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Review Article

Rabies Vaccines: Duration Of Pep From 90 Days To 7 Days

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Abstract

Rabies is a zoonotic viral disease that is caused by rabies virus (RABV) and claims the highest fatality among all infectious diseasnes. Even though no cure is possible, it can be prevented by timely and complete postexposure prophylaxis (PEP). A variety of empirical schedules and vaccine doses for post-exposure prophylaxis have been recommended over time. The post-exposure prophylaxis was initially for 90 days with 6 injections but with better understanding of the immunology, this extended regimen was reduced to 7 days by development of novel recombinant nanoparticle-based rabies G protein vaccine. The current review highlighted different PEP regimens and clinical efficacy and safety of novel recombinant nanoparticle-based rabies G protein vaccine.

Keywords: rabies; postexposure prophylaxis; schedules; rabies g protein vaccine

Introduction

Rabies disease occurs in more than 100 countries and territories in the world. Dogs are the main source of human infections and pose a potential threat to more than 3.3 billion people. In India, animal bites are the major concern and an estimated 17.4 million animal bites occur annually. The Rabies disease is mainly transmitted by dogs, being responsible for 96% of animal bite cases. Although there is no cure for clinical rabies, the disease is readily preventable through timely provision of adequate post-exposure prophylaxis (PEP). PEP consists of thorough washing of the wound with water, soap and application of antiseptics; a series of rabies vaccinations; and administration of rabies immunoglobulins (RIG) or more recently licenced monoclonal antibody products, if indicated. The PEP protocol varies according to the category of exposure, the immunological status of the patient and whether they have been previously immunized against rabies. As per 2010 recommendations, a previously immunized person refers to a person who has previously received rabies vaccine, either as a complete pre- exposure prophylaxis course or as PEP. For persons who are previously immunized against rabies, even decades earlier, RIG is not indicated, and only booster injections are recommended. These will invoke an anamnestic response and boost antibody production. A rabies virus neutralizing antibody (RVNA) titre 0.5 IU/ml on day 14 post-immunization with rabies vaccine is internationally agreed as indicative of an adequate response to immunization. This threshold is a surrogate used to measure the vaccine-induced seroconversion in studies of rabies vaccine efficacy and effectiveness. Rabies vaccines can be administered by the intradermal (ID) or intramuscular (IM) route, depending on the schedule.

A variety of empirical schedules and vaccine doses for post-exposure prophylaxis have been recommended over time, based on immunogenicity and clinical experience in different parts of the world with enzootic canine or wildlife rabies (Table 1 & Table 2).

Schedule	Route	Sites	Days	Clinic visits	Duration (days)
WHO approved PEP schedules for non-previously immunized persons[a]					
5-dose Essen (WHO 1992)	IM	(1-1-1-1-1)	0, 3, 7, 14, 28	5	28
Zagreb 2-1-1 (WHO 1992)	IM	(2-0-1-0-1)	0, 3, 7, 21	3	21
Updated Thai Red Cross (TRC) (WHO 2005)	ID	(2-2-2-0-2)	0, 3, 7, 28	4	28
4-dose Essen (ACIP 2009)[b]	IM	(1-1-1-1-0)	0, 3, 7, 14	4	14
WHO approved expedited PEP schedules for previously immunized persons (booster)[a]					
2-visit PEP	IM/ID	(1-1-0-0-0)	0, 3	2	3
Single day PEP	ID	(4-0-0-0-0)	0	1	1

Table 1: Summary of the 2010 WHO-recommended PEP schedules (prior to the 2018 update). These are recommended for persons with a category II or III exposure (plus RIG, if applicable).

[a] As per the 2010 WHO position, a previously immunized person referred to a person who can document previous complete course of pre-exposure vaccination or complete PEP.

[b] As per the 2010 WHO position, the 4-dose Essen schedule should be used only in healthy, immunocompetent patients who receive wound care, high quality rabies immunoglobulin, and WHO-prequalified rabies vaccines.

PEP regimen	Route	Sites	Days	Clinic visits	Duration (days)
WHO-recommended regimen					
1 week, two sites	ID	(2-2-2-0-0)	0, 3, 7	3	7
2 weeks	IM	(1-1-1-1-0)	0, 3, 7, 14, 28	4	28
3 weeks	IM	(2-0-1-0-1)	0, 7, 21	3	21
Alternative immunogenic ID regimens					
1 month, two sites	ID	(2-2-2-0-2)	0, 3, 7, 28	4	28
1 month, simplified four sites	ID	(4-0-2-0-1)	0, 7, 28	3	28
1 week, four sites	ID	(4-4-4-0-0)	0, 3, 7	3	7

Table 2: Summary of the 2018 WHO-recommended and alternative PEP schedules. These are recommended for persons with a category II or III exposure (plus RIG, if applicable).[1]

