Review

The Clinical Advantages of Anti-Rabies Monoclonal Antibodies in Post-Exposure Prophylaxis — Worldwide, 2016–2025

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ABSTRACT

Post-exposure prophylaxis (PEP) represents the critical intervention for preventing rabies and comprises three essential components: thorough wound cleansing, vaccination, and administration of rabies immunoglobulin (RIG) or monoclonal antibodies (mAbs) for category III exposures. The World Health Organization (WHO) endorses the use of mAb cocktails as an effective replacement for RIG in PEP protocols. Since 2016, four anti-rabies monoclonal antibodies (RmAbs) have received clinical approval for use in India and China. This article provides an overview of the current research status of RmAb. By reviewing clinical studies related to RmAb, it highlights the clinical advantages of RmAb over HRIG in terms of efficacy, accessibility, safety, acceptability, and clinical application in special populations. Additionally, it explores the future clinical prospects of RmAb, including their use in extremely high-risk cases, their impact on circulating antibodies, and their potential role in rabies treatment.

Rabies is an acute zoonotic disease with global prevalence and a case-fatality rate approaching 100%, causing approximately 59,000 deaths annually (*1*). China ranks second worldwide in rabies-related fatalities, and the number of reported deaths increased again in 2024 — the first increase following a continuous 17-year decline (*2*). The administration of RIG represents a critical component of PEP, providing essential early protection before vaccine-induced immunity develops. However, HRIG, the most widely utilized RIG, faces global supply shortages due to production constraints. In China, the utilization rate of passive immunization agents among post-exposure populations remains remarkably low at only approximately 15% (*3*). The *Guidelines for Prevention and Disposal of Rabies Exposure (2023)* includes content related to RmAb, mandating the use of RmAb at approved dosages (*4*). This paper examines the advantages of RmAb and explores its future clinical applications.

GLOBAL OVERVIEW OF RmAb RESEARCH AND DEVELOPMENT

The rabies virus glycoprotein contains six major antigenic sites: I, II, III, IV, G5, and 'a' (*5*). Through recombinant DNA technology, RmAb can be produced industrially to specifically target and bind these glycoprotein antigenic sites, thereby blocking viral interaction with nerve cells and providing rabies prevention (*6*). The WHO position paper recommends RmAb targeting two or more distinct antigenic sites as an alternative to RIG in PEP (*7*). Currently, 11 RmAb products worldwide have either reached market approval or remain under investigation, as detailed in Table 1. Four products have achieved market authorization: two from India — Rabishield (2016) and Twinrab (2019) — and two from China — Ormutivimab (2022) and Zamerovimab/Mazorelvimab (2024) (*8*–*9*).

CLINICAL ADVANTAGES OF RmAb IN PEP, COMPARED TO RIG

Superior Availability, Safety, and Patient Acceptability

The WHO initially recommended RmAb as a replacement for RIG based on availability and safety considerations in the 2018 rabies vaccine position paper (*7*).

Regarding availability, HRIG, as a blood-derived product, frequently experiences shortages in rabies-endemic countries. In contrast, RmAb demonstrates significant production and supply advantages through several key factors: 1) sustainable large-scale manufacturing ensures a stable supply and controllable

TABLE 1. RmAb Products approved and under-researched worldwide.

Name	Antigenic epitope sites	Stage	Approved Country	Active ingredient
Rabishield	Ⅲ	Approved	India (2016)	1 human-derived monoclonal antibody
Twinrab	Ⅱ, Ⅲ	Approved	India (2019)	2 murine-derived monoclonal antibodies
Ormutivimab	Ⅰ	Approved	China (2022)	1 human-derived monoclonal antibody
Zamerovimab/Mazorelvimab	Ⅲ, G5	Approved	China (2024)	2 human-derived monoclonal antibodies
GR1801	Ⅰ, Ⅲ	Under application	NA	1 human-derived bispecific antibody
NM57S /NCO8	Ⅰ, Ⅱ	Phase II	NA	2 human-derived monoclonal antibodies
CL184	Ⅰ, Ⅲ	Phase II (withdrawn)	NA	2 human-derived monoclonal antibodies
CBB1	Undisclosed	Phase I	NA	1 human-derived monoclonal antibody
RVC20 /RVC58	Ⅰ, Ⅲ	Preclinical	NA	2 human-derived monoclonal antibodies
11B6 /NP-19-9	Ⅱ, Ⅲ	Preclinical	NA	2 human-derived monoclonal antibodies
CR57/RV08 /RV3A5	Ⅰ, Ⅱ, Ⅲ	Preclinical	NA	3 human-derived monoclonal antibodies

Abbreviation: RmAb=anti-rabies monoclonal antibody, NA=not applicable.

costs, 2) industrialized quality production guarantees high batch-to-batch consistency, stable potency, and extended shelf life. For example, Rabishield (launched in India) was specifically developed to address HRIG availability challenges. This single-component, low-potency formulation (3.3 IU/kg) is priced approximately 20% higher than equine RIG (ERIG) but remains lower than HRIG, providing an affordable and accessible alternative for PEP (*9*).

