Effectiveness of Montelukast in Reducing the Risk of Severe Dengue in Dengue Fever Patients: An Evidence-Based Case Report

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ABSTRACT

Background: *Dengue fever continues to spread worldwide, particularly in tropical regions. Some patients with dengue fever may progress to severe dengue, which is associated with significantly higher morbidity and mortality. Despite this, no definitive treatment has been found to prevent its progression. Montelukast, a leukotriene receptor antagonist, has shown potential in reducing plasma leakage, a key factor in the pathophysiology of severe dengue. Therefore, this study aimed to evaluate the effectiveness of montelukast in reducing the risk of severe dengue.* ***Methods:*** *A systematic literature search was conducted on April 16, 2025, using keywords related to montelukast and dengue across four databases, which included PubMed, Taylor and Francis, Cochrane Library, and ScienceDirect. A critical appraisal was performed using the Oxford Centre for Evidence-Based Medicine framework, evaluating the validity, importance, and applicability of each study. The primary outcomes were the incidence of dengue shock syndrome and dengue with warning signs. The secondary outcomes included mortality rate and hospitalization duration.* ***Results:*** *This study included three studies involving a total of 1057 patients. Montelukast is associated with a reduced incidence of dengue shock syndrome and shorter duration of hospitalization. However, the effect of montelukast on dengue with warning signs and mortality rate was inconclusive.* ***Conclusion:*** *Montelukast shows potential as an adjuvant therapy in preventing the progression of dengue fever to severe dengue. However, further research is required before montelukast can be widely recommended for dengue fever patients in daily clinical practice and possibly integrated into dengue fever clinical guidelines.*

Keywords**:** *evidence-based case report, severe dengue, dengue fever, leukotriene receptor antagonist, montelukast.*

INTRODUCTION

Dengue fever is an acute infectious disease caused by the dengue virus, predominantly transmitted to humans via the Aedes mosquito. Four antigenically distinct serotypes of the virus, DENV-1, DENV-2, DENV-3, and DENV-4, are known to infect humans.[1] Dengue causes an estimated 50 million to 200 million infections annually, with 500,000 cases progressing to severe dengue (DHF/DSS) and over 20,000 dengue-related deaths.[2] These numbers are expected to rise, placing an even greater burden

on healthcare systems, especially in endemic tropical regions.[3]

To date, there is no specific antiviral therapy approved for dengue virus infection. Treatment strategies remain primarily supportive, focusing on symptom relief, immune system support, and prevention of complications.[4] More importantly, no drugs have demonstrated efficacy in preventing the progression of dengue infections to severe dengue manifestations.

Primary dengue virus infection is often asymptomatic and self-limiting. However, some patients might progress to a more severe clinical phenotype, including dengue with warning signs, Dengue Haemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS), as defined by the World Health Organization (WHO) guidelines.[5] Dengue with warning signs is characterized by persistent abdominal pain, recurrent vomiting, plasma leakage resulting in fluid accumulation, haemorrhagic manifestations, lethargy, or hepatomegaly. DHF is characterized by coagulopathy, increased vascular permeability, and plasma leakage. DHF may progress to cause hypovolemic shock, causing a condition called DSS.[6] These severe forms of dengue infection are associated with a significantly increased risk of morbidity and mortality. DSS is considered a prognostic factor for fatal outcomes in dengue infections.[7] Consequently, preventing the progression of dengue infections to DHF and DSS is crucial for reducing severe outcomes.

The pathogenesis of DSS involves plasma leakage caused by enhanced vascular permeability. The process is mediated by a cytokine storm and the release of inflammatory mediators during severe dengue infection.[8] A recent preclinical study has found that montelukast, a selective leukotriene receptor antagonist, shows potential in preventing plasma leakage and dengue-associated vascular pathology in animal models infected with the dengue virus.[9] Montelukast exerts its effect by inhibiting the binding of leukotrienes to cysteinyl leukotriene receptors, thereby disrupting the cascade leading to endothelial dysfunction and plasma leakage, which is key to DHF and DSS pathogenesis.[10]

CASE ILLUSTRATION

A 22-year-old male presented with an abrupt onset of high-grade fever for three days before hospital admission. The fever was intermittent with diurnal variation and was associated with generalized myalgia. The patient also reported abdominal discomfort, with intermittent pain in the epigastric region and right lower quadrant of the abdomen. In addition, the patient experienced loose stools of soft consistency, brown in colour, but without mucus or blood. Abdominal distension and nausea were also present. There were no abnormalities in urination or defecation. The patient denied experiencing systemic symptoms, such as arthralgia, epistaxis, respiratory symptoms, dyspnea, or bleeding manifestations. There was no recent travel history.

