Omicron-Based Vaccine Candidate Elicits Potent Neutralizing Antibodies in the Animal Model

Asghar Abdoli[a,b], Javad Khanali[c], Mohammadreza Azangou-Khyavy[c], Mohsen Abbasi-Kangevari[c], Seyyed-Hadi Ghamari[c], Mohammad-Reza Malekpour[c], Hamidreza Jamshidi[d], Mohammad Taqavian[e], Mehdi Lari Baghal[f], Hasan Jalili[g,*]

[a]Department of Hepatitis and AIDS, Pasteur Institute of Iran, Tehran, Iran

[b]Amirabad Virology Laboratory, Vaccine Unit, Tehran, Iran

[c]Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

[d]Department of Pharmacology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[e]Research and Development Unit, Biosunpharmed Co, Karaj, Iran

[f]Research and Development Unit, Shifa Pharmed Co, Karaj, Iran

[g]Department of Life Science Engineering, Faculty of New Sciences and Technologies, University of Tehran, Tehran, Iran

[*]Corresponding author: hjalili@ut.ac.ir

Abstract

The B.1.1.529 (Omicron) variant of SARS-CoV-2 with multiple novel mutations has reduced the neutralization potential of vaccinated individuals' sera. World Health Organization has suggested that a vaccination strategy based on repeated booster doses is unlikely to be sustainable. The objective of this commentary was to investigate the safety and neutralizing antibody induction of the Omicron-based SARS-CoV-2 vaccine candidate, BIV1-CovIran Plus, against the Omicron variant on mice and guinea pig models.

After isolation and characterization, the Omicron variant underwent chemical inactivation, purification, and was then formulated with alum adjuvant. A full human dose of BIV1-CovIran Plus was injected intraperitoneally to five female mice and two Guinea pigs for abnormal toxicity reactions evaluation and pathologic investigations. For potency evaluation, four groups of ten mice received two doses of BIV1-CovIran Plus or phosphate-buffered-saline at 7-day and 14-day intervals. The conventional virus-neutralizing test was conducted on sera acquired from vaccinated mice groups seven days after the second injection.

There was no evidence of abnormal clinical symptoms macroscopic or microscopic tissue alterations among the animal models. In all samples from the study group that received two doses of BIV1-CovIran Plus at a 7-day interval, the sera at ≥1/32 times dilution would neutralize the Omicron variant SARS-CoV-2. Similarly, the sera of all samples from the study group, which received two doses of BIV1-CovIran Plus at a 14-day interval, at ≥1/64 times dilution, would neutralize the Omicron variant SARS-CoV-2. Moreover, six out of ten (60%) of the samples in this group would neutralize

the Omicron variant of SARS-CoV-2 at 1/128 times dilution. CPE formation was observed in all samples from the control group, and no neutralizing activity was detected at any sera dilutions.

BIV1-CovIran Plus was well-tolerated in the animal models, and no safety concerns were raised. Moreover, the vaccine candidate elicited protective neutralization against the Omicron variant. Future reports will focus on the use of the updated vaccine as a booster dose and the potency of the vaccine candidate on other SARS-CoV-2 variants.

Keywords: Vaccine; Virus Neutralisation Test; Neutralizing antibody; Omicron variant; SARS-CoV-2.

The B.1.1.529 (Omicron) variant of SARS-CoV-2 was identified in South Africa in early November 2021 as a variant of concern (VOC), which rapidly became the dominant variant in many countries (1,2). With its high transmissibility and multiple novel spike (S) protein mutations, Omicron could escape from naturally acquired immunity while also challenging the effectiveness of current COVID-19 vaccines (2,3). The secondary attack rate for Omicron in fully-vaccinated and booster-vaccinated individuals is shown to be approximately 2-4 times higher than the Delta variant, demonstrating strong evidence for immune evasion (4). Emerging evidence from in-vitro studies suggests reduced neutralization potential of vaccinated individuals' sera against Omicron (1,2,5,6).

The health impacts of future SARS-CoV-2 transmission depend on evolving mitigation strategies by health systems and societies. World Health Organization has reportedly declared that vaccination strategy based on repeated booster doses is unlikely to be sustainable. In this sense, the current COVID-19 vaccines originally developed against ancestral strains may need to be updated (7). Furthermore, in case of the future dominance of the Omicron variant and others originating from this variant, the development of updated vaccines would be crucial (8). Thus, Omicron-based vaccines are being developed, and clinical trials have begun in late January 2022 (9,10).

