UJEMI PERSPECTIVES

Impacts of the Omicron Variant on the Effectiveness of Direct-Acting Antivirals: Replication-Inhibiting Small Molecules and Antibody-Based Therapeutics

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SUMMARY Since the beginning of the COVID-19 pandemic, researchers have made great progress with the development of direct-acting antiviral therapies, which are divided into two categories: small molecules targeting the SARS-CoV-2 replication machinery and monoclonal antibodies targeting the spike protein. Through rigorous clinical trials, a small number of antivirals in development have been approved in different countries. The first category of approved therapeutics is direct-acting small molecules, including the replication inhibitors Remdesivir and Molnupiravir and the 3CLpro inhibitor Paxlovid. The second category is monoclonal antibodies including Bamlanivimab, Casirivimab and imdevimab, and Sotrovimab. The effectiveness of these therapeutics is being challenged by the emergence of the Omicron Variant. Since the Omicron Variant emerged recently in November 2021, the impacts of the new mutations on the activity of antiviral therapeutics are largely unknown. It is important to investigate antivirals because they are key to reducing the severity of disease and preventing hospitalization and deaths. This article will investigate the following questions. 1) How is the effectiveness of replication-targeting small molecules being impacted by the Omicron variant? 2) How is the effectiveness of antibody-based therapy being impacted by the Omicron variant? By answering these questions, the current state of commonly used antivirals in the face of the Omicron-dominated wave of infections could be better understood, helping to determine the best way to allocate and distribute antivirals efficiently. The Omicron variant is changing the playing field for antiviral drugs. Because of this, hospitals need to adapt their arsenal of antiviral drugs.

INTRODUCTION

SARS-CoV-2 is the virus responsible for initiating the COVID-19 pandemic. The virus was first detected in Wuhan, China in December 2019, and declared a pandemic by the WHO in March 2020 (1,3). Since then, the virus has been a threat to global public health, spreading to all corners of the world (2). In the early stages of the pandemic, public health orders including lockdown, social distancing, and masking, have been imposed around the world.

Scientists around the world have made great progress in developing mRNA vaccines and antiviral therapeutics (3). It is important to investigate antiviral therapeutics because they are key to reducing the severity of disease and preventing hospitalization and deaths. In the early stages of the pandemic, therapeutics developed for previous viruses were repurposed, including Remdesivir and hydroxychloroquine (3). Soon, with more knowledge of how the virus works, they developed new ones to treat the infected. These new antivirals include the orally prescribed Molnupiravir and Paxlovid (4).

Although many of these therapeutics were promising candidates, clinical trials of many repurposed drugs yielded mixed results, and as a result, only a few of them were approved on a national level (4). Antiviral therapeutics are classified into direct-acting antivirals, which target the virus directly, and indirect-acting antivirals, which target host factors (5). Direct-acting antivirals can be further divided into two categories based on the stage of the SARS-

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CoV-2 life cycle targeted: small molecules targeting SARS-CoV-2 replication machinery and monoclonal antibodies targeting the spike protein (6). Health Canada has approved 5 different antiviral treatments against SARS-CoV-2, the virus causing COVID-19, with many more currently under review. Two of the approved therapeutics are direct-acting small molecules: the repurposed viral RNA-dependent RNA polymerase inhibitor Remdesivir developed by Gilead, and Paxlovid developed by Pfizer, consisting of a ritonavir-boosted protease inhibitor, Nirmatrelvir. The other three are monoclonal antibodies including Bamlanivimab, Casirivimab and imdevimab, and Sotrovimab (https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/treatments.html).

Even with these technologies, the pandemic drags on. The most concerning issue regarding the pandemic in 2022 is the emergence of Variants of Concern. The most recent variant that emerged in November 2021, Omicron (BA.1), has the most mutations of any variant, the highest transmissibility, and the highest immune evasion (7). Fortunately, the lethality of Omicron is less than that of Delta as shown by a lower likelihood of hospitalizations and milder symptoms on a clinical level (8). On a molecular level, Omicron has less efficient replication and a higher tropism for the upper respiratory system, meaning a weaker attack on the lungs (8, 9).

PROPOSED RESEARCH QUESTIONS

The new Omicron variant is drastically different from the Delta variant, but very little is known about how much of an impact the new variant has on the effectiveness of direct-acting antiviral therapeutics since the variant emerged so recently. The goal of this investigation is to assess the effectiveness of currently approved direct-acting antiviral therapeutics against the Omicron variant, including 1) antibody-based therapy and 2) replication-targeting small molecules. Effectiveness can be evaluated on multiple levels, starting at the molecular level and progressing to *in vitro* and clinical studies. Eventually, the science may inform public health agencies. The impacts of the Omicron variant will be compared to previous variants. A case study of a select number of direct-acting antivirals will be presented to focus on examples that are well known throughout media headlines. For monoclonal antibodies, this includes Bamlanivimab, Casirivimab and imdevimab, and Sotrovimab, which are approved in Canada. For small molecules, Remdesivir developed by Gilead Sciences, Paxlovid developed by Pfizer, and Molnupiravir developed by Merck were selected as the example drugs because of their Emergency Use Authorization by the FDA (6).

