Original Article

Safety assessment of the world's first novel cocktail of two monoclonal antibodies in WHO category-III animal-bite patients

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Abstract

Background: Rabies, a zoonotic disease, poses a significant global public health challenge, and post-exposure prophylaxis (PEP) is crucial for prevention. Monoclonal antibodies (mAbs) have emerged as a promising alternative to rabies immunoglobulins due to their high efficacy and standardized manufacturing process. **Materials and Methods:** A prospective, open-label post-marketing surveillance study was conducted with patients of WHO category-III suspected rabid animal bites. TwinRab™, a novel cocktail of docaravimab and miromavimab, was administered at a dosage of 40 IU/kg in and around the wound, along with the anti-rabies vaccine, which was administered intradermal as per Thai Red Cross regimen. **Results:** In this study, 200 subjects received TwinRab™ with a 100% completion rate. Three (1.5%) patients showed solicited local AEs, and two (1%) patients showed solicited systemic AEs, which were resolved after appropriate treatment intervention. The overall tolerability assessment showed positive ratings from doctors (94%) and patients (74%). **Conclusion:** The post-marketing surveillance study demonstrated the safety of TwinRab™ in patients who experienced category-III suspected rabid animal bites, thereby supporting its potential as an alternative option for PEP in the management of animal bite for the prevention of rabies.

Keywords: Adverse events, post-exposure prophylaxis, rabies, safety assessment, TwinRab™

Introduction

Rabies, a viral disease transmitted through animal bites, lurks as a silent threat in over 150 countries. This near-fatal infection infiltrates the central nervous system, causing excruciating symptoms and ultimately death if left untreated.[1] Though preventable through vaccination, rabies claims thousands of lives annually, primarily children in Asia and Africa.[2] The majority of human rabies transmissions, approximately 99%, are due to exposure to infected dogs, resulting in fatal outcomes. According to the National Center for Disease Control, in 2019, global rabies-related disability-adjusted life years (DALYs) were 782,052.30, which was 45.4% in 1990, and their estimated annual percentage change (EAPC) was −0.55%. Rabies is a significant public health issue, causing around 59,000 deaths each year worldwide. Dogs cause most of human infections, emphasizing the importance of widespread dog immunization initiatives. Individuals under the age of 15 years are the most

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affected by this catastrophe, making up 40% of the victims.[3] India is a significant global hotspot, accounting for 36% of worldwide deaths, with an estimated 18,000–20,000 fatalities annually.[4] Underreporting and misdiagnosis exacerbate the situation, indicating that the actual burden could be greater.[5] The economic cost amounts to US$8.6 billion yearly, but the human cost is incalculable.[6] The data highlights the critical necessity for enhanced initiatives in dog vaccination, public awareness campaigns, and better access to post-exposure prophylaxis (PEP) to achieve a rabies-free future.[7]

The American Association of Family Physicians (AAFP) plays a crucial role in providing essential guidance on rabies prophylaxis and the prevention and treatment of dog bites. Their recommendations stress the significance of immediate wound management post dog bite, emphasizing the need for prompt irrigation and infection risk assessment to prevent complications. Understanding key factors such as the circumstances of the bite, the animal's vaccination status, and the patient's medical history is vital in determining the appropriate course of action. AAFP underscores the importance of educating patients on preventive measures and recognizing infection signs to effectively manage dog bite injuries. Family physicians are pivotal in educating both parents and children on preventing dog bites and must possess the knowledge to treat bites effectively when they occur. Given the prevalence of dog bites, primary care providers and family physicians must be well-informed on managing and preventing such incidents to ensure optimal patient care and reduce the risk of rabies transmission.[8]

The National Center for Disease Control (NCDC) guidelines on rabies play a crucial role in providing essential information for healthcare professionals, especially primary care providers and family physicians. Primary care providers and family physicians are encouraged to consult these guidelines to ensure the proper handling of rabies cases, safeguarding both patients and them. The Federation of Family Physicians Association of India (FFPAI) aligns with the NCDC in a shared mission to eliminate dog-mediated human rabies deaths by 2030. This collaboration highlights the dedication of FFPAI and the NCDC to the global initiative of eradicating rabies transmitted by dogs by the year 2030.[9,10]

