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Comparison of a Novel Human Rabies Monoclonal Antibody to Human Rabies Immunoglobulin for Postexposure Prophylaxis: A Phase 2/3, Randomized, Single-Blind, Noninferiority, Controlled Study

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Background. Lack of access to rabies immunoglobulin (RIG) contributes to high rabies mortality. A recombinant human monoclonal antibody (SII RMAb) was tested in a postexposure prophylaxis (PEP) regimen in comparison with a human RIG (HRIG)–containing PEP regimen.

Methods. This was a phase 2/3, randomized, single-blind, noninferiority study conducted in 200 participants with World Health Organization category III suspected rabies exposures. Participants received either SII RMAb or HRIG (1:1 ratio) in wounds and, if required, intramuscularly on day 0, along with 5 doses of rabies vaccine intramuscualarly on days 0, 3, 7, 14 and 28. The primary endpoint was the ratio of the day 14 geometric mean concentration (GMC) of rabies virus neutralizing activity (RVNA) as measured by rapid fluorescent focus inhibition test for SII RMAb recipients relative to HRIG recipients.

Results. One hundred ninety-nine participants received SII RMAb (n = 101) or HRIG (n = 98) and at least 1 dose of vaccine. The day 14 GMC ratio of RVNA for the SII RMAb group relative to the HRIG group was 4.23 (96.9018% confidence interval [CI], 2.59–6.94) with a GMC of of 24.90 IU/mL (95% CI, 18.94–32.74) for SII RMAb recipients and 5.88 IU/mL (95% CI, 4.11–8.41) for HRIG recipients. The majority of local injection site and systemic adverse reactions reported from both groups were mild to moderate in severity.

Conclusions. A PEP regimen containing SII RMAb was safe and demonstrated noninferiority to HRIG PEP in RVNA production. The novel monoclonal potentially offers a safe and potent alternative for the passive component of PEP and could significantly improve the management of bites from suspected rabid animals.

Clincical Trials Registration. CTRI/2012/05/002709.

Keywords. rabies; postexposure prophylaxis; monoclonal antibody; rabies immunoglobulin.

Human rabies is a serious public health problem with global annual mortality of approximately 59 000 (95% confidence interval [CI], 25 000–159 000) due to canine rabies [1, 2]. Postexposure prophylaxis (PEP) treatment started with nerve tissue–derived vaccines, which were replaced in the 1960s with tissue culture–derived vaccines [3]. Rabies immunoglobulins (RIGs) were developed to provide an immediate source of rabies-neutralizing antibodies, and their efficacy in addition to rabies vaccine was demonstrated in Iran, the former Soviet Union, and China [4–7]. Current RIG products are derived from immunized horses (ERIG) or humans (HRIG). Although both products carry the risk of bloodborne pathogens or adventitious agents and ERIG also carries a risk for severe allergic reactions, ERIG is more commonly used due to availability and lower cost.

In developing countries, cost is an important factor in the use of RIG in PEP [8]. A study in India found that only 21 of 783 (2.7%) patients with category III bites were prescribed HRIG, and only 10 could afford to obtain it [9]. Other studies from India and Thailand have also shown that only 2%–3% of patients with severe animal bites receive RIG [10, 11]. It is therefore not surprising that mortality from rabies remains high.

To address this critical issue, a human monoclonal antibody against rabies virus glycoprotein (G) was developed by recombinant DNA technology. This antibody, 17C7 (also known as

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RAB1), which was later designated SII RMAb, showed strong neutralizing activity in vitro against a panel of geographically diverse rabies isolates and demonstrated protective efficacy in hamster challenge studies [12–15]. In a phase I simulated PEP study in adults, SII RMAb was found to be safe and induced rabies virus neutralizing antibody (RVNA) activity comparable with an HRIG-containing regimen [16].

The present study assessed the therapeutic role of SII RMAb when compared with HRIG for PEP in persons bitten by suspected rabid animals.

METHODS

This was a phase 2/3, randomized, single-blind, multicentric, noninferiority study conducted at 5 hospitals across India between June 2012 and March 2015. Patients with category III exposure from suspected rabid animals were provided wound care and tetanus toxoid immunization, if applicable. After written consent was obtained, patients were screened; if found eligible, they were enrolled. Patients had to be aged ≥5 years with World Health Organization (WHO) category III exposure from a suspected rabid animal presenting for care after <72 hours of exposure and <24 hours for exposures to the face, neck, hand, or fingers. Patients with previous receipt of RIG or vaccine, immunosuppressive condition/medication, pregnancy, lactation, or any other clinically significant health issue were excluded. The study was conducted in 2 parts. In part 1, 50 participants with bite wounds only to the lower limb(s) were enrolled. A planned interim analysis for futility based on day 14 RVNA activity was to be performed after all 50 participants completed the day 14 visit. Data from 47 participants were included in the analysis. The results demonstrated that there was no reason to consider stopping the study, and part 2 of the study was initiated with the approval of the Data Safety Monitoring Board (DSMB). One hundred fifty additional participants with wounds anywhere on the body were subsequently enrolled.

