Short Communication

Post-Marketing Surveillance of the World's First Novel Cocktail of Rabies Monoclonal Antibodies: TwinRab™ in Real \-World Setting

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Abstract

Rabies presents with a high fatality rate, which imposes a significant global public health challenge, and therefore the use of post-exposure prophylaxis (PEP) is crucial for prevention. Monoclonal antibodies (mAbs) have emerged as a promising substitute for rabies immunoglobulins (RIGs) due to their high efficacy and standardized manufacturing process. A prospective, open-label, post-marketing surveillance study (PMS) was conducted at Byramjee Jeejeebhoy Medical College (BJMC), Pune. The study included patients aged more than 2 years who had recently sustained Category III-suspected rabid animal bite exposures. These patients were administered TwinRabTM at a dosage of 40 IU/kg in and around the wound as intralesional transfer, along with the anti-rabies vaccine (ARV). Adverse events (AEs) grading was performed with reference to the Food and Drug Administration (FDA) toxicity grading. In this study, 215 subjects received the TwinRabTM mAb with a 100% completion rate. Out of 215 patients, three (1.3%) patients in the range of 18 to 65 years of age showed solicited local AEs, which were resolved after the appropriate treatment intervention, but causality assessment was non-assessable. The overall tolerability assessment showed positive ratings from doctors (91.63%) and patients (67.91%) for the mAb cocktail. The PMS demonstrated the safety of TwinRabTM in patients who experienced Category III-suspected rabid animal bites, thereby supporting its potential as an alternative option for post-exposure prophylaxis in the management of animal bites for the prevention of rabies

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

Introduction

Rabies is a 100% fatal yet 100% preventable disease but still, it disproportionately affects mainly people living in developing countries.[1] Worldwide, there are 59,000 deaths caused by rabies each year, mostly in Asia and Africa, 20,000 of them in India alone.[2,3] Virus-neutralizing antibodies play a major role in immunological protection against rabies.[4] A combination of anti-rabies immunoglobulin and vaccine has become the standard World Health Organization (WHO) treatment for humans with suspected exposure to rabies virus.[5] The advances in passive immunoprophylaxis, most notably shift from recommended polyclonal human or equine immunoglobulins to monoclonal antibody therapies.[6] In 2002, the Strategic Advisory Group of Experts (SAGE) of the WHO recommended that cocktails containing at least two mAbs binding to non-overlapping epitopes of rabies virus G glycoprotein should be encouraged as an alternative to eRIG or hRIG as mAbs can be produced with standardized quality in large quantities, do not use animals in the production process, and have higher effectiveness and reduced risk of adverse events.[7]

The world's first novel cocktail rabies monoclonal antibody containing docaravimab and miromavimab (TwinRab™) was developed by Zydus Lifesciences Ltd. in collaboration with the WHO and was authorized in India in 2019 and also included in the WHO essential medicines list in 2021 (22nd update).[8,9] This unique cocktail consists of two mAb, docaravimab (M777-16-3) and miromavimab (62-71-3). Miromavimab (M777-16-3) is an IgG1 antibody that targets the antigenic site II of RABV G protein, whereas docaravimab (62-71-3) is an IgG2b antibody that binds to antigenic site III of rabies virus glycoprotein.

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TwinRab™ has the potential to neutralize a broad range of zoonotic viruses when administered intralesional for 0 to 7 days as passive immunization.

This PMS of TwinRab™ was conducted to evaluate its safety in real-world public health settings in Category III animal bite victims.

Materials and Methods

A prospective, open-label, post-marketing surveillance study with 215 animal bite victims was conducted at BJMC and Sasoon Hospital, Pune. The sample size was calculated based on the primary safety endpoint, that is, adverse events (AEs). A precision-based approach was selected to calculate the sample size as the study was non-confirmatory and no formal hypothesis was tested for the primary safety endpoint. A sample size of 1,250 patients was required in the study assuming 5% of AEs through 7 days after the last dose of the Post-Exposure Prophylaxis (PEP) is a preventive treatment given after exposure to a disease to prevent the infection from occurring. In the case of rabies, PEP involves a series of rabies vaccinations and, in some cases, rabies immune globulin, to prevent the onset of rabies after a suspected exposure to the virus. PEP is crucial for preventing the onset of rabies after a suspected exposure to the virus, as rabies presents with a high fatality rate and is a significant global public health challenge. regimen with a two-sided 95% confidence interval with a width equal to 0.025. Considering around 20% of dropouts, 1,500 patients would be enrolled across India across five government tertiary care centers. We divided the sample size of 1500, amongst five government centers as per the ethics committee clearance. BJMC and Sasoon Hospital received the ethics clearance for 215 patients for this study and the same was part of a larger multicentric PMS involving five centers across India.