The greater implication of this study is to evaluate the readiness of the healthcare system given these new insights. It will also be beneficial for hospital administration, including the distribution of antivirals in the most efficient way.

PROPOSED PROJECT NARRATIVE

Research Question 1: How is the effectiveness of antibody-based therapy being impacted by Omicron?

A monoclonal antibody is created by exposing a white blood cell to a particular viral protein, which is then cloned to mass-produce antibodies to target that virus. Monoclonal antibodies have an advantage over other types of treatment for infection because they specifically target an essential part of the infectious process (10). In the clinical setting, monoclonal antibodies are most beneficial in mild to moderate COVID-19 where SARS-CoV-2 viral loads are the highest (11). They are a preferred complement to vaccination in individuals who have a high risk of getting hospitalized (12). According to a pre-Omicron study that investigated the Alpha (B.1.1.7), Beta (B.1.351), and Gamma (B.1.1.28) variants, many antibodies authorized for emergency use retain efficacy against these variants (13).

When the Omicron variant first emerged in November 2021, researchers could only predict the effects through structural-based and computational analysis of the mutations of the spike protein, which is the target of monoclonal antibodies (14, 15). Structurally, the spike protein is comprised of 2 domains. The S1 domain contains the receptor-binding domain

(RBD) and the S2 domain is responsible for membrane fusion. The RBD mediates attachment to human cells through the ACE2 receptor and is the primary target of neutralizing antibodies. Another significant target is the amino-terminal domain, or NTD (13, 14). To understand the impacts of the Omicron variant in particular, the locations of the mutations of the spike protein were discovered through cryo-EM and X-ray crystallography (14, 15). The Omicron spike protein has 37 mutations compared to the ancestral strain, which is the original strain found in Wuhan, making it the most mutated variant since the Gamma variant (14). McCallum *et* al. found that because of these mutations, the binding affinity of Omicron to the ACE2 receptor increased compared to the ancestral strain by an affinity of 2.4-fold (15). An annotation study by Fang and Shi predicted that out of eight authorized antibodies, only Sotrovimab will retain its ability to neutralize the Omicron variant (7).

Another type of research involved in-vitro experiments, where tests were done, including analysis of inhibition of cell entry (16, 17). Most of these studies agree that the neutralization efficacy of mAbs against Omicron is reduced compared to previous variants (16, 17, 18, 19). A study by Hoffmann *et al*. (2022) found that the Omicron spike protein is resistant against four out of five monoclonal antibodies used for the treatment of COVID-19 patients, as shown by reduced inhibition percentages, with only Sotrovimab retaining effectiveness (16). A study by Cameroni *et al*. (2021) found that the majority of RBM-targeting mAbs had reduced *in vitro* neutralizing activity against Omicron (17).

TABLE 1. Summary of the Background and Current State of Selected Monoclonal Antibodies against the Omicron Variant

mAb	*Mechanism (13)*	*Effectiveness Against Omicron (16)*
Sotrovimab	Targets conserved RBD epitope	Effective, but 3-fold less efficient than Delta spike
Bamlanivimab	Targets RBD	Ineffective
Casirivimab and imdevimab	Target RBD	Strongly Reduced

Both the computational studies and the experimental studies agree that Sotrovimab is the only antibody that retains effectiveness against the Omicron variant. This is no coincidence because Sotrovimab targets a non-RBM epitope conserved in many sarbecoviruses, the classification that SARS-CoV-2 belongs to (7).

These scientific discoveries led to action being taken on the public health level. Unfortunately, because of the antibody evasion of Omicron, public health institutions have already limited use of certain monoclonal antibodies. The US FDA limited Bamlanivimab and etesevimab, and REGEN-COV (Casirivimab and imdevimab) (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-certain-monoclonal-antibodies-treat-covid-19-due-omicron). However, some US hospitals are still using outdated treatments even with the mounting evidence that these antibodies are ineffective (https://www.nbcnews.com/health/health-news/covid-antibody-treatments-dont-work-omicron-still-used-states-rcna12990). This means that Sotrovimab, the only effective mAb, is in short supply. US health officials have said they will ration Sotrovimab, allotting it to states based on infection rate, hospitalizations, and prevalence of the Omicron variant (20).

Because of monoclonal antibodies failing, and the limited amount of time to find new ones, the classical method of convalescent sera is another potential avenue. Convalescent sera are the only antibody-based therapy that is up to date with the variants that are challenging monoclonal antibodies (21). This was used during the early stages of the pandemic before other antivirals were available, and in previous pandemics before the advent of modern technology (22, 23). However, the question remains if convalescent sera apply to the COVID-19 pandemic. Focosi *et al*. (2021) show that sera from vaccinated patients are effective, while sera from unvaccinated patients are not. They highlight that convalescent plasma tends to be of use during the beginning of the pandemic and the emergence of new variants (22).

However, since clinical trials take time and are not yet available due to the Omicron variant's recent emergence, clinical trials are a future avenue of research to test the effectiveness of monoclonal antibodies.

Research Question 2: How is the effectiveness of replication targeting small molecules being impacted by the Omicron variant?