The patient was fully alert, with a Glasgow Coma Scale score of 15. Vital signs were stable with a blood pressure of 104/62 mmHg, a heart rate of 61 beats per minute, and a temperature of 37.4°C. Abdominal examination revealed localized tenderness in the epigastric region and right lower quadrant. Laboratory findings showed a haemoglobin level of 15.6 g/dL, a haematocrit of 46.4%, a leukocyte count of $4.3 \times 10^3/\mu L$, and a platelet count of $189 \times 10^3/\mu L$. Liver function tests showed an AST of 38 U/L and an ALT of 17 U/L. Dengue NS1 antigen testing was positive. The complete laboratory results are summarized in Table 1. The consultant then considered initiating oral montelukast to prevent the patient from progressing to severe dengue infection. Based on this case, this study aims to analyze the effectiveness of montelukast in reducing the risk of severe dengue in patients diagnosed with dengue fever.

METHODS

PICO Framework

The population of this study consisted of adult patients diagnosed with dengue fever. The intervention evaluated was oral montelukast 10 mg administered once daily, compared to standard therapy for dengue fever, which served as the control group. The

primary outcomes assessed in this study were the incidence of dengue shock syndrome and the incidence of dengue with warning signs. The secondary outcomes evaluated in this study were mortality rates and duration of hospitalization.

Search Strategy and Article Selection

A literature search was conducted on 16 April 2025 across four databases: PubMed, Taylor & Francis, Cochrane Library, and ScienceDirect. The search was conducted with the keyword (“montelukast" OR "leukotriene receptor antagonist" OR "Singulair") AND ("dengue" OR "dengue fever" OR "dengue virus infection" OR “DENV”).

Eligibility Criteria

This evidence-based case report included studies involving adult patients diagnosed with dengue fever who received oral montelukast at a dose of 10 mg per day. The control group in each study received standard therapy without montelukast. The outcomes of interest were the incidence of DSS, the incidence of dengue with warning signs, the length of hospitalization, and mortality. This study included randomized controlled trials, cohort studies, case-control studies, systematic reviews, and meta-analyses published in the last 10 years. Only articles published in the English language were considered. Studies were excluded if they involved pediatric populations, focused solely on laboratory or molecular parameters without reporting clinical outcomes, had very short follow-up durations without reporting complications, or were deemed to have a high risk of bias.

Critical Appraisal

The critical appraisal was conducted using standardized tools provided by the Centre for Evidence-Based Medicine (CEBM), University of Oxford.[11] All included studies will be assessed for their validity, importance, and applicability based on the CEBM tools. Two reviewers independently assessed the quality of the included studies, and any disagreements were resolved through discussion with a third author until consensus was reached.

RESULTS

Search Results

Figure 1 shows a Preferred Reporting Items for a Systematic Review and Meta-Analysis (PRISMA) flowchart outlining the sequential steps applied in the selection of studies. Upon searching four databases, 8 studies were identified from PubMed, 15 studies from Taylor and Francis, 119 studies from ScienceDirect, and 5 studies from the Cochrane Library. After screening and removing duplicates, six studies were retrieved and assessed for eligibility. A total of three articles were considered relevant based on the inclusion and exclusion criteria and were therefore included in this study.

Characteristics of Included Studies

Table 1 presents the characteristics of the included studies. Three studies were included, conducted in India[12], Thailand[13], and Pakistan[14]. Of the three studies, two[13,14] were randomized controlled trials while one study[12] was a prospective observational study. A total of 1,057 participants were enrolled across the three studies, with an equal distribution between the intervention and control groups. All three studies used montelukast 10 mg once daily as the intervention group and standard therapy as the control.

Critical Appraisal: Validity

Table 2 summarizes the validity of the three included studies. Two studies[13,14] were considered to have high validity, while one study[12] was considered to be of moderate validity. The study by Dev A et al was considered to have moderate validity due to the absence of randomization and blinding, which were not feasible due to the study design.

