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56 Years of the Marburg Virus—A Review of Therapeutics

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Abstract

Background: The Marburg virus (MARV) is the causative agent of Marburg virus disease (MVD). This filovirus first appeared in 1967 and has since caused several outbreaks with case fatality rates between 23% and 90%. The earliest cases of MVD are thought to be caused by exposure to an infected animal, either a reservoir host (some bat species, e.g., *Rousettus aegyptiacus*) or a spill-over host, such as non-human primates. The virus is spread between people by direct contact with blood or other bodily fluids (including saliva, sweat, faeces, urine, tears, and breast milk) from infected individuals. Despite the high fatality rate, the Marburg virus has no vaccine or drug treatment. Recent outbreaks of the virus in 2023 in Tanzania and Equatorial Guinea have reignited the need to develop effective therapeutics, especially in the wake of the COVID-19 pandemic. **Purpose**: This review seeks to highlight the drug discovery efforts aimed at developing vaccines or possible treatments as potential therapeutics. Several existing antiviral agents are being probed, and vaccines are in pre-clinical and clinical stages. Natural products are also an important source of possible drugs or lead compounds and when coupled with computational techniques, these strategies offer possible therapeutics for the Marburg virus, especially in Africa, which has a high disease burden. **Methods**: Using the search engines Google Scholar and PubMed; keywords e.g. Marburg virus, Marburg treatments, Marburg virus drug discovery were utilized. Several results were yielded, and articles published in recent years were accepted into the final list.

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Results and Conclusion: This study shows there is a growing interest in therapeutics for the Marburg virus, especially with the recent outbreaks and pandemic preparedness. Initiatives that to support vaccine development and access like the MARVAC consort time are critical to fighting this public health threat.

Keywords

Marburg Virus, Vaccines, Antivirals, Viruses, Drug Discovery

1. Introduction

The Marburg virus (MARV), a member of the *Filoviridae* family, is an infectious, deadly, and highly contagious pathogen that causes Marburg virus disease (MVD) [1]. In humans and non-human primates (NHPs), MARV produces acute and severe haemorrhagic fever with high case fatality rates ranging from 23% to 90% [2].

MVD first appeared in August 1967, when laboratory workers in Germany (Marburg & Frankfurt) and Serbia (Belgrade) were infected with a previously unknown infectious agent [3]. The primary infections occurred when the monkeys were necropsied to obtain kidney cells to culture poliomyelitis vaccine strains. In about three months, the etiologic agent was isolated, characterised, and identified by scientists in Marburg and Hamburg [4]. The 31 patients (25 primary and 6 secondary infections) developed severe disease that progressed to fatal outcomes in seven cases (23% fatality rate). The source of infection was traced back to NHPs, to be precise the African green monkeys (*Chlorocebus aethiops*) that were imported from Uganda and shipped to the three locations described above [5].

The filoviruses, which include Ebola and Marburg viruses, are single-stranded, negative-sense RNA viruses, and the lethality of filovirus infections has been attributed to their ability to suppress host innate antiviral responses in early infection. The suppression of the host's immune response is followed by impairment and/or dysregulation of the adaptive immune system and inflammatory pathways during late infection [6].

In July 2022, Ghana reported its first two laboratory-confirmed cases of the MARV, and the outcomes were fatal in both cases [7]. In February 2023, Equatorial Guinea declared an outbreak with at least nine confirmed cases and seven deaths, as well as 20 suspected deaths caused by the virus. Another outbreak was reported in March 2023 in Tanzania with eight cases and five deaths [8].

2. Pathogenesis

MARV enters the body through skin breaches or mucosal membranes following direct contact with infected bodily fluids or direct interaction with an infected animal or person [9]. Dendritic cells, macrophages, and monocytes are the first

cells the virus infects. It then travels to the spleen, liver, and lymph nodes for early replication and subsequent spread. Antigen-presenting cells (APC) are heavily involved, resulting in an inflammatory response that releases inflammatory cytokines and chemokines and lymphoid depletion in the spleen. Inflammation throughout the body plays a crucial role in the development of illness. Several coagulation cascades are triggered by the production of inflammatory cytokines and chemokines such as prostacyclin and nitric oxide [10]. Disseminated intravascular coagulation results from this, prompting aberrant blood clotting throughout the body.

The most significant attachment component on the viral surface that facilitates binding and entrance into host cells is the MARV glycoprotein (GP). The two parts of GP are the internal fusion loop (GP2) that inserts into the cell membrane and the GP surface unit (GP1) that attaches to cellular receptors [11]. Similar processes are used by MARV and EBOV to enter host cells. Additionally, GP contributes to immunological suppression and evasion, as well as the inactivation of neutrophils [12].

After adhesion, endocytosis takes place, endosomal proteases break GP1, and the virus attaches to Niemann-Pick C1 (NPC1), an endosomal cholesterol transporter. In the cell's cytoplasm, the viral core is liberated, and transcription, translation, and replication occur [13].

