Review Article

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Evolution of SARS-CoV-2; The Omicron Variant and its Considerations, A Mini Review

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Abstract

Since the beginning of detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019, many genetic evolutions of this virus have been reported. The most recent variant that caused the fourth wave of Covid-19 infection worldwide, Omicron, has shown various mutations at its receptor binding domain therefore inducing changes in behavior compared to previous variants. According to published data, major genetic mutations, differences in clinical severity and also resistance to prevention and treatment strategies have been observed. Lower rates of disease severity, hospital and intensive care unit admissions, younger age of contamination with progression to severe disease, resistance to 2 dose vaccination, risk of re-infection and resistance to monoclonal antibodies have been some of the many differences in the recent variant of concern. In the following article some considerations and modifications of the Omicron variant with regard to its general characteristics and treatment will be discussed.

Keywords: Omicron, SARS-CoV-2, Sever acute respiratory syndrome, Variant of concern

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1. Data Selection

Data selection and search strategy was performed manually using electronic search engines such as Scopus, PubMed and Google Scholar. The search process was performed on March and April 2022. All study designs including randomized clinical trials, cohorts, case control, cross-sectional and review studies were included in the selection process. Abstracts and non-English articles were excluded. A list of related keywords was prepared and search process was performed accordingly.

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2. Introduction

After more than 2 years from the start of the Covid-19 pandemic and the excessive effort of mankind to find a solution for the control, prevention and treatment of this viral infection, still the challenge of dealing with this infection has not yet been resolved. Little primary knowledge about the genetics, molecular characteristic, pathogenicity and behavior of this newly emerging virus has led to the outburst and the inability of human beings to yet control the aggressive spread of the disease.

Since the start of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic better known as Covid-19, some variants of the virus have emerged differing in their genetics and molecular characteristics and therefore showing

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different ranges of clinical significance. Alpha, Beta, Gamma, Delta and Omicron are the five variants of concern that have been introduced to date differing in their virulence, genetic specifications and susceptibility to current therapies and vaccines. The spike protein located on the outer surface of the virus, the main protein responsible for host contamination by attaching to the angiotensin converting enzyme (ACE) receptors on host cells, may vary between the different variants. Different mutations exist between different variants of the virus, as mutations are used as a means of survival for the virus towards previously developed active and acquired immunity. The last variant that was introduced in late November 2021 was the Omicron variant first detected in South Africa that was soon responsible for the most recent wave of infection experienced worldwide (1).

2.1. Genetic variations of Omicron

Studies on the Omicron variant have shown higher rate of mutation compared to the former variant, indicating capability of better survival and therefore higher transmission and invasion rate, and infectivity (2). A total number of 50 mutations, 30 or more of which on the spike protein, have been detected for this variant of concern including 30 amino acid substitutions, 3 deletions and 1 insertion (3, 4). These mutations at select positions during the S protein cleavage have allowed the high transmissibility of the virus (5). Comparing the Delta and Omicron variants, a three times more spike proteins are located in the structure of the omicron variant compared to the delta variant (32 vs 10 respectively) and accordingly roughly three times more mutations are detected for the receptor binding sites of the omicron variant (43 vs 18) (6). As investigated, this variant has shown poor replication rate in cells with strong transmembrane serine protease 2 expression, impairing cell entry and therefore probable less intense lung involvement (7).

2.2. Omicron Detection

As stated, all available RT-PCR tests that have been developed for the detection of previous Covid-19 variants are eligible for detection of the Omicron variant. However, one of the target genes, has been reported missing known as the S-gene drop out similarly seen in the alpha variant and can be used as an indicator for Omicron detection versus the Delta variant (3). However it has been reported that due to the mutations, some single-target molecular tests may not be efficient leading to false negative results. Direct antigen detections based on nucleocapsid proteins on live virus samples may be effective but with reduced sensitivity (8). genome sequencing and Sanger detection of the S gene that is more cost effective than the former method are proposed as superior methods for the precise detection and further improvements in the development of newer and more efficient vaccines (9).