Critical Appraisal: Importance

DSS incidence outcome results were presented in **Table 3**. Dev et al found that the Montelukast group had a significantly lower risk for DSS incidence compared to the control group [RR 0.19 (95% CI: 0.07 - 0.55); ARR 7%; RRR 81%; NNT 14.71].[12] Similarly, Ahmad A et al reported a reduced risk in the montelukast group, with RR 0.29 (95% CI: 0.15 - 0.58); ARR 0.22; RRR 0.71; NNT 4.55.[14] Meanwhile, a study done

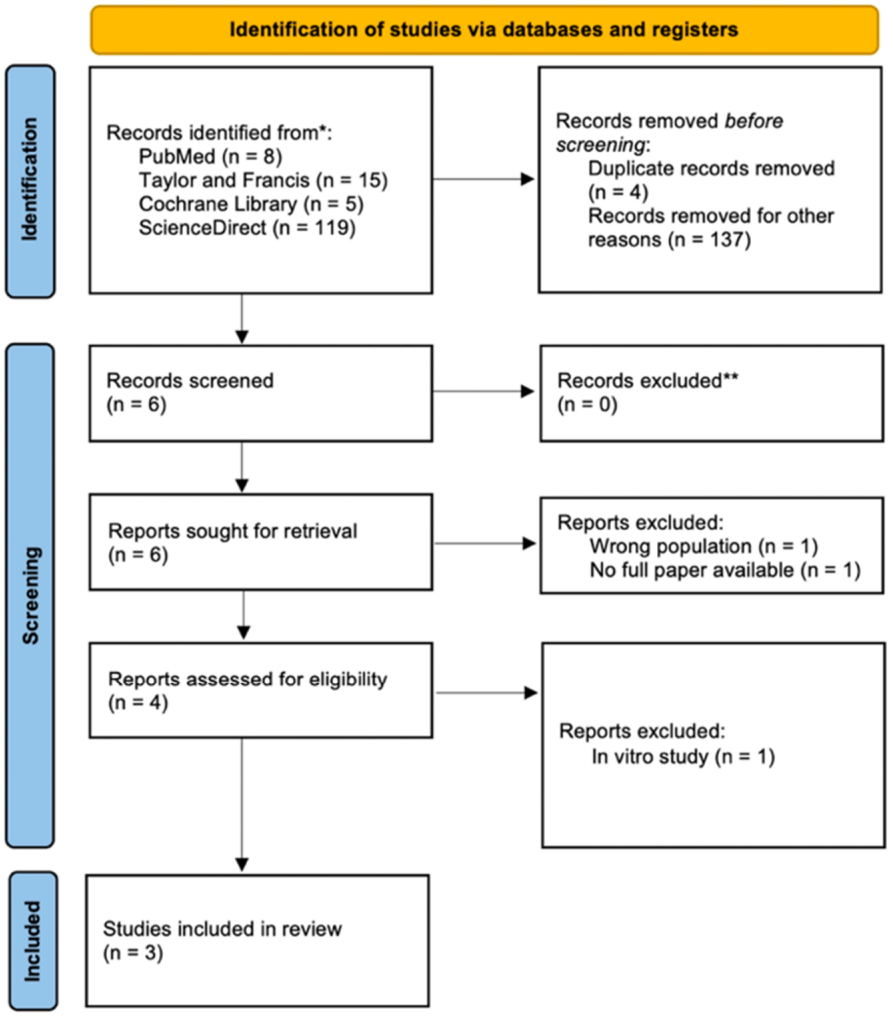

Figure 1. Flowchart of the article selection process

by Nitinai N et al found that out of 357 patients, none experienced DSS, hence relative risk could not be calculated.[13]

Table 3 presents the results for the incidence of dengue with a warning sign. Two studies evaluated the incidence of dengue with a warning sign as an outcome. Dev et al found that patients who received montelukast had a lower risk of developing dengue with warning signs [RR 0.6 (95% CI = 0.49 - 0.73); ARR 24%, RRR 40%; NNT 4.17].[12] In contrast, Nitinai N et al reported a higher risk in the montelukast group compared to the control group [RR 1.18 (95% CI = 0.88 - 1.60), ARR -5%, RRR -18%, NNT -18.45].[13]

Two studies analysed mortality rate as an outcome, and the results were presented in **Table 3**. Dev et al found that there were no significant differences in the mortality rates between the montelukast group and control group [RR 0.6 (95% CI: 0.15 - 1.17); ARR 0.03; RRR 0.58; NNT 35.71].[12] Meanwhile, another study by Nitinai N et al reported zero deaths out of 357 patients enrolled in their study, both in the montelukast and control groups.[13]

