Original Article

Is the BNT162b2 Vaccine Still Effective against the Latest Variant: XBB.1.5?

Emine Erdag, Nazife Sultanoglu[1], Cenk S. Ozverel[2]

Department of Pharmaceutical Chemistry, [1]Department of Medical Microbiology and Clinical Microbiology, [2]Department of Basic Medical Sciences, Near East University, Nicosia, Cyprus

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Abstract

Background: The XBB.1.5 sub-variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron now continues to spread rapidly due to the increased transmission rate as a result of increased affinity of the virus binding over the ACE-2 receptor – a gained property due to the mutation that occurred in spike protein. **Aim:** The protectivity of BNT162b2 antibodies produced in the serum of patients is an important parameter for preventing transmission. However, the affinity of the antibodies of patients vaccinated with BNT162b2 over the latest SARS-CoV-2 variant, XBB.1.5, is not well established. This study aimed to evaluate the efficacy of the BNT162b2 vaccine-induced antibody on XBB.1.5 by comparing the X-ray crystallographic structures and spike protein mutations of BA.5 and XBB.1.5 using *in silico* methods. **Materials and Methods:** Binding points and binding affinity values of the BNT162b2 antibody with BA.5 and XBB.1.5 spike protein were calculated using ClusPro 2.0 protein–protein docking and Discovery Studio 2021 Client software. Mutations in the genetic code of the spike protein for SARS-CoV-2 BA.5 and XBB.1.5 sub-variants were screened using the GISAID database. **Results:** Binding affinity values showed that BNT162b2 had higher negative values in the XBB.1.5 sub-variant than BA.5 at the mutation sites at the binding region. The results suggested that BNT162b2 may retain its activity despite mutations and conformational changes in the binding site of the XBB.1.5. **Conclusion:** The findings of this study shed light on the importance and usability of the current BNT162b2 vaccine for XBB.1.5 and future variants of concern.

Keywords: *BNT162b2 antibody, COVID-19, Omicron, protein–protein docking, XBB15*

Received: 22-Mar-2023; **Revision:** 30-May-2023; **Accepted:** 23-Jul-2023; **Published:** 30-Oct-2023

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an evolving virus that leads to the development of variants and sub-variants. Omicron, a variant of SARS-CoV-2, remains to be dominant worldwide.[1] Furthermore, the continuous mutation of the Omicron resulted in the evolution of sub-variants, including BA.1, BA.2, BA.5, and BQ.1. Currently, the BA.5 variant is dominant globally among these variants. Also, a diverse array of Omicron sub-lineages have emerged, such as the XBB, a recombinant of two BA.2 lineages. XBB is the other variant becoming increasingly prevalent in America and other countries.[2]

Coronaviruses use spike proteins to enter host cells. These protein structures comprise two distinct segments: an S1 segment responsible for receptor binding and an S2 segment facilitating the fusion of the virus with the cell membrane. Recent studies indicate that SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) receptors interact extensively, with a strong binding affinity at least 15 times greater than

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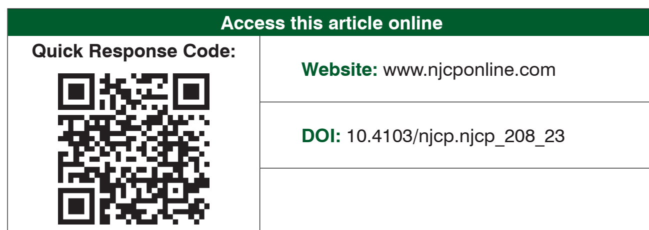

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_208_23

Address for correspondence: Dr. Emine Erdag, Department of Pharmaceutical Chemistry, Near East University, Nicosia, Cyprus. E-mail: emine.erdag@neu.edu.tr

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How to cite this article: Erdag E, Sultanoglu N, Ozverel CS. Is the BNT162b2 vaccine still effective against the latest variant: XBB.1.5? Niger J Clin Pract 2023;26:1519-24.