BIV1-CovIran is an inactivated virus vaccine developed against the Wuhan variant of SARS-CoV-2. In preclinical studies, the vaccine was safe and showed potency in inducing both humoral and cellular immunity (11). In phase III clinical trial, which is currently under peer-review, a two-dose vaccine regimen was well tolerated, with no safety concerns, and conferred 70.5% and 83.1% efficacy against hospitalization and

ICU admission, respectively. The vaccine has reduced hospitalization by 86.4% and deaths by 98.3% (12).

Exploiting our previous experience in constructing the BIV1-CovIran vaccine and commensurate with the global efforts in updating previous vaccines against omicron variant, we re-employed the inactivated virus vaccine platform to develop a novel Omicron-variant-based vaccine named as BIV1-CovIran Plus. The first case of the Omicron COVID-19 variant was identified in Iran on December 18, and the obtained virus was characterized and inactivated to prepare virus seed and the vaccine subsequently.

The objective of this commentary was to investigate the safety and neutralizing antibody induction of the Omicron-based SARS-CoV-2 vaccine candidate, BIV1-CovIran Plus, against the Omicron variant on mice and guinea pig models.

The methodology regarding vaccine preparation is fundamentally similar to the previous vaccine, BIV1-CovIran (11). The Omicron variant virus was isolated from a nasopharyngeal swab and infected mono-layer Vero cells (ATCC# CCL81) in the biosafety level-3 facility. The virus growth kinetics were evaluated up to 120 hours post-infection. The virus whole genome was sequenced by next-generation sequencing, and the virus structure was observed via electron microscopy. After passing the sterility test, vaccine master seed and working seed were prepared.

The study was carried out among female, six-to-eight-week-old BALB/c mice and Guinea pig animal models provided by the Laboratory Animal Science Department, Pasteur Institute of Iran, Karaj, Iran. A full human dose (0.5 mL) of the BIV1-CovIran Plus was injected intraperitoneally to five female mice and two Guinea pigs for abnormal toxicity reactions evaluation. The animals

were observed for seven days for any evidence of ill-health. After seven days, a veterinary pathologist evaluated organs and tissues for any signs of adverse reactions (13).

For potency evaluation, four groups of ten mice received two doses of BIV1-CovIran Plus or placebo (phosphate-buffered saline) at 7-day and 14-day intervals. The conventional virus-neutralizing test (cVNT) was conducted on sera acquired from vaccinated mice groups seven days after the second injection. Virus-specific CPEs were recorded under microscopes 72h post-infection, and the neutralizing antibody titres were determined as values of the highest dilution that inhibited CPE formation in each well. The presence of neutralizing antibodies was reported positive if the potency were ≥1:4 and reported protective if the potency were ≥ 1:16 (14–16). All animal models and maintenance procedures were under the approval of animal ethics committee guidelines of the Ministry of Health and Medical Education (Tehran, Iran; ethical code: IR.ACECR.IBCRC.REC.1399.016).

The VOC Omicron GRA (B.1.1.529+BA) SARS-CoV-2 strain first detected in Botswana/Hong Kong/South Africa was successfully isolated in Vero cells from the clinical specimen. Multiplication kinetics analysis of viral particles in Vero cells demonstrated the peak of multiplication with 106 TCID50, 72 hours post-infection (Figure 1-A). After four passages, the vaccine seed was prepared, and the virus growth was recorded by the presence of CPE (Figure 1-B).

[Figure 1]

There was no evidence of abnormal clinical symptoms, altered water or food intake, weight loss, and macroscopic tissue alterations among the mice and Guinea pigs that received BIV1-CovIran Plus. Moreover, there were no microscopic changes in the animals' liver, kidney, heart, and lung samples.

