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A Novel 3 Dose Rabies Vaccine

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ABSTRACT

Rabies is a vaccine-preventable disease. However, the compliance to the complete course of vaccines is found to be only 40%. Hence, there is a need for a safe and immunogenic, shorter course vaccine that can enhance compliance and effectively prevent the disease. In this regard, a novel 3 dose recombinant nanoparticle-based rabies G protein vaccine is developed by using Virus-Like Particle technology (VLP) that can provide improved immunogenicity and safety. The reduced number of vaccine doses leads to a reduction in number of visits and travel cost; as well as increases the compliance, which is important to prevent rabies.

Keywords: Rabies; Recombinant Rabies G Protein; VLP

Abbreviations: VLP: Virus-Like Particle Technology; RABV: Rabies Virus; PEP: Postexposure Prophylaxis; 3D: Three-Dimensional; AEs: Adverse Events

Introduction

Rabies is a zoonotic viral disease that is caused by rabies virus (RABV) and claims the highest fatality among all infectious diseases. Rabies is found in more than 100 countries and territories [1]. To prevent rabies, timely and complete postexposure prophylaxis (PEP) is necessary. Currently five doses of rabies vaccine are administered on days 0, 3, 7, 14, and 28 but the studies have shown that the compliance to complete course was only 40% [2]. Therefore, an effective way to address these limitations is the reduction of PEP doses in humans and a novel vaccine with improved immunological outcomes through an accelerated PEP schedule is desirable. In this regard, Cadila Pharmaceuticals Ltd., Ahmedabad, India has developed a novel recombinant nanoparticle-based rabies G protein vaccine (Thrabis®) prepared by using Virus Like Particle technology (VLP).

Recombinant Nanoparticle-Based Rabies G Protein Vaccine

For generation of recombinant rabies G protein vaccine using VLP platform; genetic sequences encoding the rabies G protein sequence are selected. The genes are then cloned into baculovirus and the baculovirus was made to infect insect cells (sf9). The target antigens were expressed in the sf9 cells which were purified using various chromatographic techniques. The purified target antigen exists as an assembly of polypeptides that is present in multiple copies in subunit antigens in well-ordered arrays with defined orientations [3]. 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 [4,5]. Safety is a major advantage of VLPs. Like traditional vaccines, VLPs are immunogenic and excellent to control infectious diseases. VLPs cannot replicate, recombine or undergo reassortment because they do not contain infectious DNA or RNA material; therefore, VLPs are safer than traditional vaccines. VLPs possess several advantages over the products that are produced by chemical syntheses such as smaller size, which ranges from 10 to 2000 nm, availability of high-resolution three-dimensional (3D) models of their structure, construction flexibility,

high-production yields, and structural uniformity of each type of virus or VLP [6].

Clinical Study

A multi-centric, open label, assessor blind, centre-specific block randomized, parallel design, phase III clinical 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 was to demonstrate the non-inferiority of the test vaccine on day 14 after first dose relative to the reference vaccine in terms of seroprotection rate (RVNA titer of ≥0.5IU/mL). The secondary endpoints were the seroprotection rate on day 42 post first dose of the study vaccine and the frequency of solicited and unsolicited adverse events (AEs) were reported between day 0 & 180. On day 14, 99.24% in the test 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 test vaccine arm and 100.00% in the reference vaccine were seropositive, the difference was statistically non-significant. A 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 [3].

Conclusion

The novel 3 dose recombinant rabies G protein vaccine (Thrabis®) was found to be safe & immunogenic and was comparable to 5 doses of WHO pre-qualified vaccine in simulated post exposure prophylaxis. The reduced number of vaccine doses leads to a reduction in number of visits and travel cost; as well as increases the compliance, which is important to prevent rabies and ultimately help in eliminating dog mediated human rabies by 2030 [7].

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