

Perspective

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/apjtm.apjtm_571_24

TAK003 dengue vaccine: A promising tool for dengue control

Nitika Nitika[1,2]✉, Praveen K Bharti[1,2]

[1]*ICMR–National Institute of Malaria Research, Sector 8, Dwarka, 110077, New Delhi, India*

[2]*Academy of Scientific and Innovative Research, NCR–Delhi, India*

Dengue, an arboviral disease caused by infection with one of the four distinct serotypes is one of the 10 global health threats confirmed by the World Health Organization (WHO) in 2019[1]. There has been an exponential increase in dengue cases over last few years, attributed to unplanned urbanization, climate change, and migration, *etc*. Nearly 4 billion people worldwide in more than 100 countries are at risk of dengue, and 390 million infections occur every year, with 90 million symptomatic infections[2]. The spectrum ranges from asymptomatic, mild, to severe dengue, leading to hospitalizations and even death[3]. Due to unavailability of therapeutics for treating dengue, it is imperative to expand the arsenal by including vaccines in the efforts to combat dengue worldwide.

There were several challenges in the development of dengue vaccine: absence of immune correlate of protection, lack of animal model, limited ability of vaccine to initiate homotypic immune response for all the serotypes for neutralizing the virus and at the same time, without resulting in antibody-dependent enhancement in subsequent infections. Before concluding on the safety of vaccine, it is essential to rule out that vaccine-recipients do not experience severe breakthrough infections. Despite the challenges, continuing research in the field led to successful development of few vaccines. The first breakthrough was the approval of three-dose Dengvaxia (CYD-TDV), a live attenuated vaccine built on yellow fever virus (17D) backbone in 2015; however, later it was found to increase the chances of developing severe dengue disease in seronegative vaccine recipients, and therefore, the pre-vaccination screening for ascertaining the sero-status before vaccine administration was included in the vaccination strategy. CYD-TDV vaccine is more effective against serotype 3, and 4 in comparison to 1 and 2[4], and since it is devoid of any non-structural protein of the virus, it does not elicit cellular immune response.

The second breakthrough was development of TAK003 (Qdenga) vaccine. This vaccine is built on dengue virus serotype 2 backbone and chimeric virus expressing prM and E of dengue virus serotype 1, 3, 4. By virtue of the structural design, the vaccine also has non-structural protein of the DENV-2, and thus initiates cellular immune response. The phase 3 trial for this vaccine was conducted in Latin America and South-east Asia. The vaccine showed promising results: 62% efficacy against virologically confirmed dengue and 84% efficacy against hospitalization with no important safety risks identified in the first half of the long-term follow-up phase[5]. Though the trial was conducted according to the WHO guidelines, vaccine efficacy could not be assessed for these two serotypes in seronegative individuals due to low occurrence of serotype 3 and 4. Thus, chances of occurrence of breakthrough severe disease after infection with serotype 3 or serotype 4 cannot be ruled out. Notably, for serotype 1, and 2, TAK003 confirmed protection for severe dengue even in seronegative vaccine recipients. Overall, the vaccine induced immunity seems to be independent of serostatus, and increased risk for DENV-3 though statistically insignificant, and no inference could be drawn for DENV-4 owing to fewer number of cases. The vaccine is administered subcutaneously in two doses of 0.5 mL each (at 0, and 3 months). The vaccine is approved in Europe, Brazil, UK, Argentina, Indonesia, and Thailand. The WHO in September, 2023, recommended the countries for including the Qdenga vaccine in their routine immunization programmes for 6-16 years age range and in high transmission setting. The use in low and moderate dengue transmission settings is not recommended by the WHO. Moreover, for this vaccine, pre-vaccination screening

✉To whom correspondence may be addressed. E-mail: dr.nitika11@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

©2024 *Asian Pacific Journal of Tropical Medicine* Produced by Wolters Kluwer-Medknow.

