criterion to determine eligibility for these therapeutics. A national framework should be made public and accessible to clinicians, allowing better understanding, and determining suitability of their patients for this treatment. However, one-size-fit-all criteria cannot be enforced in a pandemic. It is a essential that these agencies enforce appropriate usage of such therapeutics, with clear indications for allocation. However, these criteria should remain as general guidelines, and should not be a yes/no criteria for use of these therapeutics as the disease and patients are both dynamic and different in many ways.

Tier 3: Infectious Disease Panel

An infectious disease panel should helm the decision on allocation of COVID-19 therapeutics. This should remain the standard of care until supply of such therapeutics is sufficient for widespread prescription. Individual clinicians taking care of COVID-19 patients should request for therapeutics if they deem their patient suitable for treatment. However, to fulfil the ethical considerations of scarce drug allocation, the infectious disease team will be given the oversight of these therapeutics. This prevents compassionate use, ensure equitable allocation, and minimize unintended errors. There should be ample communication between healthcare professionals to ensure that the countermeasures are given appropriately, but this should not hinder the process of allocation. Ultimately, the use of such countermeasures should be allocated in a way to maximize the benefits to those who receive it.

Conclusion

Equity in healthcare is a well-known yet commonly avoided public health concern, especially in the current pandemic. Employing a multi-tiered approach to ensuring equitable allocation of COVID-19 therapeutics is essential in preventing hoarding and unfair practices within and amongst nations. The WHO has emphasized on the importance of provision of resources to lower income nations, to maximize overall benefit of the therapeutics to all. The entire world is suffering from the pandemic, and now is not the time to be inconsiderate.

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