3. Marburg Virus Life Cycle

The MARV replication cycle begins with the virus's attachment to the host's cell surface lectins, such as DC-SIGN and ASGP-R, which are unique to hepatocytes. After attachment, virus particles enter host cells through endocytosis [14]. Several hypotheses have been postulated, but the precise process of MARV's endocytosis is still unknown. A potential entrance mechanism has been suggested in light of macropinocytosis' structural resemblance to the Ebolavirus. Similarly, it has been proposed that caveolin and clathrin mediate the endosomal cleavage and endocytosis of glycoproteins [14]. Fusion of the virus to the endosomal membrane of the host and the release of its nucleocapsid into the cytoplasm are mediated by a cholesterol transporter known as Niemann-Pick C1 (NPC1) [14]. Subsequent release of the viral nucleocapsid into the cytoplasm triggers the transcription and replication of the RNA genome of the virus, marked by the appearance of granular material in the host cell's cytoplasm 12 hours following viral entry. Finally, replicated viral particles undergo assembly in the cell's internal and plasma membranes and are released from the cellular membrane under the control of viral protein 40 (VP40) [5].

4. Transmission

The earliest cases of MVD are thought to be caused by exposure to an infected animal, either a reservoir host (a number of bat species, e.g., *Rousettus aegyptiacus*) or a spill-over host (such as NHPs), as was the case with the first MVD outbreak [5]. Following human infection, the virus has an incubation period that

ranges from two to 21 days, with an average overall incubation period of five to nine days [15]. The virus is spread between people by direct contact with blood or other bodily fluids (including saliva, sweat, faeces, urine, tears, and breast milk) from infected individuals. Administration of treatment to sick people and handling of corpses without the use of protective gear are examples of typical exposure dangers [16]. Notably, the virus has been discovered in tears, semen, and liver tissue following biopsies conducted weeks to months after exposure [15].

5. Treatment

There are currently no recognized treatments for the MARV. Supportive care has been the cornerstone of therapy during outbreaks; the CDC and WHO have created an infection control manual [17]. Using proper personal protective equipment (PPE), disposable patient care equipment (e.g., fluid-resistant gowns extending to mid-calf) when available, limiting the use of needles and sharps, and avoiding aerosol-generating procedures. Additional infection control measures include performing frequent hand hygiene, monitoring and managing potentially exposed personnel, and restricting visitors from entering patients' rooms. Even though there are currently no approved medicines, many pharmacological substances are being developed [17].

5.1. Antivirals

One of the antiviral agents being investigated is the synthetic nucleoside analoguegalidesivir (BCX4430) (**Figure 1**), which targets viral RNA-dependent RNA polymerase. The parent drug is phosphorylated by cellular kinases to a triphosphate (BCX4430-TP), which is then incorporated into the viral RNA, causing premature chain termination [18]. BCX4430 was administered post-exposure intramuscularly to rodent models infected with the Marburg virus via intraperitoneal injection or exposure to aerosolized virus. This treatment provided protection when started within 48 hours. Additionally, Cynomolgus macaques were used to investigate BCX4430's effectiveness. After giving the macaques lethal doses of wild-type MARV, BXC4430 was administered intramuscularly twice daily for 14 days. Despite the virus killing the control, all animals treated between 24 and 48 hours after infection survived [19].

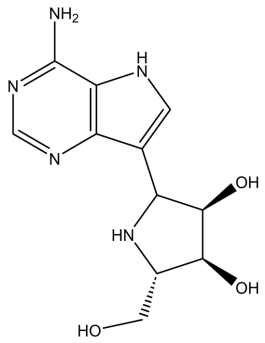

Figure 1. Galidesivir.

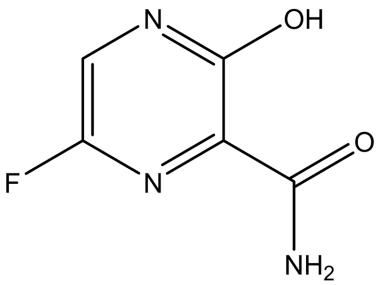

Figure 2. Favipiravir.

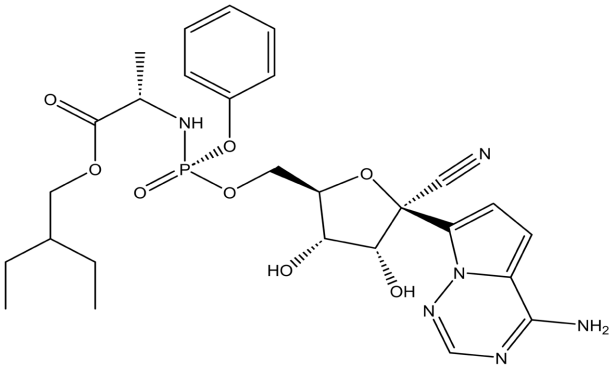

Figure 3. Remdesivir.

