DYDYK, Martyna and NOWAK, Aleksandra. Experimental Success in Marburg Virus Vaccination. Quality in Sport. 2024;22:54483. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.22.54483
https://apcz.umk.pl/QS/article/view/54483

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 20.08.2024. Revised: 13.09.2024. Accepted: 16.09.2024. Published: 17.09.2024.

Experimental Success in Marburg Virus Vaccination

1. **M.D. Martyna Dydyk**
   ORCiD: 0009-0005-5906-3406
   e-mail: dydykm@icloud.com
   Medical University of Warsaw, Żwirki i Wigury 61 street, 02-091 Warsaw, Poland

2. **M.D. Aleksandra Nowak**
   ORCiD: 0009-0009-6602-4017
   e-mail: aa.nowak17@gmail.com
   Infant Jesus Teaching Hospital, Lindleya 4 street, 02-005 Warsaw, Poland

Abstract:

The Marburg virus (MRV), classified within the Filoviridae family, was initially identified in 1967, precipitating Marburg virus disease (MARV), a severe and often fatal hemorrhagic fever. With its pronounced infectiousness, high mortality rate, and proclivity for epidemic outbreaks, MARV stands as a formidable public health menace. Despite extensive sporadic outbreaks and its designation as a priority disease, the quest for efficacious drugs or vaccines against MRV remains an ongoing challenge. Nonetheless, the relentless pursuit of scientific inquiry, augmented by the innovative application of immunoinformatics, is propelling forward vaccine development endeavors. Current vaccine candidates, spanning from VSV-based formulations to virus-like particle vaccines, exhibit encouraging outcomes in preclinical and clinical evaluations, boasting notable efficacy and safety profiles. Furthermore, the exploration of multivalent vaccine strategies, designed to target a spectrum of hemorrhagic fever viruses, holds promise in fortifying pandemic preparedness efforts.

Immunoinformatics assumes a pivotal role in this context, offering predictive insights into vaccine candidate selection and optimization, thereby facilitating expedited development tailored to diverse demographic cohorts. The integration of computational modeling techniques into vaccine development paradigms represents a transformative avenue for effectively controlling MRV outbreaks on a global scale. Sustained collaboration and continued research endeavors are imperative to fully harness the potential of these advancements in confronting the formidable challenge posed by the lethal Marburg virus and safeguarding global public health.

Keywords: Marburg virus, vaccine, Marburg virus disease

Introduction

The Marburg virus (MRV) was first identified in 1967 in Marburg. It is included, along with the Ebola virus, among the viruses of the filoviridae family (1, 2). MRV causes Marburg virus disease (MARV), which is a highly fatal hemorrhagic fever (2). As of 2023, 17 sporadic outbreaks of MARV have been described. The virus is characterized by its high infectiousness, which, combined with its high mortality rate and tendency to create epidemic outbreaks, led to its inclusion on the list of priority diseases in 2018 (3-5). Infection occurs via the droplet route, and the virus can transmit both from animals to humans and from humans to humans (4). At the moment, there is no effective drug or vaccine to protect against MRV. The search for a suitable vaccine is being aided by immunoinformatics, which makes it possible to select a highly immunogenic antigen, create a safe formulation, and target a specific population(3, 6). Vaccines currently in clinical trials, whether in animals or humans, are mainly based on the glycoprotein (GP) of the MRV envelope, and the main differences are in the vectors used (7, 8). The aim of this study is to present the current progress in Marburg virus vaccine research.

Marburg Virus

MRV is an enveloped, single-stranded RNA virus of the filovirus family. The Marburg Musoke-Angola variant was isolated from the largest epidemic outbreak. During the epidemic in Angola, 252 were described as having a mortality rate of 88% (1, 9). The virus is transmitted both zonally and interpersonally, probably through saliva, urine, and bat feces (5, 9). Its genome contains 7 genes arranged linearly, and among them, we can distinguish a glycoprotein (5). It is the main target of experimental vaccines against MRV (7, 8, 10). GP is the only protein on the cell surface, plays a big role in pathogenesis, affects immunogenicity, and produces neutralizing antibodies (5, 9).