Three key small molecule antiviral drugs include Remdesivir, Molnupiravir and Paxlovid. Both Remdesivir and Molnupiravir are nucleoside analogs that inhibit the action of RdRp by acting as mimics and mutating the viral genome, both requiring conversion to an active form. Their mechanisms are similar apart from different nucleotides being mimicked (24, 25, 26). However, their differences lie in their modes of administration. Remdesivir was developed by Gilead sciences, and was used early on in the pandemic, while Molnupiravir was developed by Merck and is relatively new. Remdesivir must be injected while Molnupiravir can be orally given as pills (24, 25). Paxlovid, developed by Pfizer, is an orally administered pill that inhibits the main protease called 3CLpro. It consists of Nirmatrelvir and Ritonavir in two separate pills. Nirmatrelvir is the main component, while ritonavir maintains its stability.

As confirmed in multiple studies, there is no or minimal loss in the effectiveness of these small molecules with the Omicron variant (27, 28, 29, 30). These studies used experimental methods such as finding IC_{50}, EC_{50}, and measuring viral genomic RNA (29). IC_{50} and EC_{50} are is the half-maximal inhibitory and effective concentrations respectively, and are the most widely used measure of a drug's efficacy, showing how much drug is required to inhibit infection by 50% (31, 32). Rosales *et al*. found that all three drugs maintain activity against all variants tested, including Omicron (27). Vangeel *et al.* came to the same conclusion, with equipotent antiviral activity against the ancestral virus and the VOCs Alpha, Beta, Gamma, Delta and Omicron (28).

TABLE 2. Summary of the Current State of Selected Small Molecules against the Omicron Variant

Small Molecule	***Mechanism***	***Effectiveness against Omicron compared to Delta Variant and Other Variants as found by (27)***
Paxlovid (Nirmatrelvir + Ritonavir)	3CLpro protease inhibitor	No loss of activity as seen through IC_{50}: 0.17 in Delta, 0.07 in Omicron (27)
Remdesivir	RdRp inhibitor	No loss of activity as seen through IC_{50}: 0.69 in Delta, 0.76 in Omicron (27)
Molnupiravir	RdRp inhibitor	No loss of activity as seen through IC_{50}: 12.79 in Delta, 10.44 in Omicron (27)

Although mutations have been reported in the RdRp and main protease, which causes some concern regarding decreased effectiveness of small molecules (18), the number of mutations is relatively few compared to the spike protein, which means it is relatively conserved (27). The small molecules remaining effective against the Omicron variant is expected, and not surprising (27).

On the public health level, the oral administration of Paxlovid and Molnupiravir provides some advantages through convenience and reducing costs (33). Although these molecules remain approved because of their high effectiveness against the Omicron variant, there is still a long way to go before the supply and distribution of these antivirals are widespread.

POTENTIAL IMPACT/CONCLUSIONS

It is evident that antibody-based therapies, including monoclonal antibodies, are challenged because they target the heavily mutated spike protein. Small molecules, on the other hand, have a positive outlook because they are broad-spectrum and target conserved processes. In summary, the effectiveness of direct-acting antivirals depends on where the mutations happened. In the Omicron variant of SARS-CoV-2, the majority of the mutations were in the spike protein, and there were few in the replication machinery (27). Initial computational and structural studies were able to hypothesize the bleak future of current monoclonal antibodies (7), and this hypothesis was confirmed by later *in vitro* studies. These studies were then able

to influence decisions by hospitals, such as the limiting of certain monoclonal antibodies that were found to be ineffective.

Since the Omicron variant is so new, there is still limited clinical data. It is important to do clinical trials to confirm that the results of the computational and *in vitro* translate to *in vivo*. The convalescent sera method depends almost entirely on clinical trials because sera from each person is different. However, there is the inherent ethical risk of doing clinical trials on COVID-19 patients with antibodies that have already been shown to be ineffective *in vitro*.

This introduces the question of the category of direct-acting antivirals to focus on in terms of funding, research and production. Since many monoclonal antibodies are ineffective against the Omicron variant, with only Sotrovimab being effective, should less funding be put towards monoclonal antibody development and production, and more funding be put towards small molecules? This is a complex issue, but the technique of combination therapy prevents the need to ask this question. This investigation focused on individual antivirals. Combination therapy is more beneficial than monotherapy to target multiple steps and prevent viral resistance (34). One study by Liang *et al*. found that a cocktail of six antibodies was effective on all variants up to the Delta variant (35). There is not much research about combination therapy and the Omicron variant because of its novelty, so this is a future avenue of research.

Finally, how the science influences decisions in the hospital need to be further investigated. Hospitals need to make decisions about deciding what antivirals to administer and how to administer them in the best way possible. These are difficult decisions given the different situations of each patient. For instance, determining whether the benefits outweigh the risks requires an understanding of the severity and stage of disease, age of the patient, co-morbidities, and whether the patient is immunocompromised. On the population level, hospitals and pharmaceutical companies must consider the mode of delivery (oral versus injected), the supply chain, and different societal attitudes towards antiviral therapeutics. Since the Omicron variant is more transmissible, more people are getting sick, so a greater number of antivirals are needed overall.

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