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Case Report

Review of Recent Outpatient Therapeutic Updates for SARS-Cov2

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Abstract

While great strides have been made within the medical community to combat the spread, mortality, and morbidity of SARS-CoV-2, there remains need for identifying effective therapeutics given the ever-evolving nature of the virus. Given the growing number of variants, it is important that medical providers are up to date on the most recent evidence-based therapeutics for the management of SARS-CoV-2. Fortunately, the progress in antivirals and monoclonal antibodies have demonstrated success as outpatient therapeutics for patients at-risk for poor disease outcomes. This article reviews therapeutics approved for outpatient management of SARS-CoV-2 in conjunction with the recently updated guidelines from the World Health Organization, Infectious Disease Society of America, National Institutes of Health, and United States Food and Drug Administration. Monoclonal antibodies *Casirivimab* plus *Imdevimab* and *Bamlanivimab* plus *Etesevimab* are no longer recommended as a therapeutic for the Omicron variant. *Paxlovid*, an antiviral, and *Sotrovimab*, a monoclonal antibody, are considered the therapy of choice for at-risk patients. Remdesivir is considered a reasonable alternative but has intravenous limitations. *Molnupiravir* is only indicated should all other approved therapeutics be either unavailable or contraindicated.

KeyWords: Molnupiravir; Sotrovimab; Caliciviral; Monoclonal; Glycoprotein

Abbreviations: SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2; RNA: Ribonucleic Acid; MRNA: Messenger RNA; CYP: Cytochrome P450; MAB: Monoclonal Antibodies; RDRP: RNA-Dependent RNA Polymerase

Introduction

Novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded ribonucleic acid (RNA) virus of the family Coronaviridae, swiftly became a chief global health concern in 2019 [1-3]. Originating from Wuhan, China, SARS-CoV-2 quickly spread throughout the world resulting in a pandemic affecting over 260 million people that has claimed at least an estimated 6 million lives based on excess mortality data [4–6]. Great strides have been made within the scientific and medical community to combat the spread, mortality, and morbidity of SARS-CoV-2, yet new avenues of unmet medical needs persist given the ever-evolving nature of the virus. The Omicron variant is the most recent variant of concern identified by the Word Health Organization (WHO) and has quickly become the dominant strain in many countries [6-7]. Most concerning are the 32 mutations in the spike protein given the current iterations of SARS-CoV-2 messenger RNA vaccines (mRNA) encode the SARS-CoV-2 glycoprotein to infer immunity [6-8]. While the development of novel vaccines to combat SARS-CoV-2 has demonstrated utility in reducing morbidity and mortality as a preventative measure, it is not a perfect remedy. Many individuals, whether due to medical

contraindications or vaccine hesitancy, are not vaccinated and are at increased risk for poor outcomes [3-10]. Emerging variants have demonstrated increased transmissibility, morbidity, and mortality -even in fully vaccinated individuals- resulting in increased breakthrough cases [3]. There remains a great unmet need for effective therapeutics.

As the virus has continued to evolve, so has the medical community to meet it. In the early days of the pandemic, many medications were repurposed off-label in efforts to find an effective treatment ranging from various antivirals, immunomodulators, corticosteroids, antibiotics, bradykinin receptor antagonists, antimalarial agents, and angiotensin II receptor antagonists. [11] Identifying an effective therapeutic has been challenging given the rapidly evolving nature of the SARS-CoV-2 and its numerous variants [5]. As the scientific method has run its course, potential effective therapeutics have begun to emerge. In addition to symptomatic management, antivirals and monoclonal antibodies (mAb) have demonstrated utility as therapeutics for SARS-CoV-2. Given the growing number of variants, it is important that medical providers are up to date on the most recent evidence-based modalities and guidelines for the management of SARS-CoV-2. This article reviews therapeutics approved for outpatient management of SARS-CoV-2 in conjunction with the recently updated guidelines from the World Health Organization (WHO), Infectious Disease Society of America (IDSA), National Institutes of Health (NIH), and United States Food and Drug Administration (FDA).

Novel Outpatient Therapeutics for SARS-CoV-2

While the advent of novel vaccine modalities has had utility as a preventive measure, there has remained the need for effective therapeutics. Fortunately, the progress in antivirals and mAb therapeutics have demonstrated success as outpatient treatment options for patients at risk for poor disease outcomes. Patients considered to be at-risk, include the elderly, immunocompromised, and those with multiple comorbidities such as cardiovascular, hypertension, diabetes, obesity, and pulmonary diseases [1-13]. (Table 1).

Table 1: Novel Therapeutic Treatment Regimens for SARS-CoV-2.

