

ORIGINAL ARTICLE

Safety of new indigenous human Rabies Monoclonal Antibody (RMAb) for Post Exposure Prophylaxis

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Citation

Shivalingaiah AH, Shankaraiah RH, Hanumanthaiah AND. Safety of new indigenous human Rabies Monoclonal Antibody (RMAb) for Post Exposure Prophylaxis. Indian J Comm Health. 2018; 30, 3: 196-201.

Source of Funding: Nil **Conflict of Interest:** None declared

Article Cycle

Received: 08/08/2018; **Revision:** 17/09/2018; **Accepted:** 19/09/2018; **Published:** 30/09/2018

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Abstract

Background: WHO recommended development of Rabies Monoclonal Antibodies (RMAb) to overcome the problems associated with rabies immunoglobulin for post exposure prophylaxis against rabies in all category III exposures. A new indigenous RMAb has been manufactured and marketed in India. The present study was conducted to monitor the post marketing clinical use of RMAb for post exposure prophylaxis. **Aims & Objectives:** To assess the safety of human rabies monoclonal antibodies for post exposure prophylaxis. **Material & Methods:** A comparative study between the new RMAb and the previously established rabies immunoglobulins was conducted at anti-rabies clinic in a Medical college Hospital, Bangalore from January to June, 2018. All the animal bite victims with category III exposure were included in the study. The details regarding their socio demographic profile, characteristics of exposure, post exposure prophylaxis provided and any adverse drug reactions following administration of RMAb were recorded. **Results:** The study included 397 subjects with category III exposure; 142 in RMAb group, 243 in equine rabies immunoglobulin group & 12 in human rabies immunoglobulin group. Majority of the study subjects were males & aged between 1 – 85 years. All the subjects were provided post exposure prophylaxis as recommended by WHO. There were no immediate adverse drug reactions; however, 8% of the subjects had delayed ADRs such as pain at the site of infiltration (4.2%), swelling (2.1%) and wound infection (0.7%); which resolved without any complications. **Conclusion:** The new indigenous human RMAb is safe for post exposure prophylaxis against rabies.

Keywords

RMAb; post exposure prophylaxis; rabies; safety; prevention

Introduction

Rabies is a vaccine preventable viral zoonosis and a neglected tropical disease-causing significant

mortality in nearly 150 countries around the world. It is an important public health problem causing about 59,000 deaths globally every year with cases

predominantly from Asia (59.6%) followed by Africa (36.4%).(1,2)

India is one of the endemic countries for rabies with nearly 20,000 deaths occurring every year which corresponds to nearly 36% of total global deaths. Rabies is predominantly transmitted through the bite/ scratch from an infected rabid animal; dog is predominantly responsible for rabies transmission.(3,4)

Rabies is practically 100% preventable; timely and correct post exposure prophylaxis (PEP) to all animal bite victims is life-saving.(4) The PEP has to be provided depending upon the severity of the animal bite wounds. Proper wound management combined with administration of complete course of anti-rabies vaccine and simultaneous wound infiltration of rabies immunoglobulin in all category III exposures is effective in preventing rabies, even after high-risk exposure.(4) Rabies immunoglobulin (RIG) given as passive immunization are neutralizing antibodies infiltrated at the site of wound for all category III or severe exposures, before the patient can begin producing their own antibodies physiologically after vaccination. It should be administered as much as anatomically feasible into or around the wound site.(5,6)

There are two types of RIGs available presently for passive immunization; which includes equine rabies immunoglobulin (ERIG) and human rabies immunoglobulin (HRIG). ERIG derived from equine source is most widely used, particularly in developing countries as it is economical; but there is the risk of severe allergic reactions as it is derived from equine source and skin sensitivity testing though not recommended by WHO is still recommended by the DCGI in India.(3,6) Human rabies immunoglobulin is an imported and expensive product; though it is safe, there is a remote possibility of transmission of blood borne infections.(7) Along with this, there was short supply of both these products in recent years because of various issues.(8,9)

To overcome these shortcomings, there was a need to develop an essential component for passive immunization against rabies. WHO recommended the development of rabies monoclonal antibody (RMAb), which can be produced by recombinant DNA technology and is suitable for large scale production ultimately overcoming the scarcity.(1,7,10) The RMAbs are capable of neutralizing a diverse range of rabies virus isolates and also is proved that neutralizing capacity of Mab

is superior to that of any pooled sera.(11) In addition it could offer a solution to address the cost, supply and safety issues associated with blood derived Rabies Immunoglobulin. In this regard, Serum Institute of India developed a new RMAb in partnership with Mass Biologics, USA and manufactured using recombinant DNA technology; licensed to be used under the trade name "Rabishield" from November, 2017.(12)