The study followed Good Clinical Practice (GCP) guidelines and ethical principles of the Declaration of Helsinki and was approved by regulatory authority and institutional ethics committees. Informed consent was given by all study participants and by parents/legal guardians in cases of children. From 19 November 2013, the consent process was audiovisually recorded per the regulatory directive [17].

Participants were randomly assigned in a 1:1 ratio to receive either SII RMAb and rabies vaccine (RMAb group) or HRIG and rabies vaccine (HRIG group). Participants and laboratory personnel were blinded to treatment group assignment.

Study Drugs

SII RMAb is a human immunoglobulin G (IgG) 1 monoclonal antibody that binds to a conformational epitope of the glycoprotein of rabies virus and is manufactured by Serum Institute of India Pvt Ltd (SIIPL), India. Study product was supplied in 2.5 mL vials with minimal potency of 100 IU/mL, and 2 batches (batch numbers RABMAB011 and RABMAB011A) were used. HRIG (Imogam/Tollwut Globulin Merieux P, Sanofi Pasteur, France) is a sterile solution of antirabies human immunoglobulin supplied in 2 mL vials with minimal potency of 150 IU/mL. Three batches (batch numbers H1290-2, J1405-2, and J1669-4) were used. Rabies vaccine (Rabivax, SIIPL, India) is a human diploid cell vaccine. Four batches (batch numbers 031B1001, 031B2029, 031L4001, and 031L4002] were used. Vaccine potency ranged 4.10–6.11 IU/mL.

Postexposure Prophylaxis Administration and Monitoring

Each participant initiated PEP treatment on the day of presentation to the rabies clinic (day 0) and per random assignment received either SII RMAb (3.33 IU/kg) or HRIG (20 IU/kg). SII RMAb or HRIG was infiltrated into all wounds to the extent anatomically feasible. Any remaining volume was administered intramuscularly at a site distant from the vaccine injection site. For multiple wounds, SII RMAb or HRIG was diluted in a solution of 0.9% sodium chloride to a volume sufficient for effective infiltration of all wounds. Rabies vaccine was given intramuscularly into the deltoid muscle as per WHO Essen Schedule on days 0, 3, 7, 14, and 28. Study participation of each subject was for 84 days.

Participants were monitored for local injection site and systemic reactions for the first 7 days. In addition, participants were to report any unsolicited adverse event occurring during the 84-day study period. Blood hematology indices, serum chemistries, and presence of antidrug antibodies were evaluated at scheduled time points. Blood samples were collected on days 0, 3, 7, 14, 28, 42 ± 7, and 84 ± 15 for immunogenicity analyses. Sera were tested for RVNA levels (IU/mL) by a validated rapid fluorescent focus inhibition test (RFFIT; Kansas State University) and for IgG antirabies G antibody concentrations (μg/mL) measured by enzyme-linked immunosorbent assay (MassBiologics).

Outcomes

The primary endpoint was the day 14 ratio of the geometric mean concentration (GMC) of RVNA activity of the RMAb group to the HRIG group. Secondary endpoints included determination of GMCs of RVNA and antirabies G antibodies and the percentage of participants with RVNA ≥ 0.5 IU/mL (seroresponse) on days 3, 7, 14, 28, 42, and 84. Safety outcomes included occurrence of solicited adverse reactions, unsolicited nonserious and serious adverse events, use of concomitant medications, and detection of antidrug antibodies in each treatment group.

Statistical Analysis

The sample size required for 80% power to show noninferiority of the RMAb group to the HRIG group, based on the ratio of the GMC of RVNA activity on day 14 of PEP for the RMAb group to the GMC for the HRIG group, was determined to be

31 recipients of each treatment. Assumptions were a 2-sided *t* test on $\log_{10}$–transformed day 14 RVNA activity at a 1-sided 0.025 significance level, a standard deviation of 0.415 for $\log_{10}$–transformed day 14 RVNA activity from the HRIG and vaccine cohort in the phase 1 study [16], a noninferiority margin of 0.5 for the GMC ratio (as is commonly done in such trials [18–20]), and a true underlying GMC ratio of 1. The criterion for noninferiority was that the lower limit of a 2-sided 96.9018% confidence interval of day 14 GMC ratio be >0.5. To provide a larger safety database, 100 participants were enrolled in each study group.

Missing data were assumed to be missing at random, and no imputation was performed.

The GMCs of RVNA or antirabies G antibody were compared between groups by 2-sample *t* test. Proportion of participants with a seroresponse and detection of antidrug antibodies were compared between groups by 2-sided Fisher's exact test. The percentage of participants who experienced at least 1 solicited reaction was compared between groups by a 2-sided *z* test of proportions.

