Repurposing a Flu Treatment For Severe Dengue Patients in Colombia

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SUMMARY STATEMENT

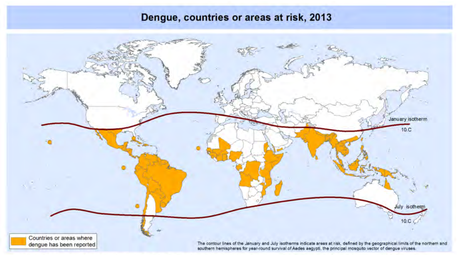
A proof-of-concept clinical trial to test the efficacy of an influenza medication to treat vascular permeability syndrome during severe dengue fever.

DISEASE/CONDITION

- Dengue viruses are among the leading causes of pediatric morbidity and mortality globally, affecting over 100 countries.
- The burden of dengue disproportionately affects those in LMICs due to increased environmental risk and decreased health care
- Dengue vascular permeability syndrome, the syndrome whereby dengue infection leads to leaking blood vessels and shock, is the primary cause of death in dengue infections.

CURRENT TREATMENT

There is currently no specific effective treatment for dengue infection and management involves supportive care only.

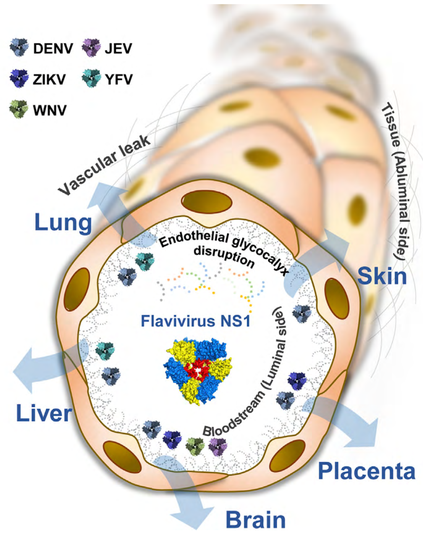


PROPOSED TREATMENT

Repurposing an approved influenza medication, Zanamivir, to protect leaky blood vessels, which is the primary cause of dengue-related death.

Dengue virus non-structural protein-1 (NS1) contributes to the vascular permeability syndrome that is characterized by leaking blood vessels that can lead to shock and death. After being secreted by infected cells, dengue NS1 can bind to the surface of blood vessel endothelial cells. NS1 increases the expression of the sialidase enzymes such as Neu1, Neu2, and Neu3 that lead to destruction of sialic acid on the surface of endothelial cells causing degradation of the cellular layer protecting the blood vessel, thus resulting in barrier dysfunction and leakage.

Zanamivir is an inhaled medication approved to treat influenza A and B. It is considered to be safe for use in adults and children. Zanamivir significantly inhibits Neu 2 and Neu3 sialidases that are upregulated in dengue infection and cause blood vessel leakage. In-vitro experiments have demonstrated that Zanamivir administration inhibits sialic acid destruction. These studies are further supported by a mouse model showing that Zanamivir stopped the increased leakage observed following dengue infection. Therefore, evidence from in-vitro and animal models indicate that Zanamivir may be a safe and effective treatment for dengue vascular permeability syndrome in humans.



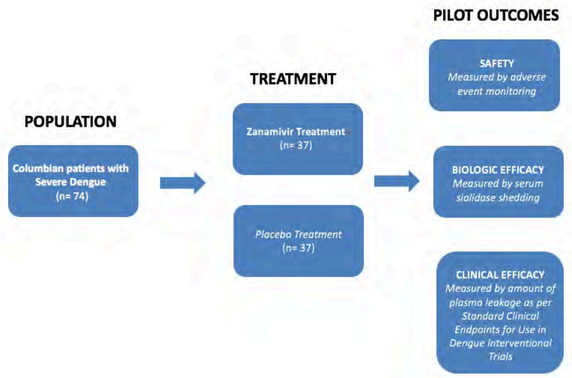
Puerta-Guardo H, Glasner DR, Espinosa DA, et al. Flavivirus NS1 Triggers Tissue-Specific Vascular Endothelial Dysfunction Reflecting Disease Tropism. Cell Reports. 2019;26(6):1598-1613.e1598

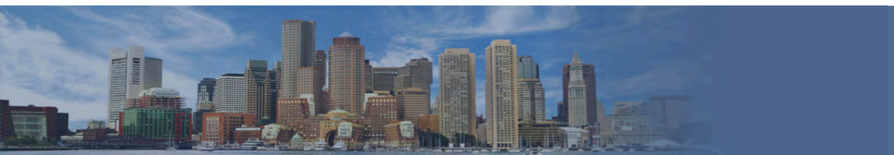
PROJECT

A randomized, placebo-controlled pilot to evaluate the preliminary safety and efficacy of Zanamivir treatment during severe dengue infection.

Patients with dengue with alarm signs or severe dengue (N=74) at our clinical sites in Barranquilla, Cúcuta and Fundación, Colombia, which are sites of endemic transmission of dengue fever, will be randomized to receive Zanamivir (5 mg two puffs inhaled 2x daily) for 5 days versus placebo. Patients will receive daily study visits during treatment including symptom questionnaires and blood draw to assess hematocrit and concentrations of Neu2, Neu3, and sialic acid during therapy and 2 weeks following therapy.

- The potential for translation to routine human use is great because this drug is already widely used in adults and children.
- This pilot trial allows testing of a desperately needed medication for dengue fever affecting ~96 million people per year.
- Data gained will build the foundation for a larger confirmatory trial.





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