Pathogenesis and Treatment of the Omicron BA.2 lineage

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The epidemic curve of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is silently rising again. Worldwide, the dominant SARS-CoV-2 variant of concern (VOC) is Omicron, and its virological characteristics, such as transmissibility, pathogenicity, and resistance to both vaccine- and infection-induced immunity as well as antiviral drugs, are an urgent public health concern. The Omicron variant has five major sub-lineages; as of February 2022, the BA.2 lineage has been detected in several European and Asian countries, becoming the predominant variant and the real antagonist of the ongoing surge. Hence, although global attention is currently focused on dramatic, historically significant events and the multi-country monkeypox outbreak, this new epidemic is unlikely to fade away in silence. Many aspects of this lineage are still unclear and controversial, but its apparent replication advantage and higher transmissibility, as well as its ability to escape neutralizing antibodies induced by vaccination and previous infection, are rising global concerns.

1. Pathogenesis

The rapid emergence of the BA.2 lineage is associated with its replication advantage, its capacity for immune evasion (compromised serum-neutralizing activity and reduced vaccine effectiveness), and its high transmissibility.

1.1. Replication Advantage

The recent increment in the number of BA.2 lineage cases in many countries around the world has suggested that BA.2 has a selective growth advantage over other circulating variants [1][2]. In addition to the previously mentioned U.K. Health Security Agency data, a Bayesian model was constructed to quantify the growth advantage of BA.2, revealing an effective reproduction number 1.40-fold higher than that of BA.1 (95% confidence interval) [3]. This may also be linked to the higher environmental stability shown by the Omicron variants both on plastic and skin surfaces, with approximately two-fold longer survival times when compared to the original Wuhan strain [4]. Although this high replication rate has been confirmed by several organizations around the globe, the growth rates may be overestimated, especially early during the emergence of a new variant [5].

1.2. Immune Escape

The ability of BA.2 to evade neutralizing antibodies induced by vaccination or infection is unclear [1]. In New York, both sera from people vaccinated with three doses and sera from patients infected during the Omicron surge produced neutralizing antibodies that were just slightly better at fending off infection by viruses belonging to the BA.1 lineage than BA.2's [1]. Moreover, in animal models, hamsters and mice infected with BA.1 produced antibodies that were less effective against BA.2, suggesting the in vitro possibility of reinfection [3]. The small difference in overall potency against the two variants means that an ability to evade immunity is unlikely to explain BA.2's ascent worldwide [2]. Similarly, a recent analysis using pseudo-viruses compared BA.1, BA.2, and BA.3 for sensitivity to neutralization by vaccination- and infection-induced antibodies. In particular, considering sera from convalescent patients infected during the first (February to May 2020) and second (December 2020 to February 2021) waves, the neutralizations of BA.1 and BA.3 were at least 32 times lower (BA.1 $p = 0.0020$; BA.3 $p = 0.0020$) in comparison with the neutralization of B.1 (which was quite similar to the original wild-type strain) [6]. This means that the neutralization of BA.2 was less pronounced than that measured for the other Omicron subvariants (9.2 times less than B.1; $p = 0.0020$). Moreover, BA.1 infection elicited similar levels of cross-neutralization against BA.2 and BA.3, although at a decreased efficiency that was 4.2- to 4.4-fold lower than that against BA.1 [7]. Similarly, double-vaccination-induced neutralization showed a 17-fold reduction when comparing BA.1 or BA.3 to B.1 (BA.1 $p = 0.0020$; BA.3 $p = 0.0020$), whereas the neutralization of BA.2 was just 9-fold reduced ($p = 0.0020$)

[6]. A study currently under revision has proposed a mechanism to explain the BA.2 lineage's broad immune escape: the S371L/F mutation in the RBD seems to induce dynamic conformational changes of the spike trimer, reducing antibody neutralization without detrimental effect on viral fitness [8]. However, according to another analysis, the immune escape capacity of BA.2 seems to be less effective in comparison to that of BA.1 [9]. Other viral or host factors are perhaps involved in driving the rapid surge of this new lineage.

Real-world data from an experiment in Israel showed that unvaccinated, double-vaccinated, and boosted individuals were found to be more susceptible to BA.2 infection than to BA.1 infection [2]. Although rare, Omicron BA.2 reinfections in vivo may occur, especially shortly after BA.1 infections [10]. In addition, in antigen-naïve individuals, the immunologic response following infection with the BA.2 lineage is lower than that following BA.1 infection [11]. This may have crucial global implications as a lower neutralization response may contribute to the prolonged circulation of the virus in the population [11].