How to cite this article: Nitika N, Bharti PK. TAK003 dengue vaccine: A promising tool for dengue control. Asian Pac J Trop Med 2024; 17(11): 477-478.

Article history: Received 12 September 2024 Revision 30 September 2024
Accepted 17 October 2024 Available online 6 November 2024

for ascertaining the sero-status is not recommended, thus easing the vaccine roll-out process. Recently, the vaccine has been adopted by Brazil health system and initiated the vaccinations in January, 2024 through the National Immunization Program.

With the hope and optimism of tackling dengue with the wider use of TAK-003, there are a few unanswered questions necessitating continuing research: (1) As the disease burden is spreading beyond childhood and adolescence, it is essential to determine the effectiveness of the vaccine in adults and elderly population; (2) Effect of genetic diversity and complexity in virus on the vaccine efficacy; (3) How the vaccine performs in real world settings; (4) Requirement of booster dose, if yes, what is the appropriate gap after which it should be administered; (5) How the vaccine performs against other serotype (DENV-3, and DENV-4) infections; (6) Requirement of immuno-bridging studies or full trial for other countries; (7) Cost-effectiveness of vaccine; (8) How the waning immunity increases the chances of developing the severe disease in vaccine recipients; (9) Risk of antibody dependent enhancement in case of secondary infection with DENV-3 and DENV-4 in seronegative vaccine recipients; (10) Contribution of cellular immune response in protecting vaccinated individuals; (11) Chances of severe breakthrough dengue disease for serotype 3 and 4.

Despite all the above-stated points, TAK003 vaccine has the potential to revolutionize dengue control and will aid in reducing hospitalizations episodes and mortality. The trial has provided results up to 4.5 years; however, it is worthy to see the duration of protection beyond 5 years, and pharmacovigilance should be done in the countries using the vaccine through their public health system, for identifying any long-term side-effects of the vaccine. With other vaccines in pipeline, like single dose TV005 providing balanced protection against all the serotypes of dengue, eventually comparing the real-world effectiveness and feasibility of usage in varied settings will become pertinent. In addition, research to study the effectiveness of sequential vaccination (as used for coronavirus disease and HIV) using TAK003 followed by CYD-TDY, and its effect on immunogenicity and protection in the vaccine recipients is necessary. Notably, public-health usage in large setting will require upscaling of manufacturing for uninterrupted supply of vaccines. To conclude, TAK003 vaccine with rapid onset of protection, efficacy against DENV-1 and -2 and durable protection seems to be promising, and can revolutionize the fight against dengue in tropics and subtropics and in saving human lives.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Funding

The authors received no extramural funding for the study.

Authors' contributions

NN drafted the manuscript, and conceived the idea. PKB provided critical inputs and drafted the manuscript

References

[1] Friedrich MJ. WHO's top health threats for 2019. *JAMA* 2019; **321**(11): 1041.

[2] Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: An analysis from the Global Burden of Disease Study 2013. *Lancet Infect Dis* 2016; **16**(6): 712-723.

[3]Sahu MC, Samantaray RK, Pal A, Pati S. Recent advances on pathogenesis, diagnosis, prevention, immunological aspects, and vectors of dengue: A review. *Asian Pac J Trop Biomed* 2023; **13**(8): 325-338.

[4] Flasche S, Jit M, Rodríguez-Barraquer I, Coudeville L, Recker M, Koelle K, et al. The long-term safety, public health impact, and cost-effectiveness of routine vaccination with a recombinant, live-attenuated dengue vaccine (Dengvaxia): A model comparison study. *PLoS Med* 2016; **13**(11): e1002181.

[5] López-Medina E, Biswal S, Saez-Llorens X, Borja-Tabora C, Bravo L, Sirivichayakul C, et al. Efficacy of a dengue vaccine candidate (TAK-003) in healthy children and adolescents 2 years after vaccination. *J Infect Dis* 2022; **225**(9): 1521-1532.

Publisher's note

The Publisher of the *Journal* remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Edited by Zhang Q, Pan Y, Lei Y