Marburg virus-induced hemorrhagic fever

The virus first attacks macrophages and dendritic cells, followed by endothelial cells. The incubation time ranges from 3 to 21 days. There are three phases of MARV (5, 11). Phase one – the generalization phase begins with flu-like symptoms (5). Phase two - early organ phase with a high fever and neurological symptoms. In 75% of patients, there are hemorrhagic symptoms, among which can be indicated bloody vomiting, bloody diarrhea, and tarry stools.

At the time of a late-stage infection, either the patient progresses to the late organ stage or dies (5, 11). Phase three – the convalescence phase often leads to kidney failure and multi-organ dysfunction (11). Typically, death occurs within 8–16 days of the onset of the first symptoms, most likely because of shock and multi-organ damage (5).

VSV-based vaccine

Vaccines containing recombinant vesicular stomatitis virus (rVSV) are already being used to protect against the Ebola virus in the Democratic Republic of the Congo (7). Of interest among researchers is the cross-reactivity within other viruses in the filoviridae group. The rVSV-ZEBOV vaccine was created to combat the Ebola virus, as mentioned earlier, of the Zaire species. Upon analyzing cross-reactions, it was discovered that, on average, 42.5% of antibodies recognize the glycoprotein (GP) of other viruses, including Ebola, Ebola-Bundibugyo, and Ebola-Sudan. Additionally, four antibodies reactive against MRV have been identified (7). A vaccine also based on rVSV targeting the GP of MRV is in clinical trials. A vaccine based on vesicular stomatitis virus binding to the GP of MRV (VSV-MARV) provides uniform protection in primates (other than humans) (12, 13). VSV-MARV can be called a sister to the rVSV-ZEBOV due to its considerable similarity. GP is a viral antigen, a single dose of vaccines based on it protects monkeys, but to be effective, it must be administered 28 days before provocation (12). For further studies, human homologs were used, which were inoculated and then provoked after 7 or 14 days. A strong immune response and immediate induction of inflammatory response genes were observed, protecting 100%. On the other hand, vaccination 3 days before provocation, provided 75% survival, indicating its suitability for use during an epidemic during which the priority is to provide rapid protection (12, 13). In comparison, a previous study showed the effectiveness of a single dose when administered 35 days before provocation (12). The success, indicating the vaccine's rapid effect, prompted the idea of testing the efficacy of VSV-MARV with a smaller dose. 100% protection was achieved when the vaccine was administered 28 days before the MRV provocation. This is important because, with limited capacity, more people can be protected with a single vial (14). Because of the additional information indicating safety and high efficacy at a low dose, the VSV-MARV vaccine is a promising candidate to combat the deadly virus. However, it requires human clinical trials to confirm its efficacy. Nevertheless, the information gathered so far points to its possible use as an interventional vaccine (12, 15).

Virus-like particle vaccine

The MVA-MARV-VLP vaccine combines the features of the Modified Vaccinia virus Ankara (MVA) vaccine vector and the authentic conformation of virus-like particles (VLPs) containing the envelope GP and matrix protein (VP40) of MRV. Thanks to the presentation of antigens in their native conformation, the vaccine has high immunogenicity. However, it requires several doses to protect against death. More importantly, it only protects against death without protecting against disease (8, 16).

Replication-defective chimpanzee adenovirus type 3 (ChAd3)-vectored vaccine

The vaccine, which uses replication-deficient chimpanzee adenovirus type 3 (ChAd3) and GP MRV (ChAd3-MARV) as the vector, is characterized by the safety of the vector, as confirmed by previous studies. In studies conducted on macaques, 100% protection was achieved, as was its durability 1 year after a single vaccination (10). The vaccine is currently in clinical trials evaluating its efficacy in humans. Results indicate a sustained antibody response in 70% of participants 48 weeks after vaccination. Although it requires further clinical trials in emergencies, it may be considered an emergency vaccine (17, 18).

Multivalent vaccine

The co-occurrence of many different hemorrhagic fever viruses in one area is an undeniable problem. A vaccine effective against multiple infectious agents significantly reduces the risk of a pandemic, and in the case of hemorrhagic fever viruses, recent research has focused on vaccines targeting a specific disease. In animal studies (mice, guinea pigs, and primates other than people), a cellular and humoral response was achieved with a multivalent vaccine targeting Ebola and Marburg viruses (19).

