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LATEST UPDATES ON DENGUE TREATMENTS

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Abstract: Objective: To review and analyze the latest developments in therapeutic approaches to dengue, including pharmacological treatments, vaccines and intervention and prevention approaches, evaluating their efficacy, safety and implications for the clinical management of the disease. **Methodology**: Narrative bibliographic review, which used the electronic database PubMed. The search terms were used in combination with the Boolean operators "AND" and "OR", using the following strategy: (Dengue) AND ((Therapeutics) OR (Vaccine) OR (Antiviral) AND ((Prognosis) OR (Efficacy). A total of 21 articles were selected for detailed analysis. **Review**: Discussing treatments for dengue, several therapeutic approaches emerged as promising. In addition, a clinical trial highlighted that the probiotic Lactococcus lactis plasma strain (LC-Plasma) significantly reduces the duration of dengue symptoms, pointing to a potential use of probiotics in modulating the immune response. Another strategy includes the repurposing of fluoroquinolones, with enoxacin suppressing Zika virus replication, indicating potential applicability against flaviviruses. These innovations represent significant advances in the clinical management of dengue, offering new hope for more effective treatments. **Final Considerations**: Advances in vaccines and therapies against dengue are highlighted, but highlights the variation in the effectiveness of these interventions due to the history of exposure to the virus and the type of dengue. It emphasizes the need for more accurate diagnoses and personalized treatments, in addition to pointing to the importance of integrated approaches and continuous research to overcome existing limitations in combating the disease.

Keywords: Dengue; Vaccine; Treatment; Antivirals.

INTRODUCTION

Dengue is a pathology of notable epidemiological importance with profound global impact. Aedes aegypti, its main vector, adapts effectively to densely populated urban environments in tropical and subtropical regions (Hok et al., 2022). The dengue virus, composed of four serotypes (DENV-1, DENV-2, DENV-3, DENV-4), is capable of causing mild cases to hemorrhagic forms of the disease (Pinheiro-Michelsen et al., 2020).

Currently, it is estimated that around 390 million cases of dengue occur annually, making it the fastest growing vertically transmitted disease in the world. Clinical conditions range from asymptomatic to severe forms, such as dengue hemorrhagic fever (Vasey et al., 2020). In many countries, the situation is characterized by hyperendemicity, interspersed with epidemic outbreaks that mainly affect young people, increasing pressure on already fragile health systems (Pinhero-Michelsen et al., 2020).

Although there is no specific antiviral therapy and the limitations of vaccines persist, control strategies aimed at vectors are insufficient to contain their spread (Norshidah; Vignesh; Lai, 2021). Even with the elimination of infected mosquitoes, susceptible vectors remain present. Although a vaccine is available, recent studies raise concerns about long-term safety, especially among those vaccinated without prior exposure to the virus (Sow; Diallo; Cherifi, 2024).

Faced with the global epidemic, the search for a specific and effective treatment is intense, with an increasing number of cases each year (Kok et al., 2023). The complexity in the development of medicines and vaccines continues to be a challenge for the efficient clinical management of the disease. There are currently around six dengue vaccines in development, with only one licensed for use in endemic countries. This reflects the great challenge of balancing the benefits and risks of such interventions (Pinheiro-Michelsen et al., 2020; Nascimento et al., 2023). Therefore, the present study aims to review and analyze the most recent developments in therapeutic measures for dengue, including pharmacological treatments, vaccines and intervention and prevention approaches, in order to evaluate the efficacy, safety and implications in the clinical management of the disease in the face of such possibilities.

METHODOLOGY

Bibliographic review, narrative developed according to the criteria of the PVO strategy, acronym that represents: population or research problem, variables and outcome. Used to prepare the research through its guiding question: "What are the latest updates and advances in dengue therapies, and how do they impact clinical management and patient outcomes?" The searches were carried out using the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) database. The search terms were used in combination with the Boolean operators "AND" and "OR", using the following search strategy: (Dengue) AND ((Therapeutics) OR (Vaccine) OR (Antiviral) AND ((Prognosis) OR (Efficacy).