In terms of safety, HRIG poses inherent risks as a blood-derived product, including potential transmission of blood-borne pathogens and the presence of multiple heterologous proteins. ERIG presents additional safety concerns as a heterologous protein product, carrying risks of anaphylactic reactions that necessitate mandatory skin testing prior to administration. In contrast, RmAb demonstrates superior safety characteristics with its precisely defined composition and complete absence of blood-borne pathogen transmission risk. The two human-derived monoclonal antibodies approved in China utilize advanced manufacturing processes, achieving purities exceeding 99.9% while remaining completely free of heterologous proteins. Clinical evidence from the Phase III trial (NCT04644484) demonstrates that Zamerovimab/Mazorelvimab produces significantly lower rates of injection site adverse reactions compared to HRIG: swelling (16.9% *vs.* 34.4%), pain (4.7% *vs.* 7.6%), and erythema (4.3% *vs.* 5.6%) (*10*). This enhanced safety profile substantially improves patient compliance and promotes better wound healing outcomes during PEP.

Regarding patient acceptability, RmAb offers considerable practical advantages over traditional immunoglobulins. The viscosity of RmAb is approximately one-fourth that of HRIG, approaching isotonic conditions that facilitate easier infiltration injection with minimal resistance. Furthermore, the required volume is significantly reduced: only 1 mL of RmAb per 10 kg body weight compared to 2 mL of HRIG for the same weight category. These characteristics enable RmAb to deliver more comprehensive neutralizing antibody coverage at anatomically restricted exposure sites, substantially reducing the tissue distension-related pain commonly experienced during clinical administration. This improved tolerability profile makes RmAb significantly more acceptable to patients undergoing PEP treatment.

Enhanced Efficacy

The WHO recommends using mAb cocktails that target at least two non-overlapping antigenic epitopes as alternatives to RIG in PEP, thereby reducing the risk of immune escape following rabies virus mutations. Both Twinrab (a murine-derived mAb cocktail) and Zamerovimab/Mazorelvimab (a humanized mAb cocktail) satisfy WHO criteria and have demonstrated dose-dependent protective effects in animal models, with significantly superior efficacy compared to HRIG (*11*–*12*). Compared to Twinrab, Zamerovimab/Mazorelvimab has been validated against a broader spectrum of rabies virus strains and confirmed to achieve 100% neutralization efficacy in *in vitro* neutralization experiments (*13*). Due to its potential interference with vaccines, HRIG is restricted to a clinical dose of 20 IU/kg (*14*), and live virus vaccines (e.g., measles) must be avoided within three months after HRIG administration. However, RmAb

demonstrates minimal interference with vaccines. Twinrab at 40 IU/kg and Zamerovimab/Mazorelvimab at 0.3 mg/kg have both significantly exceeded the HRIG dose (20 IU/kg); notably, Zamerovimab/Mazorelvimab at 0.3 mg/kg (*13*), when converted to potency units, is approximately 447.6±156.6 IU/kg (*14*). In the phase III clinical trial (NCT04644484), Zamerovimab/Mazorelvimab demonstrated the ability to generate higher levels of early rabies virus neutralizing antibodies (RVNA) than HRIG for the first time, providing rapid and sufficient RVNA protection during the two-week window before vaccine-induced antibodes take effect (*10*).

Enhanced Evidence Base for RmAb Use in Special Populations

In PEP protocols, elderly individuals, pregnant women, and children represent special populations requiring heightened safety considerations due to potentially compromised immune responses and stricter drug safety requirements. For these vulnerable groups, physicians have historically relied on empirical treatment approaches, as evidence-based clinical trial data remained unavailable. The two RmAb products approved in China have undergone comprehensive research in these populations, providing robust clinical evidence. Regarding elderly patients, the phase III trial of Ormutivimab enrolled 11 participants aged ≥65 years, demonstrating comparable efficacy and safety profiles to participants <65 years (*15*). Similarly, the phase III trial of Zamerovimab/Mazorelvimab enrolled 137 participants aged ≥60 years, showing equivalent efficacy and safety outcomes compared to younger participants (*10*). For pregnant population, data from the phase III clinical trial of Zamerovimab/Mazorelvimab included seven pregnant participants and revealed no adverse reactions in either the mothers or their fetuses. Ormutivimab has successfully completed pediatric clinical trials and received expanded indication approval for children aged two years and above in 2024. Zamerovimab/Mazorelvimab has initiated comprehensive pediatric clinical trials (CTR20244297), enrolling subjects across three age groups: 12–17 years, 6–11 years, and 0–5 years, with the objective of expanding application to all pediatric populations. Compared to HRIG, both RmAb products marketed in China demonstrate superior safety profiles and enhanced reliability for use in these special populations.