The impact of immunoinformatics on vaccine development

Immunoinformatics makes it possible to predict the role of specific proteins in a vaccine. On this basis, it has been possible to select three proteins that play a major role in the formation of infectious particles: VP24, VP30, and the envelope GP (6). The accuracy of the prediction is confirmed by the fact that clinical trials are being conducted on vaccines based on GP MRV (8, 10, 12). Modeling can accurately identify epitopes that are highly antigenic, safe, and non-allergenic. In addition, they indicate that the adjuvant in this case is proposed as beta-defensin-3, creating a formulation for a stable, potentially effective vaccine (3, 20). The main advantage of computerized vaccine design is that it can be tailored to a specific population. In addition, computer models reduce the time needed to create them (3). The role of informatics does not end with the creation of the vaccine; thanks to them, we can compare different vaccination strategies and choose the one that most effectively controls MRV outbreaks (21).

Conclusions

Given the threat posed by the Marburg virus, we urgently need a tool to protect people from contracting the disease. Immunoinformatics plays a crucial role in predicting vaccine efficacy, identifying antigenic epitopes, and streamlining formulation processes. Its ability to customize vaccines, reduce development time, and inform vaccination strategies enhances our capacity to combat infectious diseases effectively. Currently, the first human vaccine trials are already underway giving us real hopes of presenting a safe and effective vaccine to protect people from the effects of hemorrhagic fever soon.

Authors` Contributions:
Conceptualization, M.D. Literature review, M.D. and A.N.; Writing – Abstract, M.D.; Writing – Marburg Virus A.N.; Writing – Marburg virus-induced hemorrhagic fever M.D.; Writing – VSV-based vaccine A.N.; Writing – Virus-like particle vaccine A.N.; Writing – Replication-defective chimpanzee adenovirus type 3 (ChAd3)-vectored vaccine M.D.; Writing - Multivalent vaccine M.D.; Writing - The impact of immunoinformatics on vaccine development A.N.; Writing – Conclusions M.D. and AN.; Editing and reviewing M.D.

All authors have read and agreed with the published version of the manuscript.

Funding Statement:
This research received no external funding.

Conflict of Interest Statement:
The authors declare no conflict of interest.

References
1. Cross RW, Longini IM, Becker S, Bok K, Boucher D, Carroll MW, et al. An introduction to the Marburg virus vaccine consortium, MARVAC. PLoS Pathog. 2022;18(10):e1010805.
2. Ilinykh PA, Huang K, Santos RI, Gilchuk P, Gunn BM, Karim MM, et al. Non-neutralizing Antibodies from a Marburg Infection Survivor Mediate Protection by Fc-Effector Functions and by Enhancing Efficacy of Other Antibodies. Cell Host Microbe. 2020;27(6):976-91.e11.
3. Albaqami FF, Altharawi A, Althurwi HN, Alharthy KM, Qasim M, Muhseen ZT, et al. Computational Modeling and Evaluation of Potential mRNA and Peptide-Based Vaccine against Marburg Virus (MARV) to Provide Immune Protection against Hemorrhagic Fever. Biomed Res Int. 2023;2023:5560605.
4. Asad A, Aamir A, Qureshi NE, Bhimani S, Jatoi NN, Batra S, et al. Past and current advances in Marburg virus disease: a review. Infez Med. 2020;28(3):332-45.
5. Mitu RA, Islam MR. The Current Pathogenicity and Potential Risk Evaluation of Marburg Virus to Cause Mysterious "Disease X"-An Update on Recent Evidences. Environ Health Insights. 2024;18:11786302241235809.
6. Soltan MA, Abdulsahib WK, Amer M, Refaat AM, Bagalagel AA, Diri RM, et al. Mining of Marburg Virus Proteome for Designing an Epitope-Based Vaccine. Front Immunol. 2022;13:907481.
7. Ehrhardt SA, Zehner M, Krähling V, Cohen-Dvashi H, Kreer C, Elad N, et al. Polyclonal and convergent antibody response to Ebola virus vaccine rVSV-ZEBOV. Nature Medicine. 2019;25(10):1589-600.
8. Malherbe DC, Domi A, Hauser MJ, Meyer M, Gunn BM, Alter G, et al. Modified vaccinia Ankara vaccine expressing Marburg virus-like particles protects guinea pigs from lethal Marburg virus infection. NPJ Vaccines. 2020;5(1):78.
9. Kortepeter MG, Dierberg K, Shenoy ES, Cieslak TJ. Marburg virus disease: A summary for clinicians. Int J Infect Dis. 2020;99:233-42.