The WHO recommendation for PEP of category-III exposures consists of both rabies vaccine and rabies immunoglobulins (RIGs). RIGs are limited to only those individuals who have not been previously treated with a vaccine.[11,12] There are two types of serum-derived RIGs (human [HRIG] and equine [ERIG]) that have been available for decades, and recently, one humanized monoclonal antibody (mAb)-based RIG has been licensed in India.[13] The WHO points out that approximately 25% of exposures need to be given RIGs in endemic countries, but less than 1% end up receiving it.[14] In India, only 2%–3% of category-III animal-bite victims receive RIGs as part of PEP. This is because these RIGs, especially HRIG, are available at high cost only and are always in limited supply; having been derived from serum, they are associated with the risk of blood-borne pathogens. Furthermore, horse-derived RIGs have also been associated with anaphylactic reactions and serum sickness.[15,16] These limitations have led the WHO to recommend the development of alternative therapies.[17] Despite the availability of vaccines and immunoglobulins for rabies prevention, these treatments are often inaccessible to those in need, particularly in regions with limited access to medical care. Furthermore, the current vaccines have limitations, including barriers to adherence to recommendations and confusion about risk categories.[18]

A novel approach called TwinRab™ has been developed to address the challenges of rabies prevention. TwinRab™ is a combination of two monoclonal antibodies, docaravimab and miromavimab, which are monoclonal antibodies targeting specific epitopes within antigenic sites II and III of the rabies virus glycoproteins. Extensive preclinical and clinical studies have demonstrated the safety and non-inferiority of TwinRab™ to human RIG (HRIG) in terms of protective effect. It has been approved for use in India and is considered a significant advancement in the field of rabies prevention, offering a safe alternative to existing treatments.[19]

The present study was conducted to assess the safety of the TwinRab™ (cocktail of monoclonal antibodies docaravimab and miromavimab) in category-III animal-bite patients.

Methodology

Study design

In this open-label, single-arm, post-marketing surveillance study, the safety of the cocktail of monoclonal antibodies docaravimab and miromavimab (TwinRab™) was assessed in patients who received treatment for category-III animal bite.

Objective

The objective of this study was to assess the safety of TwinRab™ in patients according to WHO guidelines for category-III suspected rabid animal bites.

Study participants

A total of 200 healthy subjects (aged >2 years) who had not previously been administered anti-rabies vaccine (ARV) or had no history of animal bites in the past were enrolled for the assessment of the safety of the study vaccine (TwinRab™). Eligible subjects were males and females who fell under WHO category-III exposure(s) by a suspected rabid animal <72 hours prior to enrollment and <24 hours if exposed to the face, neck, hand, or fingers. Exclusion criteria for the participants included a history of any clinically significant disease that may interfere with the study outcomes, a history of thrombocytopenia or known bleeding disorders, subjects with known major congenital defects or serious chronic illness, and

subjects who had participated in any other clinical study within the last 30 days. All subjects gave written informed consent before randomization. TwinRab™ was infiltrated around the bite wound as per the WHO recommendation along with the ARV (given intradermal), which was administered intradermal on day 0. Routine general and systemic examination was also performed on day 0, 3, 7, and 28.

Ethical committee approval

The study was registered in the CTRI on November 2, 2022, with registration number CTRI/2022/11/046994, and approval was obtained from the independent ethics committee of Maulana Azad Medical College and Associated Hospital, New Delhi (Ref. No.: F.1/EC/MAMC/94/06/2022/06 Dated January 9, 2023).

Procedure

In this study, 200 individuals with suspected rabies exposures falling under WHO category III were recruited. TwinRab™, a novel cocktail of docaravimab and miromavimab, was administered at a dosage of 40 IU/kg in and around the wound, along with the ARV, which was administered intradermal as per Thai Red Cross regimen.

In the study assessing the safety of the TwinRab™ cocktail of monoclonal antibodies in patients with category-III animal bites, the FDA Toxicity Grading Scale was instrumental in evaluating the severity of adverse events related to rabies treatment. This standardized scale categorizes adverse events based on specific criteria, ensuring an objective assessment of the intervention's safety profile. By employing the FDA Toxicity Grading Scale, researchers systematically classified adverse events, providing a comprehensive understanding of the safety outcomes associated with the treatment.