From this search, 461 articles were found, subsequently submitted to the selection criteria. The inclusion criteria were: articles published in the period from 2019 to 2024 and which addressed the themes proposed for this research, studies of this type; review, meta-analysis, observational studies, experimental studies and made available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. application of the inclusion and exclusion criteria, 21 articles were selected to compose the collection of the present study.

REVIEW

Dengue has become an increasingly prevalent cause globally. In the manifestation of severe dengue, defects in coagulation and hyperfibrinolysis are observed, reinforcing the importance of monitoring markers such as activated partial thromboplastin time and D-dimer. Standardizing disease progression into phases allows for more effective statistical analysis and standardized comparison. Differentiating between mild dengue fever and severe forms remains a challenge, especially in the early stages of infection. Falconi-Agapito et al. (2022) highlighted the PG-9 peptide, which proved to be 73% sensitive for detecting dengue in recently infected patients (less than 8 days since the onset of symptoms). The FPG-1 peptide was the most effective for identifying dengue fever in patients in the recovery phase (more than 10 days since the onset of symptoms), with a sensitivity of 86%. Combining all samples, PM-22 and FPG-1 peptides showed the best diagnostic performance, with sensitivities of 60% and 61.1% and areas under the curve (AUC) of 0.7865 and 0.8131, respectively (Raafat et al.,2019).

Current dengue diagnosis methods have limitations and, apart from adequate hydration, there is no specific treatment. Dengue classification guidelines have been updated to improve detection of severe cases, although specificity remains a challenge. The commercially available Dengvaxia vaccine is restricted to individuals with a prior history of dengue due to safety concerns. Understanding pathogenesis and identifying early biomarkers is crucial for developing diagnostic tests and supportive strategies and for guiding vaccination studies.

Facing potential treatment approaches, Shukla et al. (2023) found that the aqueous extract of Cocculus hirsutus stem (AQCH), Sinoloculin, was effective both in vitro and in vivo against DENV, decreasing serum viremia, viral load and expression of pro-inflammatory cytokines (Shukla et al., 2023). A study by Hengphasatporn et al. (2021) suggested that flavonoids are significant anti-flavivirus agents.

In this study, a terminal alkyne was added to the hydroxyl group of the B ring of flavonoids, showing low toxicity to the organism (Hengphasatporn et al., 2021).

Khor et al. (2021) in a randomized, double-blind, placebo-controlled trial, evaluated the effectiveness of ingesting Lactococcus lactis plasma strain (LC-Plasma) tablets in reducing the severity and duration of dengue symptoms in healthy volunteers. The results showed a significant reduction in the duration of symptoms such as fever, arthralgia, myalgia and retro-orbital pain compared to the placebo group (Khor et al., 2021). Scroggs et al. (2020) tested three fluoroquinolones - enoxacin, difloxacin, and ciprofloxacin - against DENV. They found that enoxacin suppressed Zika virus (ZIKV) replication at an intermediate step in the virus's life cycle, while the other two quinolones showed a broader window of effectiveness. In mice treated with enoxacin, reduced serum levels of ZIKV were observed in the testis (Scroggs et al., 2020).

Finally, Gunale et al. (2024) demonstrated that monoclonal antibodies against dengue were safe and well tolerated, with grade I and II adverse reactions, all treatable. The study also highlighted the need for further investigation into the long-term efficacy and safety of these antibodies (Gunale et al., 2024). Falconi-Agapito et al. (2022) also highlighted the PG-40 peptide as a potential biomarker for determining serostatus, essential to guide vaccination with Dengvaxia, which is not approved for children under 9 years of age nor for individuals without previous exposure to dengue (Huy and Toàn, 2022).