The neutralization potency of two doses of BIV1-CovIran Plus was assessed against the Omicron variant. In all samples from the study group that received two doses of BIV1-CovIran Plus at a 7-day interval, the sera at ≥1/32 times dilution would neutralize the Omicron variant SARS-CoV-2. Similarly, the sera of all samples from the study group, which received two doses of BIV1-CovIran Plus at a 14-day interval, at ≥1/64 times dilution, would neutralize the Omicron variant SARS-CoV-2. Moreover, six out of ten (60%) of the samples in this group would neutralize the Omicron variant of SARS-CoV-2 at 1/128 times dilution. CPE formation was observed in all samples from the control group, and no neutralizing activity was detected at any sera dilutions (Figure 2).

[Figure 2]

BIV1-CovIran Plus was well-tolerated in the animal models, and no safety concerns were raised. Moreover, the vaccine candidate elicited protective neutralization against the Omicron variant in 100% of mice studied a week after the second injection.

The isolated virus used in the study was genetically identical to the B.1.1.529 variant, initially identified in South Africa (17). Since the identification of Omicron in November 2021, vaccine manufacturers have begun developing variant-based vaccine candidates (9,10). While the initial Omicron peaks could plummet before these vaccines are commercially available (18), this variant seems to have the potential to become a persistent variant that healthcare systems need to deal with. Moreover, other SARS-CoV-2 variants could emerge and further challenge the effectiveness of current vaccines (18). Thus, developing variant-specific COVID-19 vaccine candidates as boosters could be potential mitigation strategies (19). The process of virus inactivation, validation, purification, and formulation was done in a month-length timeline, indicating the early response capacity to potential new circulating variants of concern.

In this sense, it remains unclear whether the immunologically naïve populations should be offered the vaccines originally manufactured against the Wuhan variant or the variant-based vaccine candidates (20).

Even though the promising preliminary results of the use of BIV1-CovIran Plus vaccine candidate against the Omicron variant is presented here, using the updated vaccine as a booster dose for BIV1-CovIran as well as the potency of the vaccine candidate on other SARS-CoV-2 variants have been investigated and will be reported in the upcoming publications.

Ethical approval

All animal models and maintenance procedures were under the approval of animal ethics committee guidelines of the Ministry of Health and Medical Education (Tehran, Iran; ethical code: IR.ACECR.IBCRC.REC.1399.016).

Contributors

Conceptualization: A.A., Hamidreza J., M.T., M.LB., Hassan J.; Data curation: A.A., M.T.; Formal Analysis: A.A., M.T.,; Funding acquisition: A.A., M.T.; Investigation: Hamidreza J., Hassan J.; Methodology: A.A., M.T., Hassan J.; Project administration: Hassan J.; Resources: Hassan J., Hamidreza J.; Supervision: Hassan J., Hamidreza J.; Validation: Hassan J., Hamidreza J.; Visualization: M-R.M., J.K., M.A-K., S-H.G., M.A-K.; Writing – original draft: J.K., M.A-K., S-H.G., M.A-K., M-R.M.; Writing – review & editing: A.A., J.K., M.A-K., M.A-K., S-H.G., M-R.M., Hamidreza J., M.T., M.LB., Hassan J.

Funding

Shifa-Pharmed Industrial Group

Competing interests

Mohammad Taqavian and Mehdi Lari Baghal are employees of Shifa Pharmed, with no stock options or incentives. Hamidreza Jamshidi and Hasan Jalili are the chairman and managing directors of the vaccine research and development unit in Shifa Pharmed, respectively. Asghar Abdoli is the founder and scientific director of Amirabad Virology Lab.