2.3. Clinical importance of the Omicron Variant

According to data released by previous studies, it has been observed that severity of clinical symptoms presented by hospitalized patients were least with the Omicron variant although risk of disease severity and progression to critical illness still exists (1, 10, 11). Approximately 10% of cases have been reported as asymptomatic, meanwhile symptomatic cases mostly showed upper respiratory symptoms including nasal congestion, cough and sore throat. Headaches were also a common symptom reported in these patients. Only 10% of patients have been reported to complain of shortness of breath, indicating less lower respiratory involvement (12). This variant has been introduced with the probability for high risk of reinfection (13). although double vaccination for the reinfected cases has been confirmed showing symptoms at both episodes of contamination (12). Unlike previous waves affecting older adults, the Omicron variant mainly affected young children showing the higher infectivity of Omicron (14). Also reduced risk of hospitalization was observed in the Omicron wave compared to previous variants (15, 16). Nevertheless it was reported that admission rate in patients with only 2 doses of vaccination was similar to the Delta variant, insisting on efficacy of the booster dose of vaccine (17). It has been reported that Omicron related hospital admissions while being symptomatic lasted a lot shorter than the Delta variant. A 70% shorter mean duration of hospital admission was reported. Generally

lower hospital and ICU admissions and less probability for mechanical ventilation was observed with the Omicron variant (1). It has been suggested that the higher replication rate of the current variant in the bronchi and less in the lung parenchyma, may be a reason for less severe lung disease and therefore less hospital and ICU admissions (18). Risk factors attributed to worsening conditions of the Delta infection including male gender, older age (>80), prior history of medical conditions were less highlighted for the latter variant of concern (1). However, the role of subsequent vaccination in addition to the less virulence and probably lower affinity of the mutated spike proteins towards infecting the host cells must be considered (11) although immune bypass from previously gained immunity is a major concern with this variant.

2.4. Vaccination efficacy against Omicron

Diminished vaccination efficacy was observed with this variant, showing immune escape due to modified epitopes at the receptor binding domains of the virus (5, 19, 20). It has been observed that booster vaccination with a third dose can increase the neutralization capacity and immunization to some extent (11, 19, 20). It has been also proposed that if reduced neutralizing antibody efficacy against Omicron variant is confirmed, pre-existing non-spike memory T-cells may be the protecting element against further invasion of the virus and more severe forms of the infection through cellular mediated immunity (21-23).

2.5. Omicron and Approach to its Treatment

As mentioned previously, high rates of immune escape of the omicron variant requires a prompter action towards preventing development of the disease to its severe forms. A recent study showed that early administration of the antiviral agent, Remdesivir that was formerly known to only shorten hospital stay, may prevent a mild disease from progressing to its sever forms. Later by the introduction of the Omicron variant that was soon learned to be escaping neutralizing antibodies and the past acquired immunity, remdesivir was introduced as an early outpatient treatment recommended to be initiated in the first 7 days of symptom onset in the high-risk population for severe disease. It was shown that a three-day course of intravenous (IV) treatment, reduced risk of hospital admission by 87% (24). Considering that the Omicron variant has no specific mutations on the target of remdesivir action (RNA-polymerase), it is expected for remdesivir to function efficiently on this variant (25).

Nirmatrelvir a protease inhibitor that has been introduced in combination with ritonavir under the name of Paxlovid® has been tested for efficacy against Omicron and it has proven to be effective. Also, Molnupiravir, a prodrug, inhibiting SARS-CoV-2-RNA replication via incorporation of nucleoside analogue β-d-N4-hydroxycytidine triphosphate in place of cytidine triphosphate or uridine triphosphate in the viral RNA, has also retained full activity against Omicron (26). Both agents must be started as soon as infection is confirmed at the most within 5 days of confirmed contamination. These agents are recommended for outpatient use in mild to moderate disease with high risk of progression to severe disease. Both agent are used per oral (25).

The monoclonal antibodies Tixagevimab/Cilgavimab introduced by AstraZeneca as a combination directed against Covid-19 spike proteins was suggested as pre-exposure prophylaxy for select patients with immunodeficiency that may not have adequate response to vaccination or for whom vaccination is not suggested due to severe reaction. However, due to the numerous mutations of the receptor binding domain on Omicron spike proteins, it has been shown that the efficacy of this cocktail has reduced by 40 folds (27).

Sotrovimab, another monoclonal antibody used as a single agent for post-exposure prophylaxy in preventing severe disease in high-risk patients, is very susceptible to developing rapid mutations. As a result of mutations, a 100-fold loss of efficacy has been observed after exposure to these antibodies (28). Although unlike other monoclonal antibodies, its efficacy has remained almost intact against Omicron showing a 3-fold reduced efficacy (29).

Bebtelovimab has been introduced as an antiviral monoclonal antibody with potential neutralizing capacity on all variants of concern including Omicron. Binding sites of this antibody has

been reported to have not been affected by mutations and can be a viable choice of treatment for patients at high risk of developing severe disease (30). Single dose IV administration of the medication is recommended within 7 days of confirmed viral infection.