Moreover, the ECDC has raised awareness regarding BA.4 and BA.5 emergence due to the limited availability of data from in vitro studies evaluating sera from unvaccinated individuals who have experienced a prior BA.1 infection, which indicates that both BA.4 and BA.5 are capable of escaping the immune protection induced by infection with BA.1 [12]

1.3. Increased Transmissibility

It is known that the Omicron variant has a higher affinity for the ACE2 receptor and, consequentially, the potential for increased transmission [13]. The hACE2 receptor bound to the Omicron BA.2 spike trimer with a dissociation constant approximately 11-fold higher than that for the WT spike trimer and nearly 2-fold higher than that for the BA.1 spike trimer [14]. Among the Omicron sub-lineages, BA.2 and BA.3 have higher transmission potentials compared to BA.1: BA.2 has a docking energy of −974, which is higher than that of BA1.1 (−946.8) and BA.1 (−943.4) but lower than that of BA.3 (−999.3) [15]. However, according to a preprint analysis carried out in Denmark, the difference in terms of the transmission rate appears to be less than that between Delta and Omicron [16]; nevertheless, an enhanced attractivity towards the strongly electronegatively charged ACE2 receptor protein can still be predicted [17]. An algebraic topology-based model was used to evaluate the infectivity of the Omicron sub-lineage. It was estimated that BA.2 was approximately 20, 4.2, and 1.5 times as infectious as the ancestral SARS-CoV-2 wild-type strain, the Delta variant, and BA.1, respectively [18].

The RT-qPCR cycle threshold (Ct) value of a SARS-CoV-2 infection represents the inverse of viral load, and it can be used as a proxy for SARS-CoV-2 infectiousness. BA.2 was associated with 3.53 fewer cycles (95% CI: 3.46–3.60) when compared to BA.1, signifying higher infectiousness [19].

An interesting experiment that highlighted the exceptionally high transmissibility of the BA.2 lineage occurred in a single housing estate in Hong Kong. This outbreak, which was fortunately promptly controlled with the lockdown of three buildings, had a very short doubling time of 1.28 days (95% confidence interval: 0.560–1.935), and the phylogenetic analysis showed that these sequences clustered together [20].

To sum up, it is logical to wonder whether increased transmissibility or immune escape best explain the Omicron BA.2 surge. No conclusive studies are currently available. However, in vitro entry assay studies state that Omicron variant infection is not enhanced by TMPRSS2, and no particular difference has been seen between Delta and Omicron entry that might explain the overtake of Delta by Omicron [21]. This result, together with the Danish real-world data [16], tends to indicate that the increased transmissibility of Omicron over Delta may be more a consequence of increased immune evasion.

2. Treatment

2.1. Antivirals

The antiviral drugs active against the Omicron variant of SARS-CoV-2 are inhibitors of the RNA-dependent RNA polymerase (RdRp) and of the 3CLpro (3C-like protease) that is the main protease of the virus. Despite several mutations described in the Omicron variant, these molecules seem to maintain activity against this newly emerged VOC [13]. Remdesivir and molnupiravir are both nucleoside analogues that inhibit the RdRp of *Coronavirdae*, while nirmatrelvir and other drugs currently in clinical trials, such as S-217622 (phase 3), are inhibitors of 3CLpro [22][23]. The effects against BA.2 of approved antiviral drugs and those under investigation are still uncertain.

The in vitro susceptibility of BA.2 to remdesivir, molnupiravir, and nirmatrelvir appears to be similar to that of the ancestral strain and other variants of concern [22][24]. Moreover, in animal models, the therapeutic efficacy of these compounds was

assessed in hamsters infected with BA.2. There was no decrease in viral titers in the nasal turbinates of the animals treated with molnupiravir or nirmatrelvir, while treatment with S-217622 reduced the number of virus titers in the upper respiratory tract. Notably, all the compounds tested considerably reduced the number of lower respiratory tract virus titers [25].

The few data available suggest that antiviral drugs remain active against BA.2, even though clinical data and real-world experiments are not currently available.

2.2. Monoclonal Antibodies

The use of monoclonal antibodies against SARS-CoV-2 has characterized the recent treatment scenario [26]. BA.2 appeared to retain in vitro sensitivity to some NTD-targeting mAbs. Mutations in the N1-loop moderately decreased binding for class II, III, and IV mAbs and, in combination with G142D, BA.2 completely escaped antibody recognition at this site. Thus, BA.1 and BA.2 effectively evaded class III and IV mAbs but showed different binding for class I and II mAbs.