References

1. Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa. N Engl J Med [Internet]. 2021 Dec 29 [cited 2022 Jan 31]; Available from: https://pubmed.ncbi.nlm.nih.gov/34965358/
2. Fu Tseng H, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants. medRxiv [Internet]. 2022 Jan 21 [cited 2022 Jan 31];2022.01.07.22268919. Available from: https://www.medrxiv.org/content/10.1101/2022.01.07.22268919v2
3. Bok K, Sitar S, Graham BS, Mascola JR. Accelerated COVID-19 vaccine development: milestones, lessons, and prospects. Immunity [Internet]. 2021 Aug 10 [cited 2022 Jan 31];54(8):1636–51. Available from: https://pubmed.ncbi.nlm.nih.gov/34348117/
4. Lyngse FP, Mortensen LH, Denwood MJ, Christiansen LE, Møller CH, Skov RL, et al. SARS-CoV-2 Omicron VOC Transmission in Danish Households. medRxiv [Internet]. 2021 Dec 27 [cited 2022 Jan 31];2021.12.27.21268278. Available from: https://www.medrxiv.org/content/10.1101/2021.12.27.21268278v1
5. Garcia-Beltran WF, St. Denis KJ, Hoelzemer A, Lam EC, Nitido AD, Sheehan ML, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. Cell [Internet]. 2022 Jan [cited 2022 Jan 31]; Available from: https://pubmed.ncbi.nlm.nih.gov/34995482/
6. Wilhelm A, Widera M, Grikscheit K, Toptan T, Schenk B, Pallas C, et al. Reduced Neutralization of SARS-CoV-2 Omicron Variant by Vaccine Sera and Monoclonal Antibodies. medRxiv. 2021 Dec;2021.12.07.21267432.
7. WHO. Interim Statement on COVID-19 vaccines in the context of the circulation of the

Omicron SARS-CoV-2 Variant from the WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC). 2022.

8. Gagne M, Moliva JI, Foulds KE, Andrew SF, Flynn BJ, Werner AP, et al. mRNA-1273 or mRNA-Omicron boost in vaccinated macaques elicits comparable B cell expansion, neutralizing antibodies and protection against Omicron. bioRxiv [Internet]. 2022 Feb 4 [cited 2022 Feb 11];2022.02.03.479037. Available from: https://www.biorxiv.org/content/10.1101/2022.02.03.479037v1

9. Moderna - Moderna Announces First Participant Dosed in Phase 2 Study of Omicron-Specific Booster Candidate and Publication of Data on Booster Durability Against Omicron Variant.

10. Pfizer and BioNTech Initiate Study to Evaluate Omicron-Based COVID-19 Vaccine in Adults 18 to 55 Years of Age | Pfizer.

11. Abdoli A, Aalizadeh R, Aminianfar H, Kianmehr Z, Teimoori A, Azimi E, et al. Safety and potency of BIV1-CovIran inactivated vaccine candidate for SARS-CoV-2: A preclinical study. Rev Med Virol [Internet]. 2021 Oct 26 [cited 2021 Oct 27];e2305. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/rmv.2305

12. Mirahmadizadeh A, Heiran A, Lankarani KB, Serati M, Habibi M, Eilami O, et al. "Effectiveness of COVID-19 Vaccines in preventing Infectiousness, Hospitalization and Mortality: A Historical Cohort Study Using Iranian Registration Data During Vaccination program." medRxiv. 2022 Jan;2022.01.18.22269330.

13. Forster R. Study designs for the nonclinical safety testing of new vaccine products. J Pharmacol Toxicol Methods [Internet]. 2012 Jul [cited 2022 Jan 31];66(1):1–7. Available from: https://pubmed.ncbi.nlm.nih.gov/22561062/

14. Wang X, Zhao X, Song J, Wu J, Zhu Y, Li M, et al. Homologous or heterologous booster of inactivated vaccine reduces SARS-CoV-2 Omicron variant escape from neutralizing antibodies. Emerg Microbes Infect [Internet]. 2022 Dec 31 [cited 2022 Feb 11];11(1):477–81. Available from: https://pubmed.ncbi.nlm.nih.gov/35034583/

15. Abdoli A, Aalizadeh R, Aminianfar H, Kianmehr Z, Teimoori A, Azimi E, et al. Safety and potency of BIV1-CovIran inactivated vaccine candidate for SARS-CoV-2: A preclinical study. Rev Med Virol [Internet]. 2021 [cited 2022 Jan 31]; Available from: https://pubmed.ncbi.nlm.nih.gov/34699647/

16. Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W, et al. Development of an Inactivated Vaccine Candidate, BBIBP-CorV, with Potent Protection against SARS-CoV-2. Cell [Internet]. 2020 Aug 6 [cited 2022 Feb 11];182(3):713-721.e9. Available from: https://pubmed.ncbi.nlm.nih.gov/32778225/

17. Viana R, Moyo S, Amoako DG, Tegally H, Scheepers C, Althaus CL, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. Nat 2022 [Internet]. 2022 Jan 7 [cited 2022 Feb 11];1–10. Available from: https://www.nature.com/articles/s41586-022-04411-y

18. Waltz E. Does the world need an Omicron vaccine? What researchers say. Nature. 2022 Jan;

19. Fauci: Omicron-specific vaccines "prudent" but may be unnecessary | TheHill.

20. Gagne M, Moliva JI, Foulds KE, Andrew SF, Flynn BJ, Werner AP, et al. mRNA-1273 or mRNA-Omicron boost in vaccinated macaques elicits comparable B cell expansion, neutralizing antibodies and protection against Omicron. bioRxiv. 2022 Feb;2022.02.03.479037.

