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Review Article

A Promising Future in Rabies Prevention: A Review of RBI-4000, a Self-Replicating RNA Vaccine

Vanya Gupta[1], Jugal Kishore[2], Seema Rani[3], Sanjeev Bansal[4]

[1]Post Graduate, [3]Professor & Head, Department of Pharmacology, BPSGMC, Sonipat, Haryana, India
[2]Director Professor & Former Head, Department of Community Medicine, VMMC, New Delhi
[4]Professor, Department of Orthopedics, BPSGMC, Sonipat, Haryana, India
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I N F O

Corresponding Author:
Jugal Kishore, Department of Community Medicine, VMMC, New Delhi
E-mail Id:
jk@drjugalkishore.com
Orcid Id:
https://orcid.org/0000-0001-6246-5880
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A B S T R A C T

Rabies remains a significant global health burden, claiming an estimated 59,000 human lives annually, predominantly in low-resource settings. Traditional vaccines, while effective, pose logistical challenges related to multi-dose regimens, cold chain requirements, and accessibility. Recent advancements in RNA-based vaccine technology offer promising alternatives. RBI-4000, a self-replicating RNA (srRNA) vaccine developed by Replicate Bioscience, is emerging as a potential breakthrough in rabies prophylaxis. This review gives a detailed look at how RBI-4000 was developed, how it works, its testing results, its benefits compared to current vaccines, and its possible impact on eliminating rabies worldwide. It also discusses potential applications of the self-replicating RNA platform for other viral diseases and explores challenges related to vaccine hesitancy, regulatory approval, and large-scale deployment.

Keywords: Rabies, RNA Vaccine, Prophylaxis, RBI-4000

Introduction

Rabies is a viral zoonotic disease caused by the rabies virus, a member of the Lyssavirus genus. It is an acute viral zoonotic disease that affects the central nervous system (CNS) of all warm-blooded animals, including mammals, and is found in more than 150 countries and territories. As there is no treatment available to save those affected, the disease is invariably fatal. But, with the presently available different rabies immunobiological, i.e., anti-rabies vaccines (ARV) and rabies immunoglobulins (RIG), the disease is almost 100% preventable. Globally, approximately 59,000 deaths occur due to this disease annually, and dogs the primary vectors in almost 99% of the cases.[1] From India alone, there are about 1/3rd, i.e., approximately 20,000 deaths are due to human rabies, and 97% of them are caused by dogs.[2,3] The disease has a nearly 100% fatality rate once clinical symptoms appear, making prophylaxis critical. Current rabies vaccines require multiple doses and adjuvants, posing challenges in regions with limited healthcare access. The advent of RNA-based vaccines has revolutionised immunisation strategies, with RBI-4000 leading the way as a novel self-replicating RNA vaccine designed for rabies prevention.

This article provides a comprehensive review of RBI-4000, its scientific foundation, clinical development, immunological efficacy, and its potential implications for the future of rabies prophylaxis. It also explores the broader implications of self-replicating RNA technology

in vaccine development, its potential for integration into global vaccination programmes, and future avenues for research and development.

Rabies Prophylaxis: An Overview

Current Vaccination Strategies

Currently, rabies prophylaxis involves:

- **Pre-exposure prophylaxis (PrEP):** This is given to high-risk individuals such as veterinarians, laboratory workers, and travellers to endemic areas.
- **Post-exposure prophylaxis (PEP):** Consisting of immediate wound care, rabies immunoglobulin (RIG), and a series of rabies vaccine doses administered over multiple weeks. Rabies Monoclonal Antibodies (R-mAb) are much cheaper, permit longer-term storage, etc., and hence could offer a more standardised, accessible, affordable, and equally efficacious and safer alternative to RIG.[4]

Challenges with Current Vaccines

The need for multiple doses, high production costs, cold chain logistics, and occasional shortages limit widespread accessibility, particularly in rural and low-income regions. With the PEP, the compliance for the full course of ARV is less than 50%.

Need for Novel Vaccination Strategies

The limitations of traditional rabies vaccines necessitate the exploration of novel approaches that offer:

- Enhanced immunogenicity with lower doses.
- Single-dose efficacy to increase compliance and reduce logistical burdens.
- Scalability for mass production and rapid deployment in outbreak situations.
- Improved thermostability to reduce dependency on cold chain infrastructure.

Literature Review

Historical Perspective on Rabies Vaccines

The first rabies vaccine was developed by Louis Pasteur in 1885, marking a milestone in medical history. Since then, rabies vaccines have evolved from nerve tissue-based formulations to modern cell culture vaccines. Early vaccines, such as the Semple vaccine, were associated with adverse effects, including neurological complications, leading to the development of safer alternatives like human diploid cell vaccines (HDCV) and purified Vero cell rabies vaccine (PVRV).[5]

Existing Rabies Vaccines and Their Limitations

The existing rabies vaccines have been extensively studied, with primary reliance on inactivated virus vaccines such as the human diploid cell vaccine (HDCV) and purified Vero cell rabies vaccine (PVRV). These vaccines have demonstrated high efficacy but require multiple doses over extended periods, leading to challenges in compliance and accessibility.[6] This prolonged vaccination schedule can be challenging in endemic regions where access to healthcare is limited. Additionally, the dependence on a cold chain for vaccine storage and transportation poses logistical challenges in low-resource settings (WHO, 2018). Efforts to develop alternative vaccine strategies that reduce dosing regimens and cold chain dependency have led to novel research avenues, including RNA-based vaccines.