A modified intention-to-treat (mITT) analysis was used for efficacy analysis. The mITT population was defined as those participants who received SII RMAb or HRIG on day 0 as per randomization and all rabies vaccine injections on the days specified by the protocol through the day for which the endpoint analysis was being done and for whom relevant RFFIT antibody data were available. The intention-to-treat (ITT) population was used for safety analysis and included all randomized participants who received at least 1 dose of study drugs. Per-protocol (PP) population analyses were also performed for efficacy outcomes. A result with 2-sided $P \leq .05$ was considered statistically significant, except for the primary analysis of day 14 RVNA concentration, which required a 2-sided $P \leq .031$ (corresponding to 96.9018% CI). All analyses were performed using SAS (version 9.2 or later) or NCSS 10, and model test assumptions were examined graphically and analytically. The trial was registered in the Clinical Trial Registry of India: CTRI/2012/05/002709.

RESULTS

A total of 205 participants were screened. Of the 200 eligible participants enrolled, 101 were randomized to receive SII RMAb and 99 were randomized to receive HRIG; 1 participant randomized to receive HRIG withdrew consent before study intervention, resulting in 98 participants for analysis. One hundred ninety-nine participants were included in the ITT safety analysis, and 192 were included in mITT primary endpoint analysis (Figure 1).

The majority of participants were adult males; 28 children were enrolled (n = 25 boys and n = 3 girls). Dogs were responsible for >90% of the suspected rabid exposures, with the majority of participants presenting with multiple wounds. Seventeen participants had high-risk exposure involving face, neck, hand, or fingers (Table 1). For 36 participants in the RMAb group and for 1 participant in the HRIG group, dilution was required to infiltrate all wounds. The entire dose of SII RMAb was injected into the wound(s) for 66 participants, whereas 70 participants in the HRIG group had the remaining volume injected intramuscularly at a site separate from the wound.

The day 14 GMC ratio of RMAb group to HRIG group was 4.23 (96.9018% CI, 2.59–6.94) for the mITT population and 4.32 (96.9018% CI, 2.61–7.15) for the PP population. The GMCs were comparable between the 2 groups at baseline, with the day 14 GMC statistically significantly higher in the RMAb group (mITT, 24.90 IU/mL) compared with the HRIG group (mITT, 5.88 IU/mL). The GMCs of RVNA activity were not significantly different between the groups on days 28, 42, and 84 (Table 2; Supplementary Figure 1 and Supplementary Table 2).

At day 0, 3 participants in the RMAb group (2.97%) and 1 participant in the HRIG group (1.02%) had an RFFIT value ≥0.5 IU/mL ($P = .62$). Additional analyses were performed excluding these 4 participants with a seroresponse at baseline. The day 14 GMC ratio remained statistically significant at 4.12 (96.9018% CI, 2.53–6.71), with no significant differences in GMC ratio at the other time points (Table 3) as observed with the mITT (Table 2) and PP analyses (Supplementary Table 2).

The proportion of participants with a seroresponse at each time point was evaluated. There were no statistically significant differences between the treatment groups on days 3 and 7, with <10% achieving a seroresponse. On day 14, 98.97% (95% CI, 94.39–99.97) of participants in the RMAb group and 91.58% (95% CI, 84.08–96.29) of participants in the HRIG group had a seroresponse ($P = .02$) (Table 4). Similar results were seen when those participants with baseline seroresponse were excluded from the analysis (Table 5).

The GMCs of IgG antirabies G antibodies were comparable at baseline but were significantly higher in the RMAb group compared with the HRIG group on days 3, 7, and 14. The GMCs on days 28, 42, and 84 were similar between the groups (Table 6).

There were no deaths, cases of rabies, or any other serious adverse event reported during the study period. A total of 461 adverse events were reported, of which 83.7% were solicited events and 16.3% were unsolicited events. Of the 386 solicited events reported within the first 7 days of PEP, 250 (64.8%) were injection site reactions (n = 112 at wound site, n = 40 at other site of remaining HRIG or SII RMAb volume injection, and n = 98 at the site of rabies vaccine injection), and 136 (35.2%) were solicited systemic reactions, with 85 from 28 participants in the RMAb group and 51 from 20 participants in the HRIG group (Tables 7–10). All solicited reactions were of mild to moderate severity except for 3 events of redness, 1 event of pain, and 1 case of fever (41.3°C) assessed as severe, all in the HRIG group. Seventy-five unsolicited events were reported from 57 participants during