The newly developed RMAb is safe & efficacious as demonstrated in the clinical trials and is required in lesser dose per Kg body weight (3.33 IU/ KG body weight).⁸ WHO also recommended a registry to be maintained to monitor the clinical use and outcomes of RMAb products for rabies PEP; hence this study was undertaken to assess the safety of new RMAbs for use in PEP.(1)

Aims & Objectives

To assess the safety of human rabies monoclonal antibodies for post exposure prophylaxis.

Material & Methods

Study Type: Descriptive study. **Study Population:** All the patients with category III exposure visiting the study site during the study period & consenting the study were included. **Study Duration:** January 2018 to June 2018. Sample Size calculation: 397 subjects **Inclusion Criteria:** Subjects with category III animal bite exposure & subjects consenting for the study. **Exclusion Criteria:** Subjects with history of complete post exposure prophylaxis in the past. **Strategy for collection:** It was a comparative study with the objective to assess the safety of Human rabies monoclonal antibodies for post exposure prophylaxis, when compared to the standard ERIG & HRIG. The details pertaining to socio demographic profile which included age & gender, details of biting animal, characteristics of bite wound, wound wash, details of active & passive immunization and details of immediate adverse events following biological administration were collected using a case record form. All the study subjects were followed up by telephonic follow-up to ask for the occurrence of any delayed reactions after the treatment. The collected data was divided into three groups based on the biological received for passive immunization i.e., Equine rabies immunoglobulin (ERIG), Human rabies immunoglobulin (HRIG) and Rabies Monoclonal Antibodies (RMAb). **Ethical Approval:** Obtained. **Consent:** Informed consent obtained from all the study subjects. **Data Analysis:** Descriptive statistics

like frequencies, percentages, mean & standard deviation was used and inferential statistics like chi-square test was used. Data was entered into Microsoft excel 2007 & analyzed using SPSS 16.

Results

A total of 397 subjects with category III exposure were included in the study. Among them, 142 subjects received RMAb, 243 subjects received ERIG & 12 subjects received HRIG. Majority of the study subjects were males (66.2%) & the age range of the study subjects being 1 – 85 years.

Dog (> 90%) was the common biting animal & majority of the bites were provoked and > 40% of the biting animals were suspected rabid i.e., sick, dead, killed or non-traceable. ([Table 1](#)) Most of the bites were on the lower limbs (66.8%), followed by upper limbs (30.2%), trunk (10.8%), head & neck (5.5%). Abrasions (54.4%) were the common type of wounds followed by punctured wounds (34.5%) and lacerations (31.5%). Most of the bite victims (> 90%) had washed the wound immediately after the exposure. ([Table 2](#))

All the study subjects were provided with post exposure prophylaxis as per the WHO recommendations. Wound wash was done at the anti-rabies clinic and majority (66.7%) of the subjects received purified vero cell rabies vaccine (PVRV) most commonly by Intramuscular route (91.6%) for active immunization; a subset of 8.4% subjects had received the vaccine by the Intradermal route in government health facility & had come to the study site, only for passive immunization. Passive immunization was provided by using one of the three available biologicals which included Rabies monoclonal antibodies (35.8%), Equine rabies immunoglobulin (61.2%) and Human rabies immunoglobulin (3%). These were mostly administered locally in majority (91.6%) of the study subjects.

The mean volume of RMAb injected was 3.3ml with a range of 0.8 – 7.5 ml, ERIG 7.2 ml with a range of 1.3 – 10 ml and HRIG 4.3ml with a range of 1-10 ml thus indicating the amount of RMAb required was much less than ERIG & HRIG. No dilution was required in majority of the subjects who received these biologicals. ([Table 3](#))

Skin sensitivity test was done for all the subjects who were to receive ERIG as per package insert and 42 (19.1%) of the subjects had positive reaction. Pain was the most common adverse drug reaction seen in

all the three subject groups which was 4.2% in subjects receiving RMAb, 5.3% in subjects receiving ERIG and 16.7% in subjects receiving HRIG. A total of 2.1% of the subjects after receiving RMAb and 1.6% of subjects after receiving ERIG developed swelling at the site of administration. Wound infection at the site of passive immunization was seen in 0.7% in case of RMAb & 0.4% in case of ERIG. Erythema was seen in only 1.2% of subjects who received ERIG. There was no significant difference between the ADRs of all the three groups. All the ADRs resolved with symptomatic treatment without any complication and all the study subjects of all three groups completed the PEP.