Two studies reported duration of hospitalization as an outcome and were presented in **Table 4**. Dev et al found that montelukast significantly shortens the duration of hospitalization compared to the control group with a mean difference of 2.02 days (95% CI: 1.63 - 2.41).[12] In contrast, Nitinai N et al. reported no statistically significant difference between the montelukast and control groups [MD 0.35 days (95% CI: -0.05 to 0.75)].[13]

Critical Appraisal: Applicability

All three included studies applied to the patient described in this case report, as they included only patients with confirmed

Table 1. Study characteristics

Author	Year	Location	Study Design	Total Subjects		Age (Mean ± SD)		Gender (M: F)		Intervention	Control	Inclusion Criteria	Exclusion Criteria	Dengue Diagnosis
				E	C	E	C	E	C					
Dev A et al	2024	India	Prospective observational	250	250	35.00 ± 10.00	36.00 ± 9.00	151:100	145:105	Montelukast 10 mg is administered once daily.	Standard therapy	Adults aged 18 years or older with a confirmed diagnosis of dengue fever.	Adults with any contraindications to montelukast; those with a concurrent diagnosis of other fever-related conditions, such as malaria or heat stroke; pregnant women; adults with critical illnesses requiring intensive care; those unable to take oral medication; or those with communication barriers.	Positive NS1 antigen test or ELISA for dengue.
Nitinai N et al	2024	Thailand	RCT	179	178	23.15 ± 1.11	23.23 ± 1.48	154:25	148:30	Montelukast 10 mg is administered once daily.	Standard therapy	Adults aged 20 years or older with a confirmed diagnosis of dengue fever.	Adults with any warning signs of dengue; those with a concurrent diagnosis of other fever-causing conditions, such as malaria or heat stroke; pregnant women; adults unable to take oral medication; those with critical illness requiring intubation or ICU admission; those unable to communicate; or those with any contraindication to montelukast.	Clinical diagnosis of dengue infection, confirmed by either a positive NS1 antigen test or a positive PCR test, irrespective of illness duration.
Ahmad A et al	2018	Pakistan	RCT	100	100	28.08 ± 14.59	27.55 ± 12.56	68:32	65:35	Montelukast 10 mg is administered once daily.	Standard therapy	Adults aged 13–65 years with a confirmed diagnosis of dengue fever.	Adults with ischemic heart disease, malignancy, co-morbidities including positive viral hepatitis serology, chronic liver disease, malaria, typhoid fever, or chronic renal disease; a history of bleeding disorders; pregnant women; or adults admitted in a state of shock.	Clinical diagnosis according to WHO Dengue Guidelines, confirmed serologically by measuring serum IgM or NS1 levels using ELISA kits.

E: experimental group; C: control group; RCT: randomized controlled trial

Table 2. Validity of included studies

Criteria	Dev A et al	Nitinai N et al	Ahmad A et al
Was the assignment of patients to treatments randomized?	No	Yes	Yes
Were the groups similar at the start of the trial?	Yes	Yes	Yes
Aside from the allocated treatment, were the groups treated equally?	Unclear	Yes	Yes
Were all patients who entered the trial accounted for? And where were they analysed in the groups to which they were randomized?	Yes	Yes	Yes
Were measures objective, or were the patients and clinicians kept "blind" to which treatment was being received?	No	Yes	Unclear

Table 3. Clinical outcomes across studies

Author	Year	EER	CER	RR	ARR	RRR	NNT
Dengue shock syndrome incidence							
Dev A et al	2024	4/250	21/250	0.19	0.07	0.81	14.71
Nitinai N et al	2024	0/179	0/178	N/A	0.00	N/A	N/A
Ahmad A et al	2018	9/100	31/100	0.29	0.22	0.71	4.55
Dengue with warning sign incidence							
Dev A et al	2024	90/250	150/250	0.60	0.24	0.40	4.17
Nitinai N et al	2024	63/179	53/178	1.18	-0.05	-0.18	-18.45
Mortality rate							
Dev A et al	2024	5/250	12/250	0.60	0.03	0.58	35.71
Nitinai N et al	2024	0/179	0/178	N/A	0.00	N/A	N/A

EER: experimental event rate; CER: control event rate; RR: relative risk; ARR: absolute risk reduction; RRR: relative risk reduction; NNT: number needed to treat.