Furthermore, all adverse events linked to the rabies vaccine in the study were defined using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0 vocabulary. MedDRA serves as a standardized medical terminology that facilitates the uniform coding and analysis of adverse event information in clinical studies, enhancing the accuracy and consistency of safety data reporting.[20]

Data capturing and statistical analysis

An electronic data capturing (EDC) system was utilized to transition patients' data from physical Case Report Forms (CRFs) to electronic CRFs. This enabled efficient and accurate data collection, storage, and management. Subsequently, statistical analysis was conducted using SAS®, Version 9.4 (SAS Institute Inc., USA).

Safety assessment

The safety was assessed by recording the adverse events (AEs) occurring during the study. All abnormalities found in clinical examination were noted as AEs. The solicited (injection site and systemic) AEs were recorded for 7 days post vaccination, and unsolicited (other) AEs were recorded for 35 days (+7 days) following the final dose of the PEP regimen for rabies.

Results

Disposition of participant

A total of 200 of the consented subjects enrolled in the study were randomized to receive TwinRabTM along with ARV injections. Of the 200 subjects, 193 subjects (96.5%) completed

Table 1: Disposition of participants

	Statistics	TwinRab™
Number of subjects enrolled	N	200
Number of subjects in safety population	N	200
Number of subjects who completed the study	*n* (%)	193 (96.5)
Number of subjects who did not complete the study	*n* (%)	7 (3.5)

Abbreviations: N = Number of subjects in the safety population which is used as the denominator to calculate percentages; n = Number of subjects for specific category.

Table 2: Demographic and baseline characteristics

Characteristic (unit)	Statistics	TwinRab™ (*n*=200)
Gender		
Male	*n* (%)	156 (78.00)
Female	*n* (%)	44 (22.00)
Age (years)	*n*	200
	Mean±SD	29.5±12.77
	IQR (Q1, Q3)	(20.0, 38.5)
	Min, Max	6.0, 67.0
Height (CM)	*n*	200
	Mean±SD	164.1±11.52
	IQR (Q1, Q3)	(160.0, 172.0)
	Min, Max	125.0, 185.0
Weight (KG)	*n*	200
	Mean±SD	57.3±15.61
	IQR (Q1, Q3)	(50.0, 66.0)
	Min, Max	19.0, 125.0
Age group		
Child (≥5 and ≤12 years)	*n* (%)	17 (8.50)
Adolescent (≥13 and ≤17 years)	*n* (%)	20 (10.00)
Adult (≥18 and ≤65 years)	*n* (%)	162 (81.00)
Geriatric (>65 years)	*n* (%)	1 (0.50)
Vital signs		
Respiratory rate: beats/min	*n*	200
	Mean±SD	17.3±1.29
	IQR (Q1, Q3)	(16.0, 18.0)
	Min, Max	15, 20
Systolic blood pressure, mmhg	*n*	200
	Mean±SD	123.1±8.16
	IQR (Q1, Q3)	(116.0, 129.0)
	Min, Max	102, 143
Diastolic blood pressure, mmhg	*n*	200
	Mean±SD	82.0±5.94
	IQR (Q1, Q3)	(77.5, 86.0)
	Min, Max	66, 100

the study and seven subjects were prematurely terminated due to lost to follow [Table 1].

Demographic and baseline characteristics

The demographic and baseline characteristics, as well as the history and location of animal bite wounds, are presented in Tables 2 and 3, respectively.

Safety

A total of five adverse events were reported in five (2.50%) subjects with TwinRab™. All reported adverse events had no relationship with the study vaccines. All the reported AEs resolved completely with/without supportive treatment during the study period. Local reactions were observed in 1.5% (n = 3) subjects. Most reported local reactions were swelling (1.00%) and erythema (0.50%).

Table 3: History and location of animal bite wound

History of bite wound	Statistics	Total (n=200)
Biting animal		
Dog	n (%)	180 (90.00)
Cat	n (%)	12 (6.00)
Monkey	n (%)	8 (4.00)
No. of category-III wounds		
Single or multiple transdermal bites	n (%)	200 (100)
Location		
Lower body - Legs	n (%)	175 (87.50)
Lower body - Thigh	n (%)	121 (60.50)
Lower body - Buttocks	n (%)	28 (14.00)
Lower body - Feet	n (%)	16 (8.00)
Lower body - Lower back	n (%)	5 (2.50)
Lower body - Genitals	n (%)	3 (1.50)
Lower body - Toes	n (%)	2 (1.00)
Upper body - Fingers	n (%)	9 (4.50)
Upper body - Hands	n (%)	8 (4.00)
Upper body - Upper arm	n (%)	4 (2.00)
Upper body - Head	n (%)	2 (1.00)

These local reactions were mostly reported in adults and geriatrics subjects (aged ≥18 and ≤65 years). Two subjects reported one systemic adverse event "fever" (1%). There were no serious adverse events (SAEs) or treatment-emergent adverse events leading to study termination or subject withdrawal from the study. The summary of AEs recorded during the study is presented in Table 4.