Advancements in RNA-Based Vaccine Technologies

Recent developments in RNA vaccine technology have shown promise in addressing the limitations of traditional rabies vaccines. Messenger RNA (mRNA) vaccines have been successful in preventing infectious diseases such as COVID-19, demonstrating rapid adaptability and high efficacy.[7] Self-replicating RNA (srRNA) vaccines represent an evolution of this technology, enabling prolonged antigen expression and stronger immune responses with lower doses.[8]

Comparative Studies on Novel Rabies Vaccines

Several preclinical studies have explored the efficacy of RNA-based vaccines in rabies prophylaxis. Studies conducted on animal models indicate that srRNA vaccines can elicit neutralising antibody titers comparable to those induced by traditional rabies vaccines.[9] Additionally, phase I clinical trials on RNA-based vaccines for other viral diseases, including influenza and Zika, have demonstrated their potential for rapid scalability and adaptability to emerging pathogens.[7] The ability to induce strong cellular and humoral immune responses with fewer doses further supports the application of RNA vaccines for rabies prevention and control.

Challenges in RNA Vaccine Implementation

Despite the promising nature of RNA vaccines, challenges remain in terms of public acceptance, regulatory approvals, and large-scale production. Vaccine hesitancy, fuelled by misinformation about RNA technology, has posed hurdles in the deployment of new vaccines.[10] Additionally, while lipid nanoparticle (LNP) delivery systems enhance RNA stability, further research is needed to improve thermostability and long-term storage options for global distribution.[11]

Mechanism of Action

Self-replicating RNA (srRNA) vaccines use engineered RNA molecules encoding viral antigens, along with replicase enzymes that allow in vivo amplification. This mechanism prolongs antigen presentation and enhances immune responses, allowing for lower initial dosing. Unlike conventional mRNA vaccines that rely on external amplification, srRNA vaccines leverage intracellular

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replication, leading to prolonged protein expression and a stronger immune response.

Advantages of srRNA Vaccines

- **Dose-sparing effect:** Effective immunity with lower antigen levels reduces production costs that could lead to the availability of the vaccine at a lower cost.
- **Prolonged antigen expression:** This srRNA vaccine provides extended immune system stimulation compared to traditional inactivated or subunit vaccines.
- **Reduced cold chain dependency:** The vaccine is a more stable formulation compared to conventional vaccines, improving accessibility in resource-limited regions.
- **Potential for rapid adaptability:** Its modular design allows for rapid modifications to address emerging viral variants.

Development of RBI-4000

Engineering of RBI-4000

RBI-4000 was developed using:

- Codon- optimised sequences for enhanced protein expression and immunogenicity.
- Regulatory RNA elements to increase stability and translation efficiency.
- A lipid nanoparticle (LNP) delivery system for effective cellular uptake, ensuring RNA integrity and targeted immune stimulation.

Preclinical Studies

- **Animal Models:** Mouse, ferret, and non-human primate studies demonstrated high seroconversion rates, indicating strong protective immunity.
- **Neutralising Antibody Response:** Induced high titres of virus- neutralising antibodies within two weeks, surpassing WHO-recommended protective levels.[6]
- **Safety Profile:** No adverse reactions, significant inflammatory responses, or toxicity were noted in preclinical trials, suggesting a strong safety profile compared to traditional live-attenuated vaccines.

Clinical Evaluation of RBI-4000

Phase I Clinical Trial

A first-in-human Phase I clinical trial assessed RBI-4000 in healthy adult volunteers. A randomised, placebo-controlled, dose-escalation study spanning multiple sites across the U.S. and Europe was carried out involving 100 individuals who were divided into different dosing cohorts, including single-dose and prime-boost regimens. The endpoints were safety, tolerability, and immunogenicity, measured through seroconversion rates and neutralising antibody titres. No serious adverse events were reported, indicating a favourable safety profile. Ninety percent of participants achieved protective neutralising antibody levels after a single low-dose injection, with seroconversion rates comparable to or exceeding standard rabies vaccines.

Comparisons to Existing Vaccines

RBI-4000 is a much better vaccine than existing vaccines.[12] RBI-4000 achieved comparable or superior immunity to standard cell-culture rabies vaccines such as RabAvert and Verorab. It required fewer doses, making it advantageous for both PEP and PrEP scenarios. It provides a faster immune response, potentially reducing the critical period of susceptibility post-exposure.

Global Impact and Implementation

Addressing Vaccine Accessibility

- The low-dose efficacy of RBI-4000 allows for mass production at reduced costs, increasing accessibility in endemic regions.
- Stability at moderate temperatures could minimise cold chain dependency, making it viable for deployment in remote areas.
- RNA-based vaccines such as RBI-4000 can be produced faster than traditional vaccines, reducing the time required to respond to rabies outbreaks.
- The ability to generate large vaccine stocks with minimal infrastructure can aid in rapid immunisation campaigns in developing countries.
- Governments and global health organisations, including the WHO and GAVI, could facilitate funding and distribution strategies to enhance accessibility.