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SARS-CoV-1 binding to ACE2.[3] Multiple residues play a role in this protein–protein interaction, strengthening the affinity. The phenylalanine, F486, in the flexible loop is crucial to penetrating ACE2's long hydrophobic pocket.[3] The presence of F486P mutation in the spike protein increased the binding affinity to the ACE2 receptor, making it more transmissible and increasing its dominance worldwide.[1,2]

Recently, *in silico* studies have been preferred, especially for developing drugs and vaccines and understanding the mechanisms of action, as they constitute preliminary data.[4] Computer science plays an important role in drug and vaccine development, with new approaches and methods discovered in *in silico* studies. The effectiveness of vaccines created to combat the growing number of SARS-CoV-2 variants is a crucial subject in *in silico* research. With the help of techniques like protein–protein docking, it is now possible to analyze vital data such as the antibody response generated by vaccines, the impact of mutations on neutralization, and the binding affinities of vaccine-induced antibodies to target viral proteins without the need for animal testing and in a shorter timeframe.[4]

Vaccines are a very important component of health systems in eradicating coronavirus disease 2019 (COVID-19). In addition, conventional vaccines, mRNA vaccines, a new technology method, are very important in eradicating COVID-19. One of the widely used mRNA vaccines against COVID-19 is the BNT162b2 (Pfizer/BioNTech). BNT162b2 is usually administered as a two-dose prime-boost regimen.[5] The vaccine is considered as safe and effective against SARS-CoV-2. This vaccine is delivered intra-cellularly and contains a lipid nanoparticle shell vector that encodes the Spike protein of SARS-CoV-2. Production of the Spike protein via the vaccine promotes the adaptive immune response. Initiation of the adaptive immune response promotes the generation of T-cell and B-cell antibodies which are equal to or even stronger than the natural infection.[5]

The efficacy of the current vaccines applied in the general population is still the most important weapon against the pandemic. However, the continual emergence of the SARS-CoV-2 variants with higher rates of transmissibility, virulence, infectivity, and the gain of the ability to immune escape has challenged the efficacy of the SARS-CoV-2 vaccine.[6,7] The efficacy of the BNT162b2 vaccine is very important as it is one of the most widely applied vaccines in the world. The SARS-CoV-2×BB.1.5 variant is gaining dominance over the other sub-variants of the virus. Therefore, this study aimed to evaluate the relative changes in the efficacy of the antibody sera obtained from the BNT162b2-vaccinated individuals by the *in silico* method. This is the first study in the literature calculating the efficacy of the BNT162b2 vaccine against the XBB.1.5 sub-variant.

Materials and Methods

Preparation of the data set

Before analysis, SARS-CoV-2 BA.5 Omicron RBD complex (PDB: 7WRL) and the BNT162b2 antibody (PDB: 7XH8) structure were downloaded from the Protein Data Bank in PDB file format. Mutations in the genetic code of the spike protein for SARS-CoV-2 BA.5 and XBB.1.5 sub-variants were screened using the GISAID database, and mutation site differences between the variants were compared. Then, the genetic sequence regions mutated in the XBB.1.5 compared to BA.5 were determined. Comparative modeling[8] was performed with the Modeller program, and the three-dimensional (3D) structure for the XBB.1.5 variant was extracted. Conformational changes in the antibody binding sites of BA.5 and XBB.1.5 as a result of mutations were determined.

Protein–protein docking

This study used ClusPro 2.0 protein–protein docking and Discovery Studio 2021 Client programs.[9-12] All heteroatoms and water molecules in BA.5, XBB.1.5, and BNT162b2 antibody structures were removed before starting the docking process. The antibody mode was selected, and antibody chains were assigned as receptors. Protein–protein binding energies at all detected binding points were calculated using the PIPER algorithm.[13] When the PIPER algorithm is switched to the antibody mode, it analyzes antibody–protein complexes and reveals the asymmetry between the two sides.[14] All these processes were performed for both variants. The resulting clusters were analyzed for different binding modes. The final list of complexes and their binding affinities were calculated for BA.5 and XBB.1.5. According to the PIPER algorithm, the total energy is the sum of the terms representing the shape complementarity, electrostatic, and desolvation contributions as given in Equation 1. E_{attr} and E_{rep} represent the attractive and repulsive components, respectively. E_{elec} is the Coulombic electrostatic energy, and E_{DARS} is a pairwise interaction potential called Decoys as the Reference State (DARS).

The PIPER algorithm used in the ClusPro 2.0 protein–protein docking method is based on the fast Fourier transform correlation approach.[15-17] DARS, a new class of knowledge-based interaction potentials, has been incorporated into this algorithm, further improving the antibody–protein complex formation and docking algorithm, which is an essential step toward biological and vaccine design. This algorithm enables to distinguish between the near-natural 3D structures of antibody–

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protein complexes and the antibody paratope. In this study, BA.5 and XBB.1.5 were selected as target proteins, and BNT162b2 antibody complexes were constructed for both viruses using the same algorithm and methods. To obtain accurate results, in combination with the algorithm, other energy terms were used to evaluate near-natural fits between two viral complexes produced.