Favipiravir (**Figure 2**), a synthetic guanidine nucleoside analogue is approved in Japan for the treatment of influenza and has a broad spectrum activity [20]. When favipiravir was given intravenously twice daily for 14 days in cynomolgus macaques challenged with 1000 PFUs (MARV Angola), Bixler *et al.* demonstrated the survival of five of the six macaques, and oral dosing produced no benefit [21].

Remdesivir (**Figure 3**) is a prodrug of adenosine analogue with *in-vitro* activity against MARV and demonstrated efficacy against in MARV infected macaques 4 - 5 days post-exposure at once daily doses of either 5 mg or 10 mg for 12 days [22].

5.2. Small Molecule Inhibitors

Small molecules are compounds that bind to receptors and may have a desired activity when bound without having any intrinsic activity themselves. MARV VP40 is thought to be responsible for the suppression of type 1 interferons (IFN) by blocking the type 1 IFN-induced activation of Jak-1, thus preventing the immune system from responding to the virus [23]. This makes MARV VP40 an important potential drug target for drug discovery. A study by Luthra P *et al.*, sought to find potential small molecule inhibitors of mVP40 IFN inhibition by designing and optimising a high-throughput screening assay in 384-well plate format to identify compounds that overcame mVP40 inhibition of IFN. Three (3) hit compounds were identified, azaguanine-8, tosufloxacin hydrochloride and linezolid [24].

5.3. Monoclonal Antibodies

Monoclonal antibodies are immunoglobulins that have a high specificity for an antigen or epitope and have broad clinical and experimental medical uses. A human monoclonal antibody, MR 191-N, was studied in guinea pigs and NHPs after they demonstrated protection against MARV lethal challenge in mice [25]. In rhesus macaques at 50 mg/kg intravenously given on days 4 and 7 post-infection, all three treated animals survived. Human trials for MR 191-N are planned [26]. Several licenced monoclonal therapies have been used in other outbreaks, such as the 3-antibodycocktail (ZMapp) in the Ebola virus outbreak in West Africa, which led to improved outcomes in the recipients compared to those receiving supportive care in RCTs [25]. Thus, monoclonal antibodies remain an important class of possible therapeutics for the MARV.

6. Vaccines

Vaccine development for the MARV started soon after the discovery of the virus but with little success. The continued re-emergence of the Marburg virus highlights the need for vaccines to prevent future MVD outbreaks. The MARV glycoprotein (GP) is the main antigen used in all successful vaccine candidates and confers protection against multiple strains of the MARV and Ravn *viruses [27]*. The vaccine approaches include multi-dose, single-dose, fast-acting, live-attenuated non-replicating, and replicating viral regimens.

6.1. Adenovirus-Vectored Vaccines

A recent Phase I, open-label, dose-escalation trial of the cAD3-Marburg vaccine conducted by the Walter Reed Army Institute of Research clinical trials in the US on healthy adults aged between 18 and 50 years old showed that the vaccine was safe and immunogenic with a safety profile similar to previously tested cAD3-vectored filovirus vaccines. About 95% of the participants produced a glycoprotein-specific antibody response at four weeks after a single vaccination, which remained in 70% of participants at 48 weeks [28]. Phase II trials in Africa are planned for 2023. This is a major milestone in the development of an effective vaccine.

6.2. Recombinant Vesicular Stomatitis Virus (rVSV) Vaccine

In a study by Mire *et al*., cynomolgus macaques were immunized with rVSC-MARV-GP and challenged with MARV approximately 14 months after vaccination [29]. This resulted in the cohort of six animals having anti-MARV-GP IgG throughout the pre-challenge period. In the post-challenge period, none of the vaccinated animals showed any signs of clinical disease or viremia, whereas two controls exhibited symptoms consistent with MARV infection and both succumbed [30]. Even with 100% protective efficacy, no Phase I clinical trial has been performed yet [25].

6.3. DNA Vaccines

DNA vaccines against filoviruses have a good safety profile in NHP trials, are easy to produce, and have the potential to induce humoral or cellular immunity, although they have demonstrated limited immunogenicity in clinical trials [25].

The establishment of the MARVAC, a WHO-led consortium to promote international cooperation in the development of MVD vaccines, is a step in the right direction. This consortium will build on the previous success of WHO working groups on COVID-19 vaccines by rapidly sharing scientific findings and protocols [27].