The study included patients aged more than 2 years who had recently sustained Category III-suspected rabid animal bite exposures. These patients were administered TwinRab™ at a dosage of 40 IU/kg in and around the wound as intralesional transfer, along with the anti-rabies vaccine (ARV). The main objective of the study was to evaluate all AEs that occurred post-administration of TwinRab™ in combination with ARV consisting of purified vero cell rabies vaccine or primary chick embryo fibroblast cell cultures. AE grading was performed with reference to the FDA toxicity grading. The study's eligibility criteria required patients to be above 2 years of age, fall under the WHO category III bite, and be exposed to a suspected rabid animal within the last 72 h or less than 24 h if there was exposure to the face, neck, hand, or fingers. Patients with previous animal bites, anti-rabies vaccination, significant congenital disabilities, chronic illnesses, thrombocytopenia, bleeding disorders, recent participation in another study or re-exposure cases of suspected rabid animal bites were excluded.

Patient consent for adults and approval of the legally authorized representative for pediatric subjects were obtained. Physical examination of the wound, location, and vital signs were documented. Patients received a single dose of 40 IU/kg body weight of TwinRab™ and were monitored for safety for 42 days of study duration, starting from the day of bite or day of reporting to the doctor, referred to as day 0, and continuing until 35 days before the final evaluation, which was conducted via telephone. The follow-up period was completed on the 42nd day with a 7-day grace period. An electronic data capturing system was utilized to transition patients' data from physical case report forms (CRFs) to e-CRFs. Statistical analysis was conducted using SAS®, version 9.4. This study was registered in CTRI with registration number CTRI/2022/11/046994.

Results

In this PMS, 215 subjects received a single dose of TwinRab™ at the dose of 40 IU/kg body weight. All 215 subjects (100%) completed the study, with no exclusions or losses to follow-up. The demographic profile of study patients is shown in Table 1. Over 70% of patients (74.88%) were bitten by suspected rabid animals on their lower body parts, mainly on their fingers and legs (62.32%). The remaining patients (25.58%) had bites on their upper body parts, mostly on their hands and fingers (20.00%). TwinRab™ was administered to all 215 individuals, with a mean dose of 2196.1 IU and a standard deviation of 669.22 IU. The minimum dose administered to any individual was 400 IU, and the maximum dose was 4280 IU. Almost all individuals (99.53%) followed the updated Thai Red Cross Regimen, involving intradermal administration of the vaccine on days 0, 3, 7, and 28. However, one patient (0.47%) received the Essen Pep Regimen, involving intramuscular administration on days 0, 3, 7, 14, and 28, likely due to his/her immunocompromised status [Figure 1]. In the adult age group (18 to 65 years), only three solicited local AEs were reported, affecting about 1.3% of individuals, but they were well-managed and resolved. There were no solicited systemic AEs or unsolicited AEs in the whole study, which was encouraging. No serious adverse events (SAEs) were reported in any of the patients, which reinforced the mAb's safety and reliability.

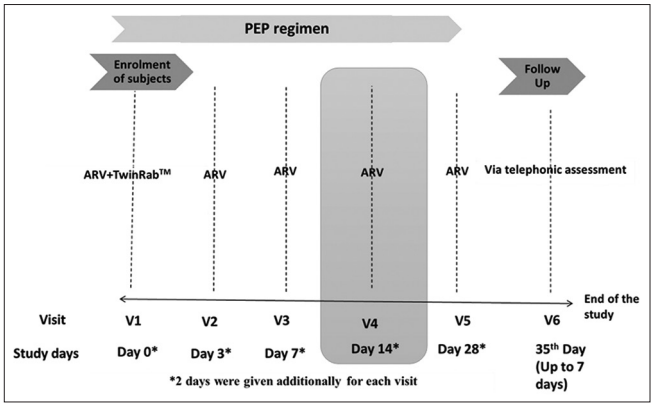

Figure 1: The cocktail of two monoclonal antibodies was administered along with ARV intradermally on days 0, 3, 7, and 28, according to the updated Thai Red Cross Regimen, and intramuscularly on days 0, 3, 7, 14, and 28 according to the Essen Pep Regimen (14th day only for the IM schedule). ARV: anti-rabies vaccine; PEP: post-exposure prophylaxis