Equation 1. $E = 0.50E_{rep} + -0.20E_{att} + 600E_{elec} + 0.25E_{DARS}$ (1)

Results

In this study, a comparison between the genetic codes of XBB.1.5 spike proteins and the mutations occurring on the BA.5 structure was analyzed. As a result, four different mutations in the binding region of the BNT162b2-induced antibody were identified specifically for the XBB.1.5 variant. These are R346T, V445P, G446S, and F490S. The presence of these specific mutation points caused a conformational change in the 3D X-ray crystallographic structures of the BA.5 and XBB.1.5 variants at the location of the BNT162b2 antibody binding site. This structural change and specific mutation points are shown in Figure 1.

Protein–protein docking studies for the BA.5-BNT162b2 antibody and XBB.1.5-BNT162b2 antibody complexes

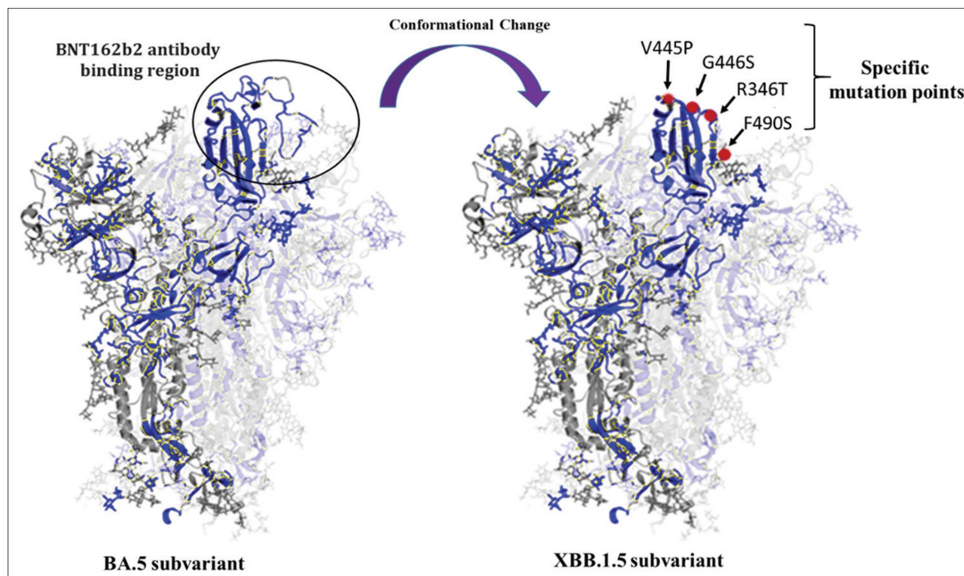

Figure 1: Conformational differences of BA.5 and XBB.1.5. The conformational comparison of BA.5 and XBB.1.5 SARS-CoV-2 Omicron sub-variants in the antibody binding region and the mutation points specific to this region (V445P, G446S, R346T, F490S) are illustrated in red

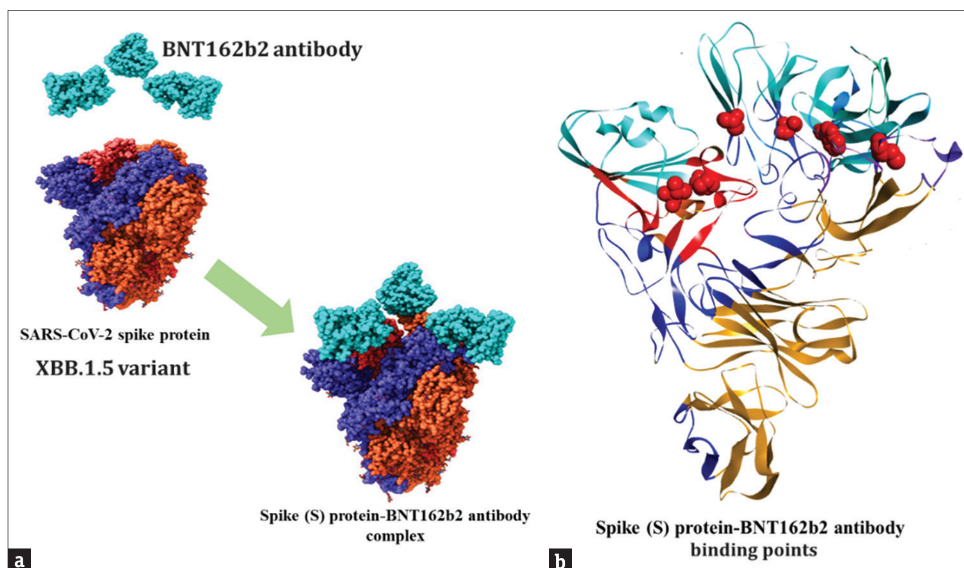

Figure 2: Antibody – complex formation of XBB.1.5 (a) BNT162b2 antibody targeting different regions on XBB.1.5 S. A gap-fill model was used to show the spike protein (dark blue-orange) and the BNT162b2 antibody (light blue) (b) Specific binding points (clusters) of the BNT162b2 antibody on 29 different regions of XBB.1.5 S. Binding spots are represented in red