7. Screening of Natural Products for Lead Compounds

Natural products comprise chemical compounds derived from living organisms such as fungi, plants, moulds, microorganisms, marine organisms, and terrestrial vertebrates, and invertebrates and have been a primary source of medicines for humanity [31]. One such product examined for possible anti-MARV activity is pinocembrin (5,7-dihroxyflavanone), a flavanone found in damiana (Turneradiffusa), ginger (*Zingiber officinale*), wild majoram (Lippiaoriganoides), honey, etc. This compound has shown antimicrobial, anticancer, anti-inflammatory, and neuroprotective activity [32]. Pinocembrin (**Figure 4**) was used by Akash S. *et al*. in a computer-aided drug design study to evaluate the activity of pinocembrin against Marburg and Monkeypox viruses [33]. The study used the Marburg virus- Musoke Kenya 1980 (PDB 4OR8) for docking with the best analogues having a binding affinity of −8.3Kcal/mol. Another natural product examined for activity against MARV is coptisine (**Figure 5**), a quaternary alkaloid generated from benzylisoquinoline through phenolic oxidation. This compound was examined in a CADD study and modified via the addition of various functional groups to assess its structure-activity relationships (SARs). The use of natural products as possible drug sources cannot be neglected, especially when we consider that most drugs in use are derived from natural sources.

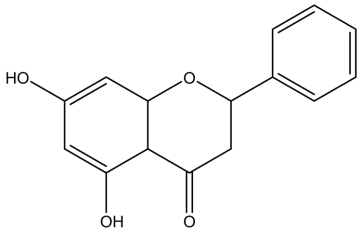

Figure 4. Pinocembrin.

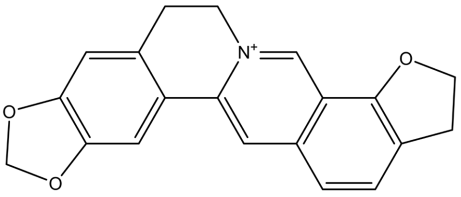

Figure 5. Coptisine.

8. Computational Methods

Drug discovery and development of a novel drug is a complex and risky process that takes 10 - 14 years and costs more than a billion dollars [34]. Computational methods have been developed to rationalize the process by reducing costs, duration, and attrition rates [35]. Quazi *et al*., (2021) used a CADD-based approach to identify the drug-like compounds inhibiting the replication of the Marburg virus' viral protein (VP40) using the antiviral agent favipiravir as the lead compound. Using PubChem, an online database, the researchers retrieved 3000 compounds based on structural similarity. Lipinski's rule was applied, followed by molecular-based docking and the selection of a screening ligand complex with VP40 based on S-score. After evaluating their binding energy using Autodock 4.2, four compounds (CID-67534452, CID-72201087, CID-123273976, and CID-153708661) were identified that showed the strongest binding energy with VP40 and a stronger inhibition effect than favipiravir.

In a study by Quazi, Gavas, *et al*. (2021), CADD was used to identify compounds that could inhibit the replication of VP40. The pharmacophoric screening was done using ZINCPharmer, a free pharmacophore search software, which yielded 32456 compounds. Lipinski's rule was used to predict drug-like compounds. One hundred compounds were found to have close interaction with VP40. A binding energy analysis of the compounds found that 50 had stronger binding energy than favipiravir after using the molecular working environment Lig-X algorithm to compare binding energy. ADMET analysis predicted five compounds (ZINC95457352, ZINC38752258, ZINC38752253, ZINC39272175, and ZINC38752377) with passable ADMET parameters and a strong effect against Marburg VP40 [36].

In yet another study, Quazi, Gavas, *et al*., (2021) used an insilico drug design technique to discover new drug-like structures that inhibited VP35 replication. The researchers used PubChem, which yielded 4260 compounds that exhibited more than 90% structural-based similarity. Molecular docking was performed using AutoDock 4.2 and ligands were selected based on docking/ S-score lower than the reference, CID-5477931. After evaluating their binding energy strength and ADMET analysis, only CID-3007938 and CID-11427396 showed the most vital bonding energy and a strong inhibitory effect with VP35 [37].

9. Conclusion

The recent outbreaks of the MARV have reignited the need for further research into new vaccines, drug therapies, and other public health interventions, especially considering the MARV's close relationship to the deadly Ebola virus, in the wake of the COVID-19 pandemic. MARV has high mortality rates that require the development of safe vaccines, drugs, and concrete government policies to reduce human-to-human transmission, especially in Africa, a continent with poor healthcare systems. Drug discovery efforts through multiple approaches are encouraged. The repurposing of currently existing antivirals is an easy approach

as the safety profile of the drugs is already established. Vaccines remain the best intervention from a public health perspective and efforts to obtain a vaccine, especially through consortiums like the MARVAC must be supported. Computational approaches to drug development through, for example, molecular docking, allow for timely and more targeted drug development while reducing the high attrition rates associated with drug discovery. Plants also remain an important source of therapeutics as several drugs are derivatives of natural products. Thus, research into possible therapeutics for MVD remains a very important tool to combat future outbreaks.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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