10. Finch CL, King TH, Alfson KJ, Albanese KA, Smith JNP, Smock P, et al. Single-Shot ChAd3-MARV Vaccine in Modified Formulation Buffer Shows 100% Protection of NHPs. Vaccines (Basel). 2022;10(11).
11. Ezie KN, Takoutsing BD, Modeste D, Ines MZ, Sybile TNL, Caleb NM, et al. Marburg Virus Outbreak in Equatorial Guinea: Need for Speed. Ann Glob Health. 2024;90(1):5.
12. Marzi A, Jankeel A, Menicucci AR, Callison J, O'Donnell KL, Feldmann F, et al. Single Dose of a VSV-Based Vaccine Rapidly Protects Macaques From Marburg Virus Disease. Front Immunol. 2021;12:774026.
13. Prator CA, Dorratt BM, O'Donnell KL, Lack J, Pinski AN, Ricklefs S, et al. Transcriptional profiling of immune responses in NHPs after low-dose, VSV-based vaccination against Marburg virus. Emerg Microbes Infect. 2023;12(2):2252513.
14. O'Donnell KL, Feldmann F, Kaza B, Clancy CS, Hanley PW, Fletcher P, et al. Rapid protection of nonhuman primates against Marburg virus disease using a single low-dose VSV-based vaccine. EBioMedicine. 2023;89:104463.
15. Cooper CL, Morrow G, Yuan M, Coleman JW, Hou F, Reiserova L, et al. Nonhuman Primates Are Protected against Marburg Virus Disease by Vaccination with a Vesicular Stomatitis Virus Vector-Based Vaccine Prepared under Conditions to Allow Advancement to Human Clinical Trials. Vaccines (Basel). 2022;10(10).
16. Warfield KL, Dye JM, Wells JB, Unfer RC, Holtsberg FW, Shulenin S, et al. Homologous and heterologous protection of nonhuman primates by Ebola and Sudan virus-like particles. PLoS One. 2015;10(3):e0118881.
17. Hamer MJ, Houser KV, Hofstetter AR, Ortega-Villa AM, Lee C, Preston A, et al. Safety, tolerability, and immunogenicity of the chimpanzee adenovirus type 3-vectored Marburg virus (cAd3-Marburg) vaccine in healthy adults in the USA: a first-in-human, phase 1, open-label, dose-escalation trial. Lancet. 2023;401(10373):294-302.
18. Hunegnaw R, Honko AN, Wang L, Carr D, Murray T, Shi W, et al. A single-shot ChAd3-MARV vaccine confers rapid and durable protection against Marburg virus in nonhuman primates. Sci Transl Med. 2022;14(675):eabq6364.
19. Jiang J, Ramos SJ, Bangalore P, Elwood D, Cashman KA, Kudchodkar SB, et al. Multivalent DNA Vaccines as A Strategy to Combat Multiple Concurrent Epidemics: Mosquito-Borne and Hemorrhagic Fever Viruses. Viruses. 2021;13(3).
20. Yousaf H, Naz A, Zaman N, Hassan M, Obaid A, Awan FM, et al. Immunoinformatic and reverse vaccinology-based designing of potent multi-epitope vaccine against Marburgvirus targeting the glycoprotein. Heliyon. 2023;9(8):e18059.
21. Qian GY, Edmunds WJ, Bausch DG, Jombart T. A mathematical model of Marburg virus disease outbreaks and the potential role of vaccination in control. BMC Med. 2023;21(1):439.