FUTURE PERSPECTIVES ON THE CLINICAL APPLICATION OF RmAbs

The Use of RmAb in Extremely High-risk Cases

Both the WHO and Chinese guidelines classify rabies exposure into three categories based on contact patterns and exposure severity (*4*,*7*). In 2022, researchers proposed an innovative academic framework that introduces a Grade IV exposure classification beyond the existing three-tier system. This additional category would identify exceptionally severe cases, such as extensive bites to the head, face, or neck regions. This enhanced classification aims to identify patients facing extremely high infection risks, where the incubation period may be as brief as one week. The corresponding patient management protocol emphasizes the urgent administration of sufficient or even ultra-high doses of passive immunization agents (*16*). Both the refined risk stratification system and the enhanced passive immunization protocols are designed to ensure optimal safety outcomes for high-risk populations. Regarding passive immunization strategies, the more potent RmAb agents not only demonstrate superior specific activity but also exhibit enhanced tissue diffusion properties compared to traditional alternatives.

Clinical Significance of RmAb-Generated Circulating Antibodies

Chinese guidelines recommend that after complete wound infiltration with passive immunization agents, any remaining product should be administered intramuscularly at sites distant from vaccine injection locations. In contrast, some countries advocate exclusively for local wound infiltration of passive immunizing agents. This divergence reflects not only considerations of agent availability and cost-effectiveness, but also varying clinical assessments of the protective value conferred by circulating antibodies generated through distant-site administration. In clinical scenarios, rabies virus may have limited residence time at wound sites before entering systemic circulation, or the virus may persist undetected in occult injuries that escape immediate treatment. Under these circumstances, early-onset circulating antibodies could provide critical neutralization capacity when viruses breach the initial wound barrier. However, the residual RIG volume remaining after wound

infiltration proves insufficient to generate protective levels of circulating antibodies when administered at distant sites. Only high-dose RmAb administration at remote anatomical locations can achieve clinically meaningful outcomes by producing adequate circulating antibody concentrations that meet seroconversion criteria rapidly, preceding vaccine-induced antibody development while avoiding interference with vaccine immunogenicity.

Potential Application of RmAb in Rabies Treatment

The development of effective rabies treatments has remained one of the most formidable challenges in clinical medicine (*17*), primarily due to the blood-brain barrier, which prevents large-molecule therapeutics from crossing from peripheral circulation into the central nervous system. Consequently, no effective treatments exist once clinical rabies symptoms manifest. Research demonstrates that even with ultra-high doses of macromolecular drugs, only a minimal fraction (approximately 0.02%) can penetrate the blood-brain barrier to reach the central nervous system (*18*). High-dose intravenous monoclonal antibody therapies have gained regulatory approval in both China and the United States for clearing intracranial amyloid-β plaques in Alzheimer's disease treatment, establishing a precedent for central nervous system penetration (*19*).

CONCLUSIONS

RmAbs demonstrate substantial clinical advantages over RIG in post-exposure prophylaxis, offering superior safety profiles, enhanced availability, and improved patient acceptability. These benefits are supported by robust evidence-based data from comprehensive clinical trials. The mAb cocktail formulations ensure broad-spectrum viral neutralization through complementary targeting of distinct antigenic epitopes, establishing an effective passive immunization strategy for clinical PEP protocols.

Critically, RmAbs overcome the inherent dosage constraints of traditional RIG, delivering substantially higher concentrations of neutralizing antibodies during the critical ultra-early post-exposure period without compromising vaccine efficacy. Beyond neutralizing viral particles at exposure sites, RmAbs rapidly elevate circulating antibody levels to achieve comprehensive immunological protection. The therapeutic potential of RmAbs for treating established rabies infections represents a paradigm shift that could transform clinical outcomes. Following successful completion of six global registration trials, Zamerovimab/Mazorelvimab has advanced to new drug applications across multiple rabies-endemic countries, including Turkey and Cambodia, in 2025. As clinical experience accumulates, RmAbs are positioned to become the preferred alternative to RIG in global PEP strategies, potentially enabling breakthrough advances in rabies treatment and supporting the ambitious goal of eliminating human rabies deaths worldwide by 2030.

CHALLENGES AND OPPORTUNITIES

Currently, RmAb products command relatively high prices compared to traditional alternatives. Additionally, given their recent market approval, RmAb-related products have not yet been incorporated into medical insurance reimbursement schemes across many regions. These dual factors substantially increase the financial burden on patients and limit widespread RmAb adoption. However, as additional products enter the market and industry competition intensifies, pricing is anticipated to become more accessible. Furthermore, RmAb products are expected to gain inclusion in national medical insurance reimbursement catalogs.

Despite numerous studies demonstrating the critical importance of passive immunizing agents in PEP, current utilization rates remain disappointingly low for both HRIG and RmAb products. This underutilization may stem from inadequate physician and patient education regarding rabies prevention protocols. Traditional passive immunizing agents possess inherent limitations that not only constrain their clinical utility but also perpetuate knowledge gaps concerning rabies passive immunization strategies. Moving forward, targeted educational initiatives for healthcare providers and patients should be implemented, leveraging the clinical advantages and evidence-based data supporting RmAbs. These efforts should be coupled with standardized PEP protocols that comply with national guidelines, ultimately supporting the global objective of achieving zero human rabies deaths by 2030.

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