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Table 1: Protein–protein docking evaluations of vaccine antibody with BA.5 and XBB.1.5. Comparison of protein–protein docking of BA.5 and XBB.1.5 variants with BNT162b2 antibody in terms of binding energy, number of binding points and amino acids for each cluster

Binding points (cluster)	Number of amino acids per cluster (member)	Binding energy (kcal/mol)	
		BA.5–antibody complex	XBB.1.5–antibody complex
1	40	-341.8	-341.8
2	40	-273.6	-273.6
3	34	-280.2	-280.2
4	34	-273.5	-273.5
5	29	-278.4	-278.4
6	23	-271.9	-271.9
7	21	-266.4	-266.4
8	18	-264.3	-264.3
9	16	-295.0	-295.0
10	16	-333.3	-769.8
11	15	-289.0	-289.0
12	15	-271.7	-271.7
13	15	-268.9	-268.9
14	14	-273.2	-273.2
15	13	-254.4	-254.4
16	13	-256.3	-256.3
17	13	-269.7	-269.7
18	12	-260.5	-260.5
19	12	-290.4	-290.4
20	12	-300.1	-300.1
21	12	-270.5	-270.5
22	10	-269.9	-269.9
23	10	-318.0	-773.3
24	10	-305.7	-819.5
25	10	-272.5	-272.5
26	10	-269.4	-269.4
27	10	-267.4	-267.4
28	9	-259.9	-259.9
29	9	-249.6	-249.6

revealed 29 different binding points in the antibody binding region [Figure 2]. The binding energy ranges at these binding points were between -249.6 kcal/mol and -333.3 kcal/mol for the BA.5-BNT162b2 complex. In the XBB.1.5-BNT162b2 complex, the binding energy values were generally between -249.6 kcal/mol and -819.5 kcal/mol. When the energy values between the BNT162b2 antibody binding points (cluster) for BA.5 were compared, cluster 10 (-333.3 kcal/mol), cluster 23 (-318 kcal/mol), and cluster 24 (-305.7 kcal/mol) were the regions with the highest binding affinity. In addition, the binding points giving the highest affinity values in the XBB.1.5-BNT162b2 antibody complex were found to be cluster 24 (-819.5 kcal/mol), cluster 23 (-773.3 kcal/mol), and cluster 10 (-769.8 kcal/mol).

On the other hand, no changes were detected in the binding affinities at binding points other than cluster 10, cluster 23, and cluster 24 in the BNT162b2 antibody complexes of both variants. The BNT162b2 antibody complex analysis results for BA.5 and XBB.1.5 are summarized in Table 1. As indicated in the table, BNT162b2 antibody binding sites were compared in clusters by calculating the number of amino acids in each cluster and the binding energies at these sites.

Discussion

As of January 2023, SARS-CoV-2 sub-variant XBB.1.5 is rapidly increasing its prevalence and dominance in some countries. XBB.1.5 is known to have various mutations making it more efficient in binding to the ACE-2 receptor. Some literature studies also demonstrated the immune evasion capabilities of the XBB.[18] However, BNT162b2 vaccine efficacy on the XBB.1.5 sub-variant still remains a big concern.

Bioinformatics can be used to investigate mutations occurring in variants of SARS-CoV-2 and the consequences of mutant proteins. Most targeted therapeutic strategies against COVID-19 involve *in silico*

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studies to obtain preliminary data. With the increase in SARS-CoV-2 Omicron sub-variants, *in silico* studies on designing new drug candidates, monoclonal antibody analyses, and the efficacy of vaccines designed to combat viral infections are in increasing trend.[19-21] Protein–protein docking studies using mutated structures of the SARS-CoV-2 S protein are critical for understanding the variations in binding energies of ligands and altered viral proteins. Alizadehmohajer *et al*. conducted a study involving the conservation analysis of the SARS-CoV-2 spike protein sequence.[19] The same study compared the binding energies of ACE2 with mutated and non-mutant spike protein interactions by the protein–protein docking method. Data were obtained using the ClusPro online server, which utilizes the scoring feature of the PIPER algorithm. The results showed that the site of the L5f and P1263l mutations and the non-mutant spike protein indicated an equal docking score (-1054.0 kJ/mol^{-1}).