In the age-specific analysis, pediatric patients between 2 and 17 years had no AE or SAE. They also had no solicited or unsolicited AEs, either local or systemic. In adults between 18 and 65 years, no SAEs were reported, and only six solicited local AEs, that is, pain, swelling, and tenderness, were observed, affecting 1.80% of the total adult subjects. These local AEs involved three individuals and were effectively managed and resolved completely. There were also no solicited systemic or unsolicited AEs in this age group. In the geriatric age group (over 65 years), there were no AEs reported in any category. A causality assessment for AEs in the safety population aged between 18 and 65 years showed that three cases (about 1.40% of the safety population) were categorized as "non-assessable" based on the investigator's judgment, whereas no SAEs were reported during the study [Table 2]. A large majority of patients (67.91%) and doctors (91.63%) rated therapy's tolerability as "excellent and good." A smaller proportion of patients (31.16%) and doctors (7.44%) rated it as "fair and poor." These outcomes demonstrate that patients and doctors had a favorable perception of TwinRab's™ tolerability.

Discussion

TwinRab™ is a novel cocktail of monoclonal antibodies (mAbs) whose specific targeting neutralizes a wide range of zoonotic viruses, making it highly efficacious in preventing the virus from causing infection and dissemination within the body and preventing viral escape phenomenon, which is unavailable with single mAb.[9] TwinRab™ exhibits several notable advantages when compared to conventional rabies immune globulins (RIGs), including both equine-derived RIGs (ERIG) and human-derived RIGs (HRIG). ERIG has been associated with AEs, such as serum sickness, necessitating the mandatory performance of a skin sensitivity test before administration. HRIG is generally regarded as safe; however, it faces challenges related to cost-effectiveness and restricted availability. TwinRab™, on the contrary, reduces the risk of AEs and hypersensitivity reactions typically associated with traditional RIGs. Moreover, its production through standardized recombinant hybridoma technology enhances its quality and scalability, potentially rendering

Table 1: Baseline details of patients enrolled in the study

Characteristic	N
Gender	
Male, *n*	162
Female, *n*	52
Age in years (mean±SD)	31.7±17.08
Height in cm (mean±SD)	158.5±18.35
Weight in kg (mean±SD)	54.9±16.73
Vital signs (mean±SD)	
Respiratory rate per minute	16.5±2.18
Systolic blood pressure in mmHg	119.5±5.63

Distribution of patients' basis the location of the wound caused by specific animal species

Age	<5 years	≥5 and ≤12 years	≥13 and ≤17 years	≥18 and ≤65 years	>65 years
Biting animal					
Dog, *n*	4	15	15	160	1
Cat, *n*	-	2	1	6	-
Body location					
Upper body, *n*	3	7	3	42	11
Lower body, *n*	1	10	18	126	-
Vaccine administration in study subjects, *n*	4	17	16	167	11
Vaccine regimen					
Updated Thai Red Cross Regimen, *n*	4	17	16	166*	11

*Essen PEP regimen (IM) was administrated in one patient (age range of 18 to 65 years) due to the immunocompromised status

Table 2: Summary of solicited adverse events

Age	Local adverse events				
	Pain	Erythema	Swelling	Tenderness	Induration
<5 years	–	–	–	–	–
≥5 and ≤12 years	–	–	–	–	–
≥13 and ≤17years	–	–	–	–	–
≥18 and ≤65 years	3%	–	1%	2%	–
>65 years	–	–	–	–	–

it more readily accessible on a broader scale.[8] TwinRab™ provides immediate passive immunization in combination with the inactivated rabies virus vaccine. This makes it a comprehensive and efficacious PEP treatment for severe Category III exposures.[10]

