

Repurposing of N-Acetylcysteine for the Treatment of Dengue Virus-Induced Acute Liver Failure

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Abstract: The prevalence of dengue infection-induced acute liver damage is increasing from time to time. Since it has no specific antiviral treatment in the world, people in endemic areas suffer more from dengue disorders. Thus, there is a need for searching options for the treatment of dengue-induced acute liver failure. N-acetylcysteine, which is used for the treatment of nasal congestion disorder and paracetamol overdose toxicity, could be used as a definitive therapy for dengue virus-induced acute liver disease. Therefore, this review discusses the therapeutic use of N-acetylcysteine for dengue-induced acute liver disease. Various case reports and case series showed that patients received NAC recovered from their clinical status. Additionally, a preclinical study showed that N-acetylcysteine has anti-dengue virus activity. Thus, N-acetylcysteine could be used as a definitive therapy in dengue virus-induced hepatitis. This might encourage researchers to further investigate the importance of N-acetylcysteine for dengue virus-induced hepatitis.

Keywords: N-acetylcysteine, dengue virus, acute liver failure

Introduction

Dengue is one of the common harmful mosquito-borne viral disease which belongs to the Flaviviridae family.¹ There are different dengue virus serotypes causing dengue disorders, including, asymptomatic infection, dengue fever, undifferentiated fever, fatal and severe dengue hemorrhagic fever. *Aedes aegypti* mosquito (main urban vector) and *Aedes albopictus* female mosquitos are the known vector for transmission of dengue virus from an infected person to others by biting.² A person exposed for a particular viral serotype develops immunity against that serotype in a secondary infection.¹ For this reason, infants who are born with dengue virus-infected mothers develop secondary immunity after passing a severe form of dengue disease during the primary infection.³

The world population, particularly those who live in endemic areas are 40% at risk of developing dengue infection. It is estimated that the world encounters 390 million dengue infections, among which 96 million are symptomatic, and 20,000 deaths occur each year in 62.8% of the world countries.⁴ The global burden of the disease doubles three times in its prevalence within five decades. This is due to the occurrence of the disease in previously sterilized countries from the dengue virus.⁵ These countries are found in the Americas, the Eastern Mediterranean, South-East Asia, Western Pacific, and Africa.¹ Moreover, the virus was identified

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in Ethiopia in 2013, in the Dire Dawa city, which was noted as a frequent dengue outbreak since then.⁶ Dengue is also expanding its domain in Ethiopia and becomes a threat in Somalia region for a few years back.⁷

The main clinical features of dengue virus-induced hepatitis are acute liver failure and fulminant.⁸ Among the other clinical features of hepatic involvement, patients may experience vomiting (49–58%), nausea, anorexia, and abdominal pain (18–63%),⁹ raised transaminase levels, clinical jaundice (1.7–17%). Hyperbilirubinemia has been detected to be as high as 48%, and death was highly associated with dengue virus-induced acute liver failure (ALF).¹⁰ Additionally, the virus can cause Guillian-Barre syndrome, myocarditis, encephalitis, and hemolytic uremic syndrome since it affects various tissues.¹¹

N-acetylcysteine (NAC) is produced after acetylation reaction of the L-cysteine amino acid. It acts both as a source of reduced glutathione and directly scavenging free radicals in the body.¹² Thus, NAC preserves the different enzymes such as catalase, mitochondrial superoxide dismutase, and the different forms of glutathione peroxidases used in reduction and oxidation reactions to be intact thereby reducing the occurrence of oxidative. Although NAC is orally absorbable drug, it will reach the systemic circulation after it passed extensive pre-systemic metabolism.¹³ Besides, NAC could also be administered through the intravenous route of administration smoothly. Therefore, due to its easy way of administration and low toxicity, NAC is currently the favorite compound for the treatment of hepatotoxicity in man regardless of the cause.¹⁴ In general, these effects show NAC may be a useful agent to preserve liver function in patients with biliary obstruction, which was the path for glutathione production.¹⁵

Life Cycle of Dengue Virus

The mature dengue virus has three different structural and functional proteins. The proteins are the capsid protein C which forms the envelop, the membrane protein M which makes the virion to be intact in structure and the nucleotide envelope E which covers the ribonucleic acid (RNA) genome.¹⁶

The dengue virus targets the following cells in the human body during its natural course of infection. These are cells of the mononuclear phagocyte lineage macrophages, monocytes, and dendritic cells, including the skin-resident langerhans cells. Over the last years, several candidate receptors and/or attachment factors have been identified, which

suggests that the dengue virus (DENV) is capable of utilizing multiple molecules to enter the cell. Dengue virus and flaviviruses use clathrin-mediated endocytosis for cell entry.^{17,18} This approach is based on a single particle lay down and rolls in the surface of the cell. This can be supported after it has been revealed that DENV-2 strain S1 particles land on the cell surface and travels in a diffusive manner toward a pre-existing clathrin-coated pit.¹⁹ This suggests that DENV particles move along the cell surface by rolling over different receptors, or migrate as virus–receptor complexes, which enables the virus to use different possible receptors for entrance.¹

After the virus enters into the cell, it will have free RNA uncoated of a nucleo-capsid, which enables it to be translated as a single polyprotein.²⁰ Then, the signal- and stop-transfer sequences of the polyprotein direct its back-and-forth translocation across the endoplasmic reticulum membrane. The polyprotein will be processed co- and post-translationally by cellular and virus-derived proteases into three structural proteins (C, M, and E) and seven nonstructural (NS) proteins (NS1–NS7). The E protein is glycosylated at amino acid residue Asn67 and Asn153 to assure proper folding of the protein.¹

Since dengue-infected mosquito and mammalian cells secrete large numbers (up to 30%) of prM-containing particles, dengue virus maturation appears to be inefficient. Numerous studies have shown that fully immature particles cannot infect cells remarkably; however, this time the virus is resistant for prM antibodies developed by the body and becomes mature to infect other cells.²¹

Pathogenic Mechanism of Dengue Virus-Induced Acute Liver Failure

The exact pathogenesis of dengue virus-induced acute liver damage is complex and poorly understood.²² Dengue virus causes a disorder of the liver ranging from direct viral injury, hypoxic, ischemic to dysregulated immune response which ultimately results in apoptosis and necrosis.²³ The dengue viremia mainly affects the liver with viral toxicity or immunological injury. During acute dengue virus infection, the level of antioxidants such as glutathione peroxidase and glutathione reductase reduced, whereas liver enzymes, including, aspartate transferase (AST) and alanine transferase (ALT) are elevated suggesting of oxidative stress induced by dengue virus.²⁴ Additionally, as investigated in the mouse model, dengue-induced acute liver failure could occur due to the release

of inflammatory cytokines, particularly interleukin-22 (IL-22) and interleukin-17 (IL-17).²⁵ Tumor necrosis factor (TNF) alpha, interleukin -2 (IL-2), interleukin-6 (IL-6) and interleukin-8 (IL-8) levels are also elevated in early dengue virus infection whereas interleukin-5 (IL-5) and interleukin-10 (IL-10) were increased subsequently.²⁶

Various histologic changes were observed in dengue-induced liver failure, including, fatty change, hepatocyte necrosis, hyperplasia, and destruction of Kupffer cells, Councilman bodies and mononuclear cell infiltrates at the portal tract.²³ According to a recent report, acetaminophen overdose can play a crucial role in causing acute liver failure in dengue-infected patients.²⁷

Current Management of Dengue Virus-Induced Hepatitis

Though there are no specific treatments for dengue-