In 2015, the first dengue vaccine was licensed, Dengvaxia or CYD-TDV, a tetravalent live attenuated virus vaccine, based on the yellow fever vaccine (Biswal et al., 2019). Recent studies demonstrate that the effectiveness of this vaccine is intrinsically linked to the individual's previous serological status. For those previously infected with the dengue virus, the vaccine has shown high efficacy and safety. However, for seronegative individuals, there is an increased risk of developing severe forms of dengue when exposed to the virus naturally (Silveira; Tura; Santos, 2019). There are several studies on the dengue vaccine that face significant challenges, mainly due to the presence of four serotypes of the virus. Some approaches test the need for single doses or combined treatments between vaccines and drugs. The intention is that the vaccine induces both neutralizing antibodies and a protective response from T cells, which are responsible for recognizing and destroying the virus. However, this can also cause an exacerbated response in cases of secondary infection, worsening the clinical picture.

Other types of vaccines, such as attenuated viruses, subunit vaccines, nucleic acid vaccines and inactive tetravalent vaccines, are still being studied to prove their effectiveness. Studies have shown that DNA vaccines based on prM and E proteins are effective. However, one problem identified was the cross-reactivity of the immune response between DENV and ZiKV, which can exacerbate pathogenesis. Recent research suggests that the dengue vaccine must be pentavalent, not just tetravalent, including Zika virus antigens (Alves; Costa; Pinto, 2021; Wilder-Smith, 2024).

Studies indicate that the first dengue infection develops a durable serotype-specific neutralizing antibody response, correlated with resistance to reinfection by the same serotype. However, if the secondary infection crosses with a different serotype than the primary infection, the immune response is exacerbated, worsening the individual's clinical condition. Another problem encountered was that the effectiveness of protection in children is not reliable, developing neutralizing antibodies for some serotypes in an ineffective way (Henein et al., 2021).

According to Dayan et al. (2020), the effectiveness of the licensed dengue vaccine was maintained for up to 6 years in seropositive individuals aged 9 years or older, being lower in seropositive individuals under 9 years of age. This greater efficacy may be related to the dengue serotype in these individuals. However, it is certain that CYD-TDV reduced hospitalizations for severe dengue for at least 5 years, although the risk for individuals who were seronegative increased.

Vasey et al. (2020) report that in around 10% of cases, the disease evolves into a serious and life-threatening syndrome. Although hematological derangement is a key indicator, the pathophysiological mechanisms of changes occurring during infection remain unclear. Therefore, clinical examination of the patient is essential to determine appropriate management. Piecewise linear mixed-effects regression models revealed significant differences in the rates of change of several blood variables between dengue cases and other febrile illnesses. Specific values of these variables, such as albumin, fibrinogen and thrombin time, have been identified as predictors of severe dengue during the critical phase of the disease, expanding our understanding of how dengue develops and offering new approaches to the diagnosis and prognosis of disease severity. (Vasey et al., 2020).

FINAL CONSIDERATIONS

The main trends and challenges in the development of effective therapies against dengue were identified and the results highlight notable advances in the efficacy and safety of existing and developing vaccines, as well as the potential for new pharmacological treatments. However, the effectiveness of these interventions varies significantly depending on the patient's virus exposure history and the type of dengue. This variation highlights the need for more accurate diagnoses and personalized treatment strategies. The studies reviewed indicate that, despite progress, we still face substantial limitations in the prevention and treatment of dengue, particularly in relation to the effectiveness of vaccines against different serotypes of the virus. This reinforces the importance of a multifaceted approach that combines vaccination, improved diagnostics and antiviral therapies to effectively manage the disease. The need for future research is evident, especially to explore treatments that may be effective regardless of individuals' viral exposure history. It is recommended that future studies focus on developing vaccines that cover all dengue virus serotypes, as well as investigating antiviral therapies that can mitigate the severity of symptoms in acute cases. International collaboration and continued investment in research are essential to overcome the challenges presented by this prevalent and potentially serious disease. Integrating these new discoveries into clinical practice could significantly transform the global healthcare landscape, improving outcomes for millions of people affected by dengue annually.

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