Overall tolerability assessment

In the TwinRab™ study involving 200 participants, both patients and doctors provided input for tolerability assessments at the conclusion of the therapy. A significant majority of patients (74.00%) and doctors (94.50%) rated the therapy's tolerability as "Excellent and Good," indicating a high level of satisfaction. In addition, a negligible 0.5% of patients fell into the "Fair" category, although no corresponding doctor assessments were recorded.

Discussion

In recent years, the emergence of TwinRab™ has offered a transformative alternative to conventional rabies immune globulins (RIGs) for PEP. By capitalizing on the inherent advantages of mAbs, TwinRab™ delivers heightened safety, efficacy, and affordability while addressing the global shortage of RIGs.[21] This study involving 200 participants demonstrated the safety and efficacy of TwinRab™ when administered alongside standard rabies vaccinations. Importantly, there were no severe complications or dropouts observed during the study period, affirming the patient's compliance with the study, the capability of the study site, and the therapy's suitability for widespread use. Dog bites were the primary cause of injuries, particularly affecting the lower limbs, underscoring the need for targeted preventive measures. TwinRab™ was shown to be non-inferior to RIGs in providing continuous protective immunity until day 84. Although there was a slight increase in adverse events compared to previous trials, the overall safety profile remained

Table 4: Adverse events occurred in the study

Age category	Local AEs	TwinRab™ (n=200)	
		No. of Subjects (%)	No. of events
In the overall age category (Child (≥5 and ≤12 years), Adolescent (≥13 and ≤17 years), Adult (≥18 and ≤65 years), Geriatric (>65 years))	Pain	0	0
	Erythema	1 (0.50)	1
	Swelling	2 (1.00)	2
	Tenderness	0	0
	Induration	0	0
Age category	**Systemic AEs**	**TwinRab™ (n=200)**	
		No. of Subjects (%)	**No. of events**
Overall (Child (≥5 and ≤12 years), Adolescent (≥13 and ≤17 years), Adult (≥18 and ≤65 years), Geriatric (>65 years))	Fever	2 (1.00)	2
	Headache	0	0
	Malaise	0	0
	Arthralgia	0	0
	Myalgia	0	0
	Nausea	0	0
	Vomiting	0	0

AE=Adverse Event; n=Number of subjects in the safety population which is used as the denominator to calculate percentages; n=number of subjects for specific category; n*=Number of subjects in specific age category. Note: The percentages are based on the safety population. If a subject had more than one local AE, they are only counted once for the relevant row of the table for the subject column, but all episodes are included in the episode column

commendable. TwinRab™ was administered at a maximum dose of 5000 IUs in this study without any AEs noted. Volume-wise, 8.33 mL of TwinRab™ was administered in our study as the maximum volume administered so far for TwinRab™ without any AEs noted.

The study by Fan *et al.* (2022)[14] compared TwinRab™ with RIGs in individuals with suspected rabies exposure, demonstrating comparable levels of protection and safety. Similarly, Kansagra *et al.*'s (2021)[22] open-label study confirmed TwinRab™'s continuous protection until day 84, matching the performance of RIGs.