As the scientific knowledge improved, the total number of rabies vaccine doses administered for PEP has decreased. The post-exposure prophylaxis was initially for 90 days with 6 injections (1-1-1-1-1-1; Original Essen regimen); but with better understanding of the immunology, this extended regimen was reduced to 30 days using 5 injections (1-1-1-1-1; Essen regimen) and to later to 21 days duration using 4 doses of vaccine (2-1-1; Zagreb regimen)., However, the studies shown that the compliance to complete course of standard Essen regimen was only 60%. Hence, the emphasis was on reducing the long duration PEP with a shorter course, resulting in saving of vaccine, reduced number of visits and travel costs. In this regard, the Cadila Pharmaceuticals Ltd., Ahmedabad, India has developed a novel recombinant nanoparticle-based rabies G protein vaccine (Thrabis®).

Novel recombinant nanoparticle-based rabies G protein vaccine

A novel recombinant nanoparticle-based rabies G protein vaccine is first of its kind can be given in only three doses as intramuscularly on days 0,3,7 and has approved in India only. It's a recombinant nanoparticle-based rabies G protein vaccine which is prepared by using Virus Like Particle technology (VLP). A genetic sequence encoding the rabies G protein sequence is selected for generating Thrabis® using VLP platform. The genes are then cloned into baculovirus. The recombinant baculovirus are made to infect insect cells (sf9). The target antigens are expressed in the sf9 cells which are purified using various chromatographic techniques. The purified target antigen exists as assembly of polypeptides that is present in multiple copies in subunit antigens in a well-ordered array with defined orientations. This can potentially mimic the repetitiveness, geometry, size and shape of the natural host-pathogen surface interactions. Such nanoparticles offer a collective strength of multiple binding sites (avidity) and can provide improved antigen stability and immunogenicity.

The efficacy and safety of novel recombinant nanoparticle-based rabies G protein vaccine was evaluated in a multi-centric, open label, assessor blind, centre-specific block randomized, parallel design, phase III clinical study. The study was conducted among 800 subjects. The eligible subjects were randomized in 2:1 ratio for recombinant rabies G protein vaccine and the reference vaccine. Subjects in recombinant rabies G protein vaccine arm received 3 doses of vaccine on days 0, 3 and 7; while subjects in reference vaccine arm received 5 doses of WHO pre-qualified vaccine on days 0, 3, 7, 14 and 28. The primary objective of study was to demonstrate the non-inferiority of the recombinant nanoparticle-based rabies G protein vaccine on day 14 after first dose relative to the reference vaccine in terms of seroprotection rate (RVNA titer of ≥0.5 IU/mL). The secondary endpoints were the seroprotection rate on day 42 post first dose of the recombinant nanoparticle-based rabies G protein vaccine and the frequency of solicited and unsolicited adverse events (AEs) were reported between day 0 & 180. On day 14, 99.24% in the recombinant rabies G protein vaccine arm and 97.72% in the reference vaccine arm were seropositive; the difference was statistically non-significant. Likewise, on day 42, 98.69% of the subjects in the recombinant rabies G protein vaccine arm and 100.00% in the reference vaccine were seropositive, the difference was statistically non-significant. The safety profile of the recombinant nanoparticle-based rabies G protein vaccine was comparable with the WHO prequalified vaccine. However, statically significant higher number of participants in the reference arm had adverse events (AEs) compared to test arm (17.2% vs 9.9%, P=0.0032). All the AEs were mild to moderate in nature, which resolved without any complications. The most frequently observed local AEs were pain, redness and swelling at the injection site. The systemic AEs were fever, headache, ear pain, urticaria, joint pain and nausea. Further studies will be initiated to assess the immunogenicity in category III exposures, and to know whether RIGs will interfere with the antibody production and long-term immunogenicity levels upto 6 months. The strength of this study includes a robust protocol, the inclusion of a fairly large number of participants from multiple sites, good compliance rate, inclusion of primary endpoints as approved by WHO and the robust analytical methods followed. There are a few limitations; as the open-label design could lead to few reporting bias as subjective outcomes and the study has not included special population (pediatric/elderly population and pregnant/lactating women, etc.); which will be considered for the future studies. The study was conducted for IM route and no data is available for ID route. The long-term safety data is also awaited from phase IV study. We hope in future lager data will be available and might be approved by WHO.

Conclusion

In past few years duration of PEP has significantly reduced from 90 days to 1weeks with fewer visits to clinics and improved compliance. The addition of novel 3 dose recombinant nanoparticle-based rabies G protein vaccine may be breakthrough this filed and we may expect to move from 3 dose just 1 dose in future to prevent rabies and ultimately help in eliminating dog mediated human rabies by 2030.

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