Discussion

Passive immunity (RMAb/ RIG) are essential & lifesaving in all Cat III exposures. Serum Institute of India has developed the 1st RMAb in the World i.e., Rabishield, which is presently available in India for post exposure prophylaxis. RMAb is produced by recombinant DNA technology and is suitable for large scale production, ultimately overcoming the scarcity of the ERIG & HRIG as the later are dependent on humans/ animals. Since they are not derived from blood serum, they have none of the safety issues associated with the blood products. RMAb needs no skin sensitivity testing & can be administered directly thus saving time of the physicians and can be administered without any fear of adverse drug reactions. This will help in increasing the use of passive immunization for all category III exposures, which are scarcely used now, because of non-availability or physicians not ready to administer, as they feared of the adverse drug reactions.

RMAb is a human monoclonal antibody developed by MBL, USA and technology transfer to Serum Institute of India Pvt. Ltd. It is a IgG-1 monoclonal antibody that binds to the ectodomain of the G glycoprotein and neutralizes a wide variety of terrestrial and bat isolates of rabies virus worldwide including all rabies virus isolates in India. It has shown to have improved safety with no transmission of blood borne pathogens and expanded availability, having unlimited production capacity with consistency in production, well characterized & well-defined potency; being concentrated, is less voluminous to administer locally.

The present study compared the safety of RMAb with ERIG & HRIG. The study confirmed that there

was no significant difference between the 3 study biologicals, thereby showing that RMAb is non-inferior to the already established ERIG & HRIG. The safety profile of the study subjects were similar to other studies conducted using ERIG & HRIG.

A post-marketing surveillance study of Equirab conducted at Mumbai involving 168 subjects showed that, 31.5% had developed one or the other immediate local adverse drug reactions which included pain 30.4%, swelling 5.4%, pruritus 3.6%, induration 1.2% and itching and erythema 0.6%; but, there were no delayed reactions in any of the study subjects.(13) Similarly, a clinical evaluation of safety of equine rabies immunoglobulin conducted at KIMS Bangalore including 859 subjects using Equirab & Abhayrig (ERIG) compared with HRIG (Kamrab) showed that there was no significant difference between the ADRs..(14)

Similarly, another non inferiority study conducted to assess the safety of new indigenously manufactured ERIG (Premirab) in post exposure prophylaxis as compared to the already established brand (Equirab) was conducted at KIMS Bangalore involving 246 subjects, showed that, 4% of subjects developed adverse drug reactions which were purely local & subsided without any complications.(15)

The HRIG though safe as evidence by clinical trials, it has disadvantages in terms of cost & availability thus just 2% of Category III exposures were prescribed HRIG as evidenced by the study conducted at a tertiary care hospital in Mumbai to assess the management practices of animal bite victims in a tertiary care hospital. Similarly, a multi centric randomized non-inferiority-controlled trial using RMAb & HRIG showed that 21.43% of the subjects receiving HRIG & 30.3% subjects receiving RMAb showed one or the other reaction within 7 days of administration of the respective biological which were mild & self-limiting thus concluded to be safe. (9,16) The study concluded that, RMAb is safe and similar to HRIG.

Conclusion

To conclude, the indigenously manufactured human RMAb made by recombinant technology is safe for post exposure prophylaxis and will eliminate the problems of availability, safety and purity of passive immunization & effective in preventing rabies. Rabishield may play a major role in eliminating dog mediated human rabies by 2030

Recommendation

This study shows that RMAb is non-inferior to the already established ERIG & HRIG, also safe & economical product for post-exposure prophylaxis use.

Limitation of the study

Study being done at only one study site.

Relevance of the study

This one of the first study on post marketing surveillance of RMAb.

Authors Contribution

All authors have contributed equally.