Figure legends

Figure 1. The virus growth curve analyzed by TCID50 (A), positive CPE resulting from virus infection (B), compared with the control sample (C).

Figure 2. The virus neutralization titres seven days after receiving two doses of BIV1-CovIran Plus with 7 (A) and 14 (B) days intervals. 1/16 sera dilution was considered as the seroprotective threshold.

Figure 1

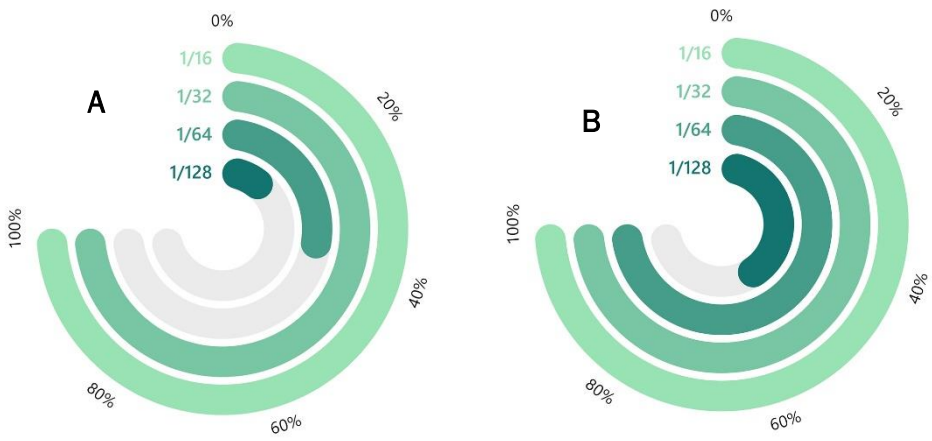
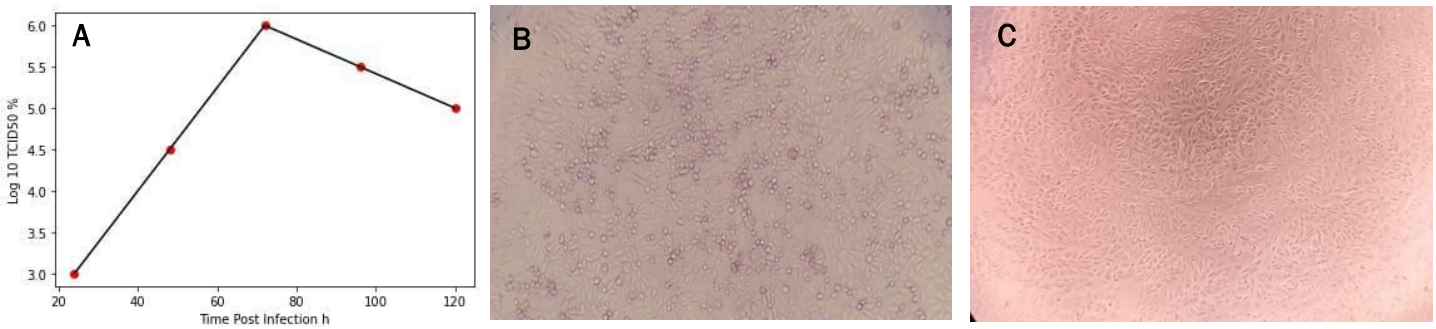

A
0%
1/16
1/32
1/64
1/128
20%
40%
60%
80%
100%
B
0%
1/16
1/32
1/64
1/128
20%
40%
60%
80%
100%

Figure 2


A
B
C
Log 10 TCID50 %
6.0
5.5
5.0
4.5
4.0
3.5
3.0
20
40
60
80
100
120
Time Post Infection h