On the other hand, Seadawy *et al*. conducted a study to evaluate the efficacy of their designed multi-epitope vaccine.[20] This vaccine was evaluated against the SARS-CoV-2 strain containing D614 G and P681R mutations on the spike protein. The study findings indicated that the developed multi-epitope vaccine exhibited an antigenic property value of 0.67. In addition, the spike multi-epitope protein of the vaccine was tested on Toll-Like Receptor 4 using the protein–protein docking method. This approach aimed to induce the activation of cytotoxic T-lymphocytes and helper T-lymphocytes. The antibody mode of the ClusPro 2.0 was employed for docking antibody and antigen pairs. The lowest energy score of -1346.3 kcal/mol was selected as the best-docked complex, suggesting that the vaccine model correctly occupies the receptor and exhibits a notable binding affinity.

Furthermore, another new vaccine candidate for SARS-CoV-2 has been proposed by Bhattacharya *et al*. through *in silico* techniques.[21] The efficacy of the vaccine was evaluated by a protein–protein docking study. The study observed that the vaccine formed a stable complex with the Toll-like receptor protein to elicit an inflammatory immune response. The vaccine candidate was reported to exhibit a significant negative binding energy of -1362.3 kcal/mol against COVID-19 infection.

Previous studies have shown that protein–protein docking is a highly effective method to analyze the interactions between antibody–antigen complexes and the effects of mutations on these complex structures. Similarly, Contractor *et al*. compared the Delta (B.1.617.2) and Omicron (B.1.1.529) spike proteins by protein–protein docking and evaluated the binding affinities of various human antibodies in these regions.[22] The results revealed some interaction differences in antibody complexes in the spike receptor binding domain. Based on these results, it was observed that the Omicron variant had considerably lower docking scores than the Delta variant. In contrast, the Delta variant did not significantly differ from the wild strain. Among the antibodies tested, CR3022 was shown to have the same docking score on both variants, while S309 and REGN10987 had higher binding affinity results with the receptor binding domain than the wild strain. The study has demonstrated the reason behind the unchanged neutralization efficiency of the tested antibodies for the Delta variant.[22] As in this study, the protein–protein docking method can be utilized to analyze if mutations in diverse variants cause any modifications in binding epitopes. *In silico* studies play a key role in developing vaccines that effectively combat future variants of concern, such as the prevalent XBB.1.5 sub-variant.

In the study of Uraki *et al*., BNT162b2 bivalent vaccine efficacy was tested against XBB.1.5. Omicron isolates to determine the humoral ability of the vaccine. They indicate that BNT162b2 still effectively provides humoral immunity to XBB.1.5.[23]

In our study, the efficacy of the antibodies of BNT162b2-vaccinated individuals was tested in terms of binding affinity to the latest dominant sub-variant of SARS-CoV-2, XBB.1.5. The presence of R346T, V445P, G446S, and F490S mutations observed in the BNT162b2-induced antibody binding site in XBB.1.5 spike protein was compared to BA.5. As a result of the conformational change, BNT162b2-induced antibody binding affinity and negative energy values in clusters 10, 23, and 24 were increased. The regions where these clusters are located also cover the points where the mutations occurred. Considering a total of 29 clusters to which the BNT162b2 antibody binds, it is clear that the structural change did not cause a significant change in binding affinity and differences in energy values in both BA.5 and XBB.1.5 complexes. The protein structures were preserved in the presence of occurred mutations, except for the antibody binding sites. Even if mutations change the 3D structure, it has been shown to increase the binding affinity of the antibody–protein complex in the region where the BNT162b2 antibody binds, resulting in values as effective as in BA.5.

Conclusion

Extensive model assumptions, including parameter distributions, are among the limitations of *in silico* studies. However, preliminary data can be provided rapidly by these studies to develop a vaccine and analyze its effectiveness. In this study, molecular analysis of the

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antibodies from BNT162b2-vaccinated patients was tested against SARS-CoV-2×BB.1.5 for the first time. The results suggested that BNT162b2 vaccination is still effective against the SARS-CoV-2×BB.1.5 sub-variant. However, boosting doses might still be needed against the aforementioned sub-variant.

Acknowledgment

None.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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