A list of all medications is brought in Table 1 with their specific considerations.

Retained effectiveness of the antiviral agents remdesivir, favipiravir and ribavirin have

Table 1. Medications with proven efficacy in Covid-19 Omicron variant.

Drug	Mechanism of action	Route of administration	Stage of efficacy	Considerations
Remdesivir	RNA Polymerase Inhibitor	Intravenous	Mild-moderate with risk of progression to severe disease	Intravenous dosage form limits ease of use, use is not recommended in renal impairment (GFR < 30 ml/min), renal impairment and rise in AST and ALT may be observed during the course of treatment
Nirmatrelvir (+ Ritonavir)	Protease Inhibitor	Per oral	Mild-moderate with risk of progression to severe disease	Strong CYP450 3A4 inhibitor, co-administration with CYP450 3A4 substrates must be considered, use is not recommended in renal impairment (GFR< 30 ml/min), sever hypersensitivity reactions and hepatitis may be encountered during treatment
Molnupriravir	Inhibition of viral replication by producing error in viral genome	Per oral	Mild-moderate with risk of progression to severe disease	Not recommended <18 years of age as it may affect bone and cartilage growth, may cause hypersensitivity reactions, not recommended in women at child bearing age.
Tixagevimab/ Cilgavimab	IgG1κ monoclonal antibody, inhibiting spike protein receptor binding domain	Intramuscular	Prophylactic (pre-exposure) use; recommended only in patients not currently infected and not having had a recent Covid-19 infection or in patients having immune compromise or those that cannot be vaccinated.	Use is in emergency use authorization only in patients >12 years of age and >40 kg. May cause myocardial infarction or cardiac failure, May cause hypersensitivity reaction, use with patients with coagulation disorders.
Sotrovimab	IgG1κ monoclonal antibody, inhibiting spike protein receptor binding domain	Intravascular	Prophylactic (post-exposure) use; Use not authorized in hospitalized patients or patients requiring increased oxygen therapy due to Covid-19 infection.	Serious hypersensitivity and infusion-related rection may occur, administration is only authorized in health care settings, may not be used in hospitalized Covid-19 patients requiring oxygen therapy or mechanical ventilation.
Bebtelovimab	IgG1λ monoclonal antibody blocking spike protein receptor binding domain	Intravascular	Patients with positive viral testing at high risk for developing severe disease	Serious hypersensitivity and infusion-related rection may occur, has not been studied in hospitalized Covid-19 patients.

GFR; Glomerular Filtration Rate; AST; Aspartate Transaminase; ALT; Alanine Transaminase; CYP450; Cytochrome p-450.

been demonstrated comparing the Delta and Omicron variants of concern (31).

Approach to routine inpatient management of Covid-19 patients according to latest guidelines presented during the Omicron wave, recommend against use of corticosteroids in patient without need for supplemental oxygen. As mentioned before, Remdesivir use may be considered if patient is at high risk of developing severe disease. If patients requiring supplemental oxygen, develop reduction in oxygen saturation despite corticosteroid therapy due to hyper inflammatory state and cytokine storm, immunomodulatory medication such as tocilizumab or baricitinib are recommended. Prophylactic dose of anticoagulation e.g., heparin, is recommended for hospitalized patients, due to the hypercoagulability state of patients with Covid-19 infection. If D-Dimer levels are higher than the upper normal limit or if the patient is suspected of a deep vein thrombosis or pulmonary emboli, the dose must be elevated to therapeutic dosing (32).

3. Conclusion

Looking at the evolution pathway of SARS-CoV-2 during the past 2 years since its unexpected outburst, the high possibility of mutations and eventual introduction of variants with genetic differences that may induce variations of clinical symptoms was seen. Although the latter variation showed less clinical significance, it must be considered that its far more transmission rate and escape from humoral immune defense built by newly developed vaccines and previous Covid-19 exposure, may still be troublesome leading to future outbreaks. Also, the inefficiency of treatment protocols that had proven to be effective for previous variants, propagate the necessity of further studies on the structural abilities and probable transformations of this viral infection. Panels of new monoclonal antibodies are being tested for action against the Omicron and probable future variants of concern. It is best for the future treatment strategies to be effective while overcoming resistance and reducing transmissibility. However due to the less involvement of the lower respiratory tract in this variant of concern, preventing transmission would be the best possible recommendation. Supportive care for non-hospitalized patients with mild disease and a 3-day early remdesivir therapy in patients with risk of progression to severe form of the disease is recommended.

Conflict of Interest

None declared

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