Integration into Rabies Elimination Programs

- The WHO's goal of eliminating human rabies deaths by 2030 could be significantly supported by RBI-4000's scalability and single-dose efficacy.
- Potential for inclusion in national immunisation schedules, improving routine vaccination coverage, and reducing overall incidence rates.
- Combining RBI-4000 with existing rabies vaccination programmes for animals could create a holistic approach to rabies elimination by controlling transmission at both human and animal levels.
- Collaborative efforts between governments, private vaccine manufacturers, and international health organisations can improve the implementation of RBI-4000 in low-income countries.
- Training healthcare professionals on the administration and benefits of RBI-4000 can enhance public trust and compliance with vaccination programmes.

Economic and Social Benefits

- Reducing rabies incidence through effective vaccination can significantly lower the economic burden associated with post-exposure prophylaxis (PEP) and long-term medical treatments.

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- A successful implementation of RBI-4000 in endemic regions can lead to improved public health outcomes, reducing mortality rates and healthcare costs.
- Increased global availability of RBI-4000 may encourage research into other RNA-based vaccines for neglected tropical diseases, fostering further innovation in vaccine technology.
- Widespread use of a single-dose rabies vaccine could decrease the need for extensive follow-up healthcare visits, reducing the strain on medical infrastructure in resource-limited settings.

Expanding access to the RBI-4000 has the potential to transform global rabies prevention efforts, reducing deaths, healthcare costs, and logistical challenges associated with traditional vaccines. By integrating this vaccine into national and international public health frameworks, significant strides can be made toward achieving global rabies elimination goals.

Addressing Vaccine Accessibility

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Integration into Rabies Elimination Programmes

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Challenges and Future Directions

Remaining Scientific Questions

- Long-term durability of immune responses and booster requirements.
- Optimisation of dosage and administration routes for maximal efficacy.
- Potential combination with other viral antigens for broader protective capabilities.

Regulatory and Ethical Considerations

- Expedited approvals through emergency regulatory pathways, considering the vaccine's transformative potential.
- Addressing public concerns regarding RNA-based vaccines, ensuring transparency in clinical trial data, and post-marketing surveillance.

Role of Industries

Various roles of the industries[13] are highlighted:

- **Role of the Pharmaceutical Industry:** In order to support innovation and research for effective dosing regimens, the pharmaceutical industries have a vital role to play. They may ensure that at every level of health facility, Anti Rabies Serum (ARS) and Anti Rabies Vaccine (ARV) are available to every animal bite victim at a lower cost so that the state and central governments can afford them for the larger population.[13]
- **Role of the Diagnostic Industry (Pathology and Laboratory Medicine):** The strengthening of diagnostic laboratories for rabies includes the introduction of a standardized protocol to be followed for diagnosis, so that a nationwide uniform process can be adopted in all diagnostic laboratories in India. In order to provide recommended antemortem as well as postmortem diagnostic facilities, it is further required to establish referral laboratories for rabies as per the programmed requirements at all levels (regional, state, and national).[13]
- **Role of IT Industry:** There is a lack of a proper method of sharing data between the veterinary and human sectors. The development of a portal has been suggested by the National Action Plan for Dog Mediated Rabies Elimination (NAPRE) along with an electronic surveillance system with GPS.[13]
- **Role of Media and Public Relations Industry:** Media houses and public relations industries may contribute to the introduction of standardised Information Education and Communication (IEC) materials for wider circulation to make people more aware of rabies. They can also help in making people understand that appropriate treatment for rabies, if provided on time, can prove to be life-saving. In order to undertake IEC activities, it is essential to develop adequate IEC material. It is also important to frame the required IEC strategy for the target audience, including but not limited to veterinary and health professionals, adolescents and youth, school and college-going students, and community workers.[13]

Future Research Prospects

- Combining RBI-4000 with adjuvants to further enhance immunogenicity.
- Investigating multivalent srRNA vaccines against additional viral threats such as Lyssaviruses and coronaviruses.

Conclusion

RBI-4000 represents a groundbreaking advancement in rabies prophylaxis. Its self-replicating RNA technology

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offers a potent, scalable, and cost-effective alternative to traditional rabies vaccines. The ability to elicit robust immune responses with a single-dose regimen has the potential to significantly improve compliance, particularly in regions where access to healthcare is limited. Additionally, the reduced dependency on cold chain storage makes it an ideal candidate for global distribution, including in low-resource settings.

Despite its promise, challenges remain in terms of regulatory approval, public acceptance, and long-term immunogenicity. Further research is necessary to assess the duration of immunity and the need for booster doses. Additionally, addressing vaccine hesitancy through public education and transparent communication about RNA-based vaccine safety will be critical for widespread adoption.

Looking ahead, the integration of RBI-4000 into global rabies elimination programmes could play a crucial role in achieving the World Health Organisation'sgoal of zero human rabies deaths by 2030.Conflict of Interest: None declared

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