Unlike single mAb therapies, TwinRab™ addresses the risk of viral escape by targeting two unique epitopes of the rabies virus glycoprotein. This dual-target approach enhances neutralization capability, even against variants with high mortality rates. Moreover, mAbs display exceptional specificity, minimal cross-reactivity, and favorable pharmacokinetics and pharmacodynamics characteristics, including longer half-lives.[23]

Passive immunization has been an essential component of PEP to prevent rabies for decades. The benefit of RIG in combination with vaccination in PEP of patients with severe bite wounds has been established through scientific evidence. Mollentze *et al.* (2014) and Haradanhalli *et al.* (2022) described efforts to prepare rabies immune globulin of human origin. A study by Hobart *et al.* (2021) led to a dose of 20 IU/kg proven to provide early protection without interfering with the active antibody response to anti-rabies vaccination. TwinRab™ at the dose of 40 IU/kg provides good protection against rabies and was found non-inferior to HRIG as per the phase-III study conducted by Zydus Lifesciences Ltd, Ahmedabad.[24-26]

The study subjects were representative of both sexes and varied age groups. In the present study, the safety profile of TwinRab™ was found to be in line with other published studies, with no SAEs reported. The current study reported only fever as a systemic reaction. Similarly, Lang *et al.* (2014) also showed only fever in a few subjects, whereas other systemic reactions were not observed. The most common local reactions (erythema and swelling) reported were also similar to those reported in other published studies.[27]

Based on the present clinical study, the safety and tolerability profile of TwinRab™ are good, with none of the patients reporting pain at the injection site. Haradanhalli *et al.*[28] (2013) reported that the incidence of local adverse events included pain at the injection site, erythema, itching, and systemic adverse events such as fever, malaise, headache, and body ache. A comparative safety study of ERIG and HRIG in children at a tertiary care hospital showed that 42.2% in the ERIG group had adverse events, whereas only 5% in the HRIG group developed adverse events, and the difference was statistically significant.[27] In a post-marketing surveillance study on TwinRab™ conducted in IDBG Hospital Kolkata, India, a total of 401 patients with suspected rabid animal bites were recruited, wherein 9.9% of the study population had mild, localized, solicited adverse events, which resolved completely compared to 2.5% in our study. Neither any systemic adverse events were reported nor was a breakthrough infection with rabies reported during the entire duration of the study. TwinRab™ was administered at 3800 IU as the maximum dose in ID and BG Hospital Kolkata study without any AEs noted compared to a maximum of 5000 IUs administered in our study without any AEs noted. Volume-wise, 8.33 mL of TwinRab™ was administered in the present study as the maximum volume administered so far for TwinRab™ without any AEs noted. Furthermore, this study reported a mucous membrane exposure with saliva of suspected rabid animal wherein the membrane was directly rinsed with TwinRab™ diluted in normal saline solution with no AEs noted. The overall tolerability of TwinRab™ was excellent or good in more than 90% of subjects as feedback from both investigators and patients in this post-marketing study.[19]

The present study showed a notable 96.5% completion rate with minimal adverse events, where 1.5% experienced localized adverse events and 1% experienced systemic adverse events, effectively managed through timely interventions. In contrast, a study by Panda and Kapoor in 2022 revealed a significantly lower compliance rate, with only 47.8% of patients adhering to the study protocol with suboptimal wound-washing practices. The importance of adherence to PEP for preventing rabies, a fatal disease, was underscored, emphasizing the need for awareness and proper wound management practices to reduce mortality rates. Factors contributing to non-compliance in the study included residential distance from the clinic, forgetfulness, fear of loss of wages, and negligence in healthcare professional counseling.[29]

Comparing both studies suggests that primary healthcare providers and family physicians, as the initial points of contact for animal-bite victims, play a vital role in counseling patients on the significance of PEP. Emphasizing adherence to the full ARV schedule and educating on proper wound management post bite are crucial aspects highlighted by the current study on TwinRab™. Addressing community misconceptions about rabies and ARV administration is identified as essential for enhancing PEP outcomes, positioning TwinRab™ as a promising alternative for PEP.

Conclusion

The study evaluated the safety of TwinRab™, the world's first novel cocktail of monoclonal antibodies docaravimab and miromavimab, in patients with WHO category-III animal bites. The research reported adverse events in 2.5% of the study population, which resolved completely and were not assessable in terms of causality to TwinRab™ administration. In addition, no unsolicited or SAEs were reported. TwinRab™ demonstrated good tolerability and received positive feedback from doctors. The post-marketing surveillance study suggests that TwinRab™ provides a safe and effective alternative to human and equine derived immunoglobulins, with

potential future public health relevance for standardized treatment in rabies PEP. However, larger clinical trials are needed to further substantiate the safety of monoclonal antibodies in rabies PEP.

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Conflicts of interest

There are no conflicts of interest.

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