Mutations in both the BA.1- and BA.2-RBDs often resulted in non-additive levels of escape from RBD-targeting mAbs. Multiple mutations were often required to escape binding completely [27]. The in vitro inhibition potency of casirivimab, imdevimab, and S309 with respect to Omicron subvariants BA.1 and BA.2 was severely impaired, in contrast to the outstanding activity of these treatments against the Wuhan strain and the Alpha, Gamma, and Delta variants. In this under-revision analysis, casirivimab did not show any antiviral activity for BA.1 or BA.2. In addition, imdevimab lost its activity against BA.1, but retained a minor level of antiviral activity that allowed it to reduce BA.2 infections. S309's antiviral activity against BA.1 was more modest than that of other variants, and its activity against BA.2 was even weaker [24]. However, BA.2 may have limited management options. Although the drug's manufacturer claimed that sotrovimab (GSK4182136 or S309) remained effective against BA.2, recent analysis suggests that the BA.2 lineage is intrinsically resistant to this monoclonal antibody [2][28][29]. As a matter of fact, the Federal Drug Administration (FDA) decided to limit the use of sotrovimab in the treatment of mild-to-moderate COVID-19 [30]. Currently, this monoclonal antibody is specifically authorized in geographic regions where infection is not likely to have been caused by the BA.2 lineage or after its certain exclusion [30]. Similarly, both etesevimab (LY-CoV016) and bamlanivimab (LY-CoV555) showed a markedly reduced neutralizing activity against the BA.2 lineage in live-virus tests [31]. There are high hopes for combination therapies. Despite its ineffectiveness against the Omicron BA.1 lineage, the well-known combination of casirivimab (REGN10933) and imdevimab (REGN10987) may inhibit the BA.2 lineage [31][32]. Likewise, another effective combination against the BA.2 lineage is tixagevimab (AZD8895) and cilgavimab (AZD1061): this combination has shown an effective synergistic effect, as supported by the analysis of spike protein-pseudo-typed lentiviruses [32][33][34]. It is noteworthy that the monoclonal antibody titer required for a 50% reduction in the number of infections has risen [31]. These new findings show that none of the currently approved or authorized monoclonal antibody therapies adequately cover all the sub-lineages of the Omicron variant [28]. Finally, a preprint study identified six mAbs that bound to the spike protein from all human alpha- and beta- coronaviruses. These mAbs target the fusion peptide region, which plays a critical role during coronavirus invasion, has an identical sequence in all SARS-CoV-2 VOCs, and is highly conserved. However, these mAbs have a significantly low in vitro neutralization potency that may be due to their relatively weak binding to the intact spike, which is enhanced only when the S1 cap is removed [35]. Many analyses are currently under revision, and one of them states that LY-CoV1404 (also known as bebtelovimab) displays potent neutralizing activity against numerous variants, including the BA.2 subvariant, as it retains binding activity to the spike proteins despite several underlying RBD mutations (K417N, L452R, E484K, and N501Y) [36].

2.3. Vaccines

The different Omicron lineages are antigenically distant from wild-type SARS-CoV-2, and this threatens the efficacy of currently available vaccines [28]. As a matter of fact, polyclonal sera from patients infected by wild-type SARS-CoV-2 showed a substantial loss in neutralizing activity against the BA.2 lineage [28]. Moreover, recent studies confirmed that neutralizing titers were lower against BA.2 compared with ancestral SARS-CoV-2 after one or two doses, as well as boosted vaccination [37][38].

However, vaccine efficacy appears to be similar against BA.2 in comparison to BA.1 and the other Omicron sub-lineages [5]. A case-control study evidenced no reduction in vaccine effectiveness against symptomatic disease or hospitalization with BA.1 and BA.2 after one or two doses of BNT162b2, ChAdOx1-S, or mRNA-1273, and after booster doses of BNT162b2 or mRNA-1273 during a period of co-circulation [39]. Recent data suggest that the mRNA vaccines induce the highest antibody titer against the Omicron variant, but a booster dose is needed to obtain consistent neutralizing antibody titers against either the BA.1 or BA.2 lineages [23][24]. A recently published, matched, test-negative, case-control study

estimated the duration of protection of the second and third/booster doses of BNT162b2 and mRNA-1273 against Omicron BA.1 and BA.2. In the first three months after the second dose, effectiveness was high against both the lineages considered, but it declined to ~10% or below thereafter. In contrast, in the first month after the booster dose, effectiveness rebounded to high levels of protection with an efficacy against COVID-19 hospitalization and death of >90% [40].

Particles harboring the S proteins of BA.2 and BA.3 showed lower neutralization than those of B.1 when exposed to vaccinated or recovered patients' sera. Triple BNT vaccination induced a potent antibody response, and only a modest evasion of neutralization was seen for particles bearing Omicron BA.2 and BA.3 S proteins. Neutralization by the antibodies induced in fully-vaccinated (three vaccine doses) individuals with breakthrough infections during the fourth wave in Germany (October 2021 to January 2022, dominated by the Delta variant) showed no significant differences between BA.1, BA.2, and BA.3 [34]. There is controversial data regarding the use of an Omicron-based vaccine (mRNA-1273.529 or Omicron-BA.1-RBD) in a complete vaccination cycle based on mRNA vaccines. Some analyses conducted in mice suggest that it seems to increase neutralizing titers and protection against BA.1 and BA.2 without less effectively inhibiting historical or other SARS-CoV-2 variants [33][41], whereas other studies suggest that an Omicron boost may not provide greater immunity or protection compared to a boost with the current mRNA-1273 vaccine [42][43]. Lastly, important public health implications were derived from the discovery that sera of patients previously infected with the BA.1 lineage seemed to have robust neutralizing antibody titers against BA.2, suggesting a substantial degree of cross-reactive natural immunity [1]. Considering the cellular response to vaccines, data under revision suggested that the introduction of a serine at position 446 of the Omicron BA.1 spike protein would be sufficient to induce enhanced T cell recognition of the NF9 epitope. This enhanced recognition was diminished against the Omicron BA.2 spike protein due to the absence of the G446S mutation. In contrast, QI9-specific T cells from the same donors produced comparable levels of IFN-γ in response to stimulation with target cells expressing all spike proteins tested [44].

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