Table 4. Mean change in duration of hospitalization

Author	Year	E	C	MD	95% CI
Dev A et al	2024	4.52 ± 1.91	6.54 ± 2.50	2.02	1.63 – 2.41
Nitinai N et al	2024	3.00 ± 1.49	3.35 ± 2.24	0.35	-0.05 – 0.00

E: experimental group; C: control group; MD: mean difference; 95% CI: 95% confidence interval

dengue fever, as defined by the WHO criteria. Montelukast is feasible for use in clinical practice, as these drugs are widely available at a relatively low cost.

DISCUSSION

This evidence-based case report included three clinical studies to evaluate the effectiveness of montelukast in reducing the risk of severe dengue among patients with confirmed dengue infection. An appraisal of methodological validity indicated that two of the three studies had high validity, whereas one was rated as moderate due to the absence of randomization and blinding in its design. Across the studies, montelukast consistently showed a trend toward reducing the incidence of dengue shock syndrome. However, results for dengue with warning signs were inconclusive. One study reported a decreased risk in the montelukast group, while another found a slightly higher, though statistically insignificant incidence. Mortality outcomes showed no significant difference between groups, with one study reporting no deaths in either group. Hospitalization duration also varied, with one study noting a significant reduction in length of stay and another finding no notable effect. Despite methodological limitations, all studies were considered clinically relevant because they involved WHO-confirmed dengue cases and evaluated an intervention that is widely accessible and cost-effective.

The main proposed mechanism for the reduction in severe dengue with oral montelukast is through the inhibition of leukotriene receptors.[10] Mast cells play a key role in maintaining vascular integrity by releasing vasoactive mediators, including leukotrienes.[15] Activation of the

leukotriene pathway disrupts the cell junctions between endothelial cells, leading to an increase in vascular permeability and, consequently, plasma leakage.[16] In severe dengue infection, mast cells become extensively activated, resulting in a massive release of leukotrienes. It will therefore lead to an enormous increase in vascular permeability and plasma leakage, which is the basis of the pathophysiology of dengue haemorrhagic fever and dengue shock syndrome.[10] Montelukast, a leukotriene receptor antagonist, exerts its effect by inhibiting this inflammatory pathway. However, there is no direct mechanism that explains montelukast's mechanism of action in preventing dengue with warning signs. This finding aligns with the results of this study, which found that the effect of montelukast on the incidence of dengue with warning signs remains inconclusive.

This study has several strengths. First, this study explored a novel topic, as montelukast is not routinely used in patients with dengue fever. This study was conducted systematically, adhering to PRISMA guidelines, and applied robust eligibility criteria to ensure that all available studies were included. A critical appraisal was also conducted to evaluate the validity, importance, and applicability of the included studies. The outcomes assessed were also clinically relevant, which is important for clinicians to apply the results of this study in daily practice. Additionally, montelukast is affordable and widely available, making this study highly applicable to clinical practice.

However, this study also has some limitations. Only three studies were included, including one prospective observational study and two randomized controlled trials, resulting in differences in methodological quality. Additionally, all included studies focused on adult patients; therefore, the results cannot be generalized to pediatric populations. Notably, the studies did not clearly specify whether participants were enrolled at the same phase of dengue infection or on comparable illness or fever days, which may affect treatment response and disease progression. Additionally, the mortality outcomes were not clearly defined, whether reported mortality referred to early mortality, in-hospital mortality, or another specific time frame.

Future large-scale, multi-center randomized controlled trials are recommended to confirm the effect of montelukast on dengue patients with warning signs and to study its safety profile, including mortality and adverse effects. Future research should also consider subgrouping patients based on dengue severity, age groups, and comorbidities to identify which subpopulations benefit most from the intervention. Additionally, the pharmacokinetics (e.g., optimal timing and duration of treatment) of montelukast in dengue patients should be analyzed. More high-quality studies are needed before oral montelukast can be widely recommended for dengue fever patients in routine clinical practice and possibly integrated into dengue fever guidelines.

CONCLUSION

Current evidence suggests that montelukast administered to dengue fever patients significantly reduces the incidence of dengue shock syndrome and shortens the duration of hospitalization. Future large-scale, multicentre randomized controlled trials are recommended before oral montelukast can be widely recommended for dengue fever patients in daily clinical practice and possibly integrated into clinical guidelines.

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None declared.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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