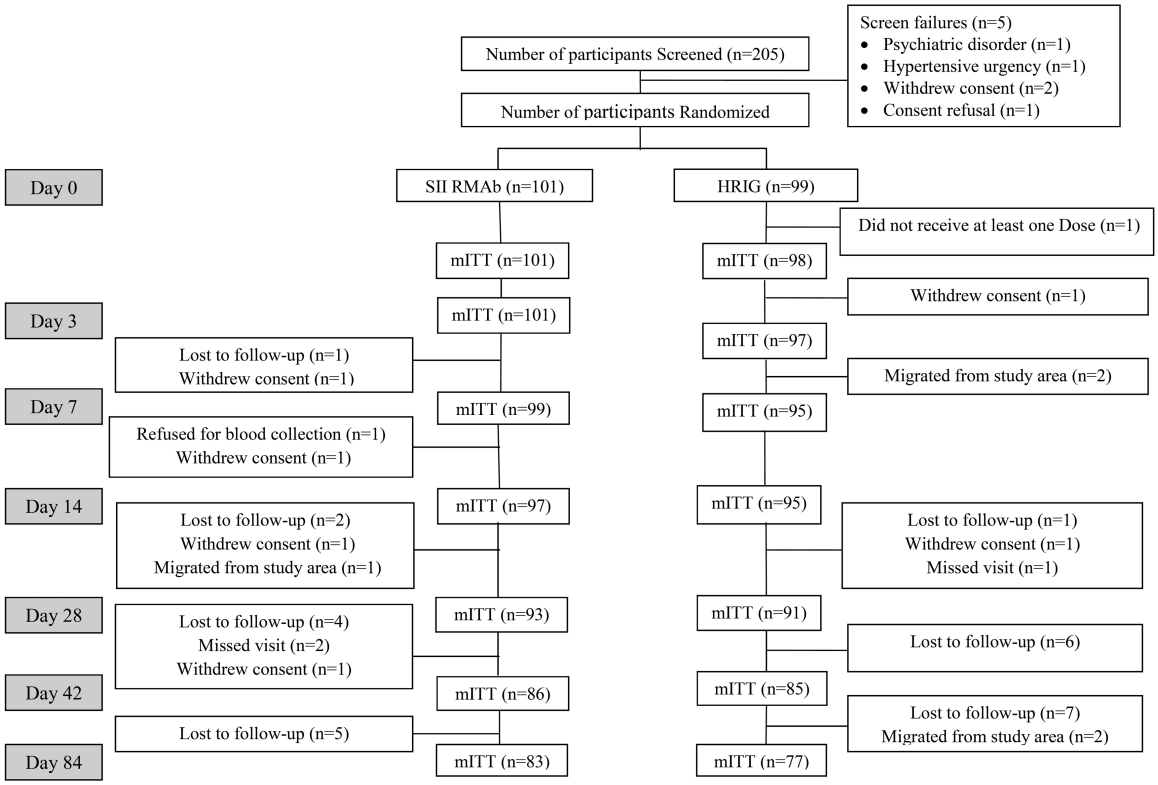

Figure 1. Study participant disposition flow chart. Abbreviation: HRIG, human rabies immunoglobulin; mITT, modified intention-to-treat; SII RMAb, a recombinant human monoclonal antibody.

the 84-day study period. All were assessed as unrelated to study treatment except for 2: itching at wound site from 1 participant in the RMAb group and injection site pain from a participant in the HRIG group (Supplementary Table 1). The mean changes in hematology and chemistry parameters from day 0 to day 28 were comparable between the groups. No antidrug antibodies were detected in any of the study participants.

Table 1. Demographics and Clinical Characteristics of Study Population (Intention-to-Treat Population)

Characteristic	SII RMAb + rabies vaccine (n = 101)	HRIG + rabies vaccine (n = 98)
Age, y, mean (SD)	34.26 (14.11)	32.17 (14.91)
Height, cm, mean (SD)	160.56 (12.88)	159.52 (14.19)
Weight, kg, mean (SD)	56.47 (15.75)	53.91 (15.76)
Male sex, no. (%)	91 (90.1)	89 (90.8)
Duration between exposure and randomization, h, mean (SD)	17.60 (13.94)	18.96 (13.70)
Animal involved, no. (%)		
Dog	94 (93.1)	91 (92.9)
Cat	4 (4.0)	7 (7.1)
Monkey	3 (3.0)	0
No. of category III wounds, no. (%)		
Single	48 (47.5)	45 (45.9)
Multiple	53 (52.5)	53 (54.1)
If multiple wounds, then total wounds, mean (SD)	2.64 (1.09)	2.57 (1.18)
High-risk exposures,[a] no. (%)	10 (9.90)	7 (7.14)

Abbreviations: HRIG, human rabies immunoglobulin; SII RMAb, a recombinant human rabies monoclonal antibody; SD, standard deviation.

[a]Exposure on face, neck, hands, or fingers.

DISCUSSION

This pivotal study demonstrated that a PEP regimen of SII RMAb and rabies vaccine produced RVNA activity on day 14 that was noninferior to that of HRIG and rabies vaccine. The Day 14 GMC was 4 times higher with SII RMAb PEP than with the HRIG-containing PEP regimen. There were no significant differences in RVNA levels at earlier or later measured time points, suggesting that SII RMAb interfered less with RVNA responses to early doses of the rabies vaccine and provided comparable neutralizing activity after the 4th and 5th doses. Rabie virus neutralizing activity serology as an indirect assessment of efficacy has been accepted by WHO and regulatory agencies as study endpoints in clinical trials of novel rabies vaccines or HRIG products [21, 22]. The binding antirabies G antibody results support the neutralization data, although significantly higher concentrations were observed on days 3 and 7 in addition to day 14 of PEP in the RMAb group with no significant differences seen after the 4th and 5th vaccine doses. There were no PEP failures in either of the treatment groups. The proportions of participants with solicited and unsolicited