Therapeutics	Mechanism of Action	Treatment Regimen
Antivirals		
Ritonavir-Boosted Nirmatrelvir (Paxlovid)	Protease Inhibitor	Adults: Nirmatrelvir-Ritonavir 300-100mg orally twice daily for five days
Remdesivir (Veklury)	Reverse Transcription Inhibitor	Adults: Remdesivir 200mg IV day one, then 100mg for two additional days. Pediatric: 5mg/kg IV day one, then 2.5mg/kg for two additional days.
Molnupiravir	RdRp Mutagenesis	Adults: Molnupiravir 800mg orally twice daily for five days
Monoclonal antibodies		
Sotrovimab	mAb targeting S protein RBD	Adults: sotrovimab 500mg IV infusion once

Table Abbreviations: RNA-dependent RNA polymerase (RdRp), Intravenous (IV), monoclonal antibody (mAb), receptor binding domain (RBD)

Outpatient Antiviral Therapeutics

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Paxlovid, developed by Pfizer Labs, is currently authorized under the FDA for Emergency Use Authorization (EUA) [12-14]. It is considered a 1st line outpatient therapy for at risk patients with clinical trials demonstrating an 89% reduction in SARS-CoV-2 related hospitalization or death [12-17]. Paxlovid is composed of two components, Ritonavir and Nirmatrelvir. Ritonavir is a potent protease inhibitor which interferes with viral transcription by inhibiting the machinery necessary for viral replication [2-19]. It is co-administered with Nirmatrelver which inhibits cytochrome P450 (CYP) 3A4 boosting the bioavailability of Ritonavir during use.14,18,19 Providers must be cautious of drug-to-drug interactions given the inhibition of CYP 3A4 with Paxlovid. It is contraindicated in patients taking other medications highly dependent on CYP 3A4 for clearance, severe renal or hepatic impairment, or hypersensitivity to the drug [14-19].

Remdesivir (Veklury)

Veklury, developed by Gilead Sciences, was the first fully FDA approved antiviral for SARS-CoV-2 in adults and is authorized under EUA for use in pediatric patients [20-21]. By directly binding viral RNA-dependent RNA polymerase (RdRp), Veklury prematurely terminates RNA transcription of SARS-CoV-2 [22]. Clinical trials demonstrated an 87% lower risk of SARS-CoV-2 related hospitalization or death in at-risk patients. [23]. Veklury is considered a second line outpatient therapy given its intravenous application limitations [12-17]. It is contraindicated in patients with concern for elevated liver enzymes or hypersensitivity to the drug. [20].

Molnupiravir

Molnupiravir, developed by Merck Sharp & Dohme Corporation, is currently authorized under the FDA for Emergency Use Authorization (EUA) [24-25]. This prodrug forces transcription errors by acting on viral RdRp resulting in significant mutagenesis and eventual error catastrophe [26]. Clinical trials demonstrated a 50% reduced risk of SARS-CoV-2 related hospitalization or death in at-risk patients [16-27]. Molnupiravir is considered a third line outpatient therapy given its concern for adverse reactions. Given its mutagenesis mechanism of action, Molnupiravir is only indicated if other treatment options are unavailable or are contraindicated [17-25]. It is contraindicated in pregnant and pediatric patients with recommendations for abstinence of any sexual activity for at least 3 months after its usage. [24,25]

Outpatient Monoclonal Antibodies Therapeutics

Casirivimab plus imdevimab (REGEN-COV) and Bamlanivimab plus etesevimab (LU-CoV555) There are currently three anti-SARS-CoV-2 mAb therapeutics with FDA EUA for outpatient treatment of confirmed SARS-CoV-2 for at-risk patients including Casirivimab plus imdevimab (REGEN-COV), Bamlanivimab plus etesevimab (LY-CoV555), and Sotrovimab.28 Both REGEN-COV and LY-CoV555 limited progression of SARS-CoV-2 by targeting the receptor-binding motif between the virus and host cell by neutralizing the SARS-CoV-2 spike protein [9-22]. While useful in earlier variants, unfortunately recent data has suggested a decline in their efficacy. This is likely due to the most recent omicron variant displaying significant mutations to the spike protein.6,7 The FDA, NIH, and IDSA no longer recommend this modality [17-28].

Sotrovimab

In contrast to REGEN-COV and LY-CoV555, Sotrovimab which is manufactured by GlaxoSmithKline, targets a much more stable epitome in the receptor binding domain of the spike protein in all sarbecoviruses [9 -29]. Clinical trials have demonstrated a reduced risk in hospitalization or death by 85% in at-risk patients and has confirmed efficacy against Omicron variant [9-29]. It is considered a first line agent alongside Paxlovid for the treatment of at-risk patients with SARS-CoV-2 [12-17].

Sotrovimab is not currently authorized for inpatient utilization and is contraindicated in patients with hypersensitivity to the drug [29].

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