The current study included 215 subjects who completed the study without any exclusions or losses to follow-up, indicating a high level of participant engagement and commitment to research. The majority of bite wounds were caused by dogs, and nearly three-quarters of the patients were bitten in their lower body parts, particularly fingers and legs in alignment with their vulnerability for the majority of such bites. To our knowledge, this is the first-ever safety study of mAbs in rabies PEP involving the lowest pediatrics age group of 2.5 years and the highest geriatric age group of 87 years wherein TwinRab™was administered without AEs. This is also the first safety surveillance of TwinRab™ involving the maximum dosage of 4280 IUs, administered safely without any noticeable solicited or unsolicited AEs directly in and around the wound.

TwinRab™ used was identical to the dose administered in phase 1 and 2 clinical trials of TwinRab™. The 40 IU/kg dose was well tolerated and was found to be safe in phase 3 trials and the findings were consistent in the present study.[9]

Out of the total enrolled population of 215, 3 subjects exhibited solicited local AEs accounting for 1.4% of the total population enrolled, whereas, in comparison, the AEs found in the phase 3 trial of TwinRab™ was 27.70%. Notably, these events were observed exclusively in patients of the adult category (≥18 and ≤ 65 years). Most local AEs recorded were pain (1.40%), followed by tenderness accounting for 0.93%, and swelling (0.47%) of the total enrolled population. Children under 15 years of age represented 40% of affected animal bite patients. In the current study, no AEs were reported in that age range, further validating the safety profile of TwinRab™ in the pediatric age group.

Fan *et al*. (2022)[8] reported the advantages of cocktail monoclonal antibodies over rabies immunoglobulins. Kansagra *et al*. (2021)[9] conducted a phase 3, open-label study that compared the effect of TwinRab™ administered in one arm and HRIG in the reference arm, in a ratio of 1:1. The findings of this trial proved that TwinRab™ is non-inferior to HRIG in terms of offering an uninterrupted window of protection up to day 84.

A similar study conducted by Haradanhalli *et al*. (2021)[11] on the use of rabies monoclonal antibodies (RmAb) reported the treatment was safe in patients having category III animal bite with an 8% adverse effect. TwinRab™ was well-accepted, with most patients and doctors providing "excellent and good" ratings for tolerability [Figure 2].

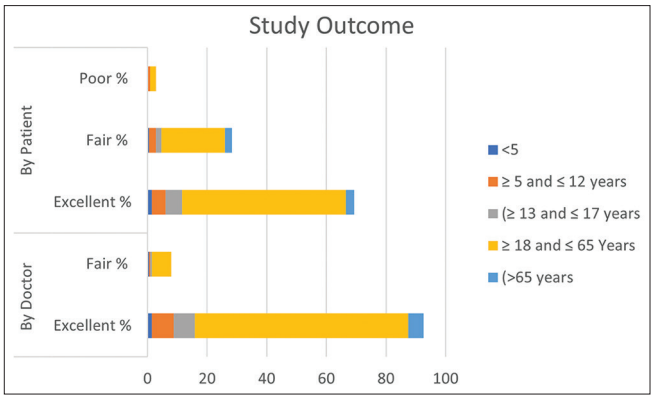

Figure 2: Overall tolerability assessment

Conclusion

Monoclonal antibodies have emerged as a promising substitute for rabies immunoglobulins (RIGs) due to high efficacy, elimination of the use of animals in the production process, standardized manufacturing process, and reduction in the risk of AEs. The advent of TwinRab,™ which is the world's first novel cocktail of two monoclonal antibodies docaravimab and miromavimab, represents a significant advancement in post-exposure prophylaxis of category III-suspected rabid animal bites. Solicited AEs reported from this study stand at 1.39%, which resolved completely, however, were not assessable in terms of causality with TwinRab™. Unsolicited AEs and SAEs were not reported. TwinRab™ reported good tolerability amongst patients and excellent feedback from doctors. This PMS indicates safe and effective alternatives to human- and equine-derived immunoglobulins and has the potential future public health relevance for standardized treatment in rabies PEP. Though this study is a part of a multi-centric large-scale real-world surveillance, larger clinical trials are required to substantiate the safety of mAbs in rabies post-exposure prophylaxis.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

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Conflicts of interest

There are no conflicts of interest.

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