Table 2. Comparison of Geometric Mean Concentration with 95% Confidence Interval and Range of Rabies Virus Neutralizing Antibodies (IU/mL) by Treatment Group (Modified Intention-to-Treat Population)

Time point	Parameter	SII RMAb + rabies vaccine	HRIG + rabies vaccine	GMC ratio
Day 0	GMC mean	0.23	0.24	0.99
	95% CI	(.22–.25)	(.22–.26)	(.88–1.11)
	Range (min, max)	(.022–3.94)	(0.22–12.53)	
Day 3	GMC mean	0.24	0.25	0.95
	95% CI	(.22–.26)	(.23–.28)	(.83–1.08)
	Range (min, max)	(0.22–11.05)	(0.22–10.43)	
Day 7	GMC mean	0.29	0.29	0.98
	95% CI	(.24–.34)	(.24–.36)	(.75–1.28)
	Range (min, max)	(0.22–52.16)	(0.22–53.75)	
Day 14	GMC mean	24.90	5.88	4.23
	95% CI	(18.94–32.74)	(4.11–8.41)	(2.59–6.94)[a]
	Range (min, max)	(0.22–250.00)	(0.22–260.82)	
Day 28	GMC mean	31.48	21.13	1.49
	95% CI	(25.38–39.03)	(15.76–28.32)	(1.04–2.14)
	Range (min, max)	(2.09–250.00)	(0.22–250.00)	
Day 42	GMC mean	31.65	31.33	1.01
	95% CI	(26.61–37.64)	(25.10–39.12)	(.76–1.34)
	Range (min, max)	(8.18–199.45)	(2.19–285.21)	
Day 84	GMC mean	9.14	9.97	0.92
	95% CI	(7.44–11.24)	(7.89–12.61)	(.67–1.25)
	Range (min, max)	(1.08–52.41)	(2.00–250.00)	

For number of participants for each time point, please refer to Figure 1.

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; HRIG, human rabies immunoglobulin; max, maximum; min, minimum; SII RMAb, a recombinant human rabies monoclonal antibody.

[a]Confidence interval was 96.9018%.

Table 3. Comparison of Geometric Mean Concentration with 95% Confidence Interval and Range of Rabies Virus Neutralizing Antibodies (IU/mL) by Treatment Group Excluding Participants With Antibody Titers ≥ 0.5 IU/mL on Day 0 (Modified Intention-to-Treat Population)

Visit		SII RMAb + rabies vaccine	HRIG + rabies vaccine	GMC ratio
Day 0	GMC mean	0.22	0.23	0.97
	95% CI	(…)	(.22–.23)	(.94–1.00)
	Range (min, max)	(0.22–0.22)	(0.22–0.46)	
Day 3	GMC mean	0.22	0.24	0.92
	95% CI	(.22–.23)	(.23–.26)	(.87–.98)
	Range (min, max)	(0.22–0.68)	(0.22–0.79)	
Day 7	GMC mean	0.26	0.28	0.91
	95% CI	(.23–.29)	(.23–.34)	(.73–1.14)
	Range (min, max)	(0.22–7.47)	(0.22–53.75)	
Day 14	GMC mean	23.29	5.65	4.12
	95% CI	(17.75–30.55)	(3.97–8.03)	(2.53–6.71)[a]
	Range (min, Max)	(0.22–250.00)	(0.22–260.82)	
Day 28	GMC mean	30.77	20.61	1.49
	95% CI	(24.68–38.36)	(15.39–27.60)	(1.04–2.15)
	Range (min, max)	(2.09–250.00)	(0.22–250.00)	
Day 42	GMC mean	31.12	30.85	1.01
	95% CI	(26.03–37.20)	(24.69–38.53)	(.76–1.34)
	Range (min, max)	(8.18–199.45)	(2.19–285.21)	
Day 84	GMC mean	8.67	9.75	0.89
	95% CI	(7.06–10.64)	(7.72–12.30)	(.65–1.21)
	Range (min, max)	(1.08–52.41)	(2.00–250.00)	

For number of participants for each time point, please refer to Figure 1.

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; HRIG, human rabies immunoglobulin; max, maximum; min, minimum; SII RMAb, a recombinant human rabies monoclonal antibody.

[a]Confidence interval was 96.9018%.