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Tables

TABLE 1 SOCIO-DEMOGRAPHIC PROFILE & CHARACTERISTICS OF ANIMAL BITES (N = 397)

Characteristics	RMAb n= 142	ERIG n= 243	HRIG n= 12	Total n = 397
Age range	1 – 85 years	1 – 84 years	1 – 62 years	1-85 years
Sex:				
Male	98(69)	159(65.4)	6(50)	63(66.2)
Female	44(31)	84(34.6)	6(50)	134(33.8)
Biting animal:				
Dog	131(92.2)	221(90.9)	12(100)	364(91.7)
Cat	10(7.1)	12(4.9)	-	22(5.6)
Monkey	01(0.7)	10(4.2)	-	11(2.7)
If Dog:				
Stray	98(74.8)	147(66.5)	7(58.3)	252(69.2)
Pet	33(25.2)	74(33.5)	5(41.7)	112(30.8)
Type of bite:				
Unprovoked	78(54.9)	91(37.4)	10(83.3)	179(45.1)
Provoked	64(45.1)	152(62.6)	2(16.7)	218(54.9)
Fate of the biting animal:				
Healthy	73(51.3)	147(60.5)	7(58.4)	227(57.2)
Sick	01(0.7)	10(4.1)	1(8.3)	12(3)
Died	09(6.4)	12(4.9)	1(8.3)	22(5.5)
Killed	13(9.2)	15(6.2)	1(8.3)	29(7.3)
Not traceable	38(26.8)	42(17.3)	2(16.7)	82(20.7)
Unknown	08(5.6)	17(7)	-	25(6.3)

TABLE 2 DISTRIBUTION OF SUBJECTS BASED ON THE BITE WOUND & ITS CARE

Characteristics	RMAb n= 142	ERIG n= 243	HRIG n= 12	Total n = 397
Site of bite:*				
Head & neck	4(2.9)	16(6.6)	2(16.7)	22(5.5)
Trunk	12(8.5)	26(10.7)	5(41.7)	43(10.8)
Upper limb	36(25.4)	80(32.9)	4(33.3)	120(30.2)
Lower limb	103(72.5)	161(66.3)	1(8.3)	265(66.8)
Type of wound:*				
Abrasion	80(56.3)	127(52.3)	9(75)	216(54.4)
Laceration	41(28.8)	80(32.9)	4(33.4)	125(31.5)
Punctured wounds	53(37.3)	81(33.4)	3(25)	137(34.5)
Wound wash: Yes	134(94.4)	230(94.6)	12(100)	376(94.7)
Application of antiseptics: Yes	32(22.5)	121(49.8)	5(41.6)	158(39.8)
Application of irritants: Yes	8(5.6)	17(6.9)	0(0)	25(6.3)

*Indicates multiple response

TABLE 3 DISTRIBUTION OF SUBJECTS BASED ON POST EXPOSURE PROPHYLAXIS

Characteristics	RMAb n= 142	ERIG n= 243	HRIG n= 12
ACTIVE IMMUNIZATION			
Vaccine used			
PCEC Vaccine	23(16.2)	41(16.9)	3(25)
PVRV Vaccine	103(72.5)	109(44.9)	8(66.7)
Don't know/Data not available	16(11.3)	93(38.2)	1(8.3)
Route of administration:			
Intra muscular	110(77.5)	183(75.3)	11(91.6)
Intra dermal	32(22.5)	60(24.7)	01(8.4)
PASSIVE IMMUNIZATION			
Route of administration			
Local	120(84.5)	190(78.2)	11(91.6)
Local + Systemic	22(15.5)	53(21.8)	1 (8.4)
Range of biological requirement (in ml)	0.8 – 7.5	1.3 - 10	1 - 10
Mean amount of the biological injected	3.2ml	7.2ml	4.3ml
Dilution:			
Yes	46(32.4)	63(25.9)	9(75)
No	96(67.6)	180(74.1)	3(25)
Range of biological requirement (in ml)	0.8 – 7.5	1.3 - 10	1 - 10

TABLE 4 DETAILS OF ADVERSE DRUG REACTIONS: (N = 397)

Characteristics	RMAb n= 142	ERIG n= 243	HRIG n= 12	X2 p value
Pain	6(4.2)	13(5.3)	2(16.7)	X2 = 3.43
Swelling	3(2.1)	4(1.6)	-	P = 0.753
Wound infection	1(0.7)	1(0.4)	-	
Erythema	-	3 (1.2)		

*Indicates multiple response