Table 4. Percentage of Participants Developing Seroresponse (Rapid Fluorescent Focus Inhibition Test Titer ≥0.5 IU/mL) Along With 95% Confidence Interval by Treatment Group (Modified Intention-to-Treat Population)

Visit	SII RMAb + rabies vaccine n/N, % (95% CI)	HRIG + rabies vaccine n/N, % (95% CI)	Group difference (95% CI)	*P* value
Day 0	3/101 (2.97%) (.62%–8.44%)	1/98 (1.02%) (.03%–5.55%)	1.95% (−6.48% to 10.38%)	.62
Day 3	4/101 (3.96%) (1.09%–9.83%)	5/97 (5.15%) (1.69%–11.62%)	−1.19% (−9.90% to 7.51%)	.74
Day 7	8/99 (8.08%) (3.55%–15.30%)	7/95 (7.37%) (3.01%–14.59%)	0.71% (−8.82% to 10.24%)	1.00
Day 14	96/97 (98.97%) (94.39%–99.97%)	87/95 (91.58%) (84.08%–96.29%)	7.39% (−1.91% to 16.69%)	.02
Day 28	93/93 (100%) (96.11%–100%)	89/91 (97.80%) (92.29%–99.73%)	2.20% (−6.32% to 10.71%)	.24
Day 42	86/86 (100%) (95.80%–100%)	85/85 (100%) (95.75%–100.00%)	…	…
Day 84	83/83 (100%) (95.65%–100%)	77/77 (100%) (95.32%–100%)	…	…

Abbreviations: CI, confidence interval; HRIG, human rabies immunoglobulin; SII RMAb, a recombinant human rabies monoclonal antibody.

adverse events were generally comparable between the treatment groups. The majority of reactions were mild to moderate in severity, resolving without sequelae. One limitation of this study was that it was not conducted in patients with confirmed rabies exposure. In India, most of the exposures are from stray dogs that cannot be traced and therefore cannot undergo brain tissue studies.

To our knowledge this is the first study of an antirabies monoclonal antibody PEP regimen evaluated in patients with suspected rabies exposure. A cocktail of 2 monoclonal antibodies has demonstrated results comparable to the HRIG regimen in simulated PEP studies [23–25]. Further clinical development has not been reported. Three additional monoclonal cocktails are in various stages of development [26, 27].

Two percent of participants in this study had RVNA ≥0.5 IU/mL at baseline, despite an exclusion criterion of history of previous rabies vaccination. The most likely explanation is that they did not recall or know they received the rabies vaccine in the past. Other studies evaluating rabies biologics have shown similar observations [28–30]. Post hoc analyses excluding these participants did not change the significant differences in RVNA between the treatment groups at day 14.

The RVNA activity elicited in this study is similar to that observed in other clinical trials. The percentage of participants with seroresponse in simulated PEP studies of HRIG and rabies vaccine ranged 0–6.7% at day 3, 1.7%-20% at day 7, and 100% at day 14 [31, 32]. One study of 90 persons receiving HRIG and HDCV PEP regimen reported seroresponse

Table 5. Percentage of Participants Developing Seroresponse (Rapid Fluorescent Focus Inhibition Test Titer ≥0.5 IU/mL) with 95% Confidence Interval by Treatment Group Excluding Participants With Antibody Titers ≥0.5 IU/ml on Day 0 (Modified Intention-to-Treat Population)

Visit	SII RMAb + rabies vaccine n/N, % (95% CI)	HRIG + rabies vaccine n/N, % (95% CI)	Group difference (95% CI)	*P* value
Day 0	0/98 (0%) (.00%–3.69%)	0/97 (0%) (.00%–3.73%)	…	…
Day 3	2/98 (2.04%) (.25%–7.18%)	4/96 (4.17%) (1.15%–10.33%)	−2.13% (−10.52% to 6.27%)	.44
Day 7	5/96 (5.21%) (1.71%–11.74%)	6/94 (6.38%) (2.38%–13.38%)	−1.17% (−10.26% to 7.91%)	.77
Day 14	93/94 (98.94%) (94.21%–99.97%)	86/94 (91.49%) (83.92%–96.25%)	7.45% (−2.01% to 16.90%)	.03
Day 28	90/90 (100.00%) (95.98%–100.00%)	88/90 (97.78%) (92.20%–99.73%)	2.22% (−6.43% to 10.88%)	.50
Day 42	83/83 (100.00%) (95.65%–100.00%)	84/84 (100.00%) (95.70%–100.00%)	…	…
Day 84	80/80 (100.00%) (95.49%–100.00%)	76/76 (100.00%) (95.26%–100.00%)	…	…

Abbreviations: CI, confidence interval; HRIG, human rabies immunoglobulin; SII RMAb, a recombinant human rabies monoclonal antibody.

Table 6. Comparison of Geometric Mean Concentrations with 95% Confidence Interval of Immunoglobulin G Antirabies G Protein Antibodies (μg/mL) by Treatment Group (Modified Intention-to-Treat Population)

Visit	SII RMAb + rabies vaccine	HRIG + rabies vaccine	GMC Ratio	*P* value
Day 0	0.42 (.39–.45)	0.45 (.40–.51)	0.93 (.80–1.08)	.33
Day 3	1.01 (.89–1.13)	0.46 (.41–.52)	2.18 (1.84–2.58)	<.0001
Day 7	1.05 (.90–1.21)	0.55 (.46–.67)	1.89 (1.49–2.40)	<.0001
Day 14	5.78 (4.54–7.37)	2.86 (2.08–3.93)	2.02 (1.36–3.01)	.0006
Day 28	17.91 (14.63–21.92)	14.62 (11.10–19.24)	1.23 (.87–1.72)	.24
Day 42	29.86 (25.29–35.25)	27.45 (22.28–33.81)	1.09 (.83–1.42)	.53
Day 84	13.56 (11.16–16.48)	15.38 (12.39–19.09)	0.88 (.66–1.18)	.39

For number of participants for each time point please refer to Figure 1.

Abbreviations: GMC, geometric mean concentration; HRIG, human rabies immunoglobulin; max, maximum; min, minimum; SII RMAb, a recombinant human rabies monoclonal antibody.

rates of 59% at day 14, 90.9% at day 28, and 98.9% at day 42; other studies reported seroresponses of 88.8%–90.7% after receipt of HRIG and 4 doses of vaccine [33–35]. In our study, seroresponse at day 14 was 98.97% in the RMAb group and 91.58% in the HRIG group, increasing to 100% and 97.80%, respectively, at day 28 and 100% for both treatment groups at day 42.

In India, rabies virus isolates group into 2 distinct lineages, Arctic-like 1 lineage and subcontinental lineage. Phylogenetic analyses demonstrate that Indian isolates are mostly canine variants and the antigenic sites of the G protein ectodomain are highly conserved [36, 37]. We analyzed 521 rabies virus G protein sequences from Asia deposited in GenBank, of which 44 were from India; all 44 had critical epitope residues of only 2 sequence variations, and both variants have been shown to be neutralized in pseudovirus assays by SII RMAb [13]. Twenty-two rabies isolates from India, Nepal, and Sri Lanka have been tested previously in vitro with SII RMAb, and all were fully neutralized [14]. Fourteen additional isolates obtained from infected dogs, coyotes, foxes, skunks, and raccoons from Argentina, Gabon, Thailand, and the United States were strongly neutralized by SII RMAb [12]. In the lethal challenge hamster model of PEP using a canine-related rabies virus isolate, SII RMAb protected hamsters from rabies at equivalent or lower doses compared with HRIG [12]. These data indicate that SII RMAb is potent against canine-derived rabies isolates that account for the vast majority of human rabies.

SII RMAb has also neutralized rabies isolates from diverse bat species worldwide by in vitro RFFIT or by pseudovirus assays [12, 13]. One report by De Benedictis et al that assessed the

Table 7. Comparison of Solicited Local Injection Site Reactions at Wound Sites Between Treatment Groups Reported for the First 7 Days of Postexposure Prophylaxis (Intention-to-Treat Population)

Local reaction	SII RMAb + rabies vaccine (n = 101)[a] X, no. (%)	HRIG + rabies vaccine (N = 98) X, no (%)
Pain	30, 14 (14.14%)	15, 11 (11.22%)
Redness	21, 15 (15.15%)	12, 9 (9.18%)
Swelling	22, 13 (13.13%)	12, 10 (10.20%)
At least 1 local reaction: wound sites[b]	73, 30 (30.30%)	39, 21 (21.43%)

X, no. (%): X = count of events (one subject may be counted more than once), no. = count of participants with at least 1 event (ie, participants counted only once), % = (no. of participants with at least 1 event/no. of participants for whom response for solicited reaction is present) × 100.

Abbreviations: HRIG, human rabies immunoglobulin; SII RMAb, a recombinant human rabies monoclonal antibody.

[a]n = 99 because 2 participants in the SII RMAb group did not provide responses for solicited local reactions

[b]*P* = .16, 2-sided *z* test of proportions.

Table 8. Comparison of Solicited Local Reactions at Other Injection Sites Between Treatment Groups Reported for the First 7 Days of Postexposure Prophylaxis (Intention-to-Treat Population)

Local reaction	SII RMAb + rabies vaccine (n = 101[a]) X, no. (%)	HRIG + rabies vaccine (n = 98[a]) X, no. (%)
Pain	7, 5 (14.29%)	23, 14 (20.00%)
Redness	2, 1 (2.86%)	3, 2 (2.86%)
Swelling	4, 2 (5.71%)	1, 1 (1.43%)
At least 1 local reaction: other sites[b]	13, 5 (14.29%)	27, 16 (22.86%)

X, no. (%): X = count of events (one subject may be counted more than once), no. = count of participants with at least 1 event (ie, participants counted only once), % = (no. of participants with at least 1 event/no. of participants for whom response for solicited reaction is present) × 100.

Abbreviations: HRIG, human rabies immunoglobulin; SII RMAb, a recombinant human rabies monoclonal antibody.

[a]Thirty-five of 101 participants in the SII RMAb group and 70 of 98 in the HRIG group were administered remaining volume intramuscularly at a site separate from the wound and from rabies vaccination.

[b]*P* = .30, 2-sided *z* test of proportions.

Table 9. Comparison of Solicited Local Injection Site Reactions at Sites of Rabies Vaccination (Deltoid) Between Treatment Groups Reported for the First 7 Days of Postexposure Prophylaxis (Intention-to-Treat Population)

Local reaction	SII RMAb + rabies vaccine (n = 101[a]) X, no. (%)	HRIG + rabies vaccine (n = 98) X, no. (%)
Pain	51, 40 (40.40%)	30, 26 (26.53%)
Redness	4, 4 (4.04%)	2, 2 (2.04%)
Swelling	9, 6 (6.06%)	2, 2 (2.04%)
At least 1 local reaction[b]	64, 40 (40.40%)	34, 26 (26.53%)

X, no. (%): X = count of events (one subject may be counted more than once), no. = count of participants with at least 1 event (ie, participants counted only once), % = (no. of participants with at least 1 event/no. of participants for whom response for solicited reaction is present) × 100.

Abbreviations: HRIG, human rabies immunoglobulin; SII RMAb, a recombinant human rabies monoclonal antibody.

[a]n = 99 because 2 participants in the SII RMAb group did not provide responses for solicited local reactions.

[b]$P = .039$, 2-sided z test of proportions.

neutralizing activity of RAB1 (produced by a transient transfection system) cautioned that 4% of circulating rabies viruses might be resistant to this monoclonal antibody [27]. This conclusion is largely based on CVS-11 pseudotyped virus results and contrasts with results obtained with Evelyn-Rokitnicki-Abelseth pseudotyped virus demonstrating neutralization [13]. Based on sequence analysis, there is only 1 variant identified from a Peruvian bat (*Histiotus montanus*) that is likely to be resistant to SII RMAb given amino-acid changes in 2 critical positions [38]. Our analysis of rabies virus glycoprotein sequences of residues critical to SII RMAb neutralization found this variant to be very rare, representing 0.07% (n = 1 of 1439) of worldwide rabies isolates analyzed. There are 2 reports of HRIG, not neutralizing in vitro a rabies variant from a North American hoary bat *(Lasiurus cinereus)* [39, 40]; SII RMAb neutralized this variant, albeit at a higher concentration of antibody [12]. Another experiment demonstrated that final formulation of SII RMAb neutralized this variant at least as well as or better than HRIG (unpublished data).

Table 10. Comparison of Solicited Systemic Reactions Between Treatment Groups Reported for the First 7 Days of Postexposure Prophylaxis (Intention-to-Treat Population)

Reaction	SII RMAb + rabies vaccine (n = 101[a]) X, no. (%)	HRIG + rabies vaccine (n = 98) X, no. (%)
Fever	2, 2 (2.02%)	3, 3 (3.06%)
Headache	24, 20 (20.20%)	16, 12 (12.24%)
Nausea	8, 7 (7.07%)	4, 3 (3.06%)
Fatigue	14, 12 (12.12%)	11, 8 (8.16%)
Chills	5, 4 (4.04%)	2, 2 (2.04%)
Myalgia	17, 15 (15.15%)	8, 7 (7.14%)
Arthralgia	15, 13 (13.13%)	7, 6 (6.12%)
Any systemic reaction[b]	85, 28 (28.28%)	51, 20 (20.41%)

X, no. (%): X = count of events (one subject may be counted more than once), no. = count of participants with at least 1 event (ie, participants counted only once), % = (no. of participants with at least 1 event/no. of participants for whom response for solicited reaction is present) × 100.

Abbreviations: HRIG, human rabies immunoglobulin; SII RMAb, a recombinant human rabies monoclonal antibody.

[a]n = 99 because two participants in the SII RMAb group did not provide responses for solicited systemic reactions.

[b]$P = .20$, 2-sided z test of proportions

These data indicate that a human monoclonal antibody targeting a highly conserved epitope of the rabies glycoprotein could be a viable alternative for the passive antibody component of PEP treatment. Our data show that a safe and potent human monoclonal antibody product (Rabishield) has been developed for PEP treatment.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. P. S. K., B. G., and D. C. M. prepared the first draft of the manuscript and all authors reviewed and approved the manuscript. P. S. K., D. C. M., and B. G. designed the protocol, trial implementation strategy, and overall trial conduct; contributed to data analyses; did data interpretation and the literature search; and designed tables and figures. D. C. M. contributed to laboratory guidance and coordination for laboratory analysis. S. M. and P. C. contributed to laboratory testing of sera samples. R. M. D. and S. S. P. contributed to development and manufacturing of SII RMAb and gave intellectual input into trial design and data interpretation. N. J., R. M., D. H. A., B. J. M., B. R. H., and V. K. were study investigators. S. T., S. K., S. D., D. K., and R. H. S. were coinvestigators/designees. The investigators/coinvestigators contributed to the acquisition of data from study participants and interpretation of study results. W. C. B. contributed to Statistical Analysis Plan (SAP), interim data analyses, and data interpretation. V. P. prepared SAP, did data analysis, and provided figures.

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Potential conflict of interest. P. S. K., B. G., S. S. P., and R. M. D. are employees of Serum Institute of India Pvt Ltd. D. C. M. and P. C. are current or former employees of MassBiologics, University of Massachusetts Medical School, Boston, which has a patent issued for the rabies monoclonal antibody used in this study and has granted a royalty bearing license to Serum Institute of India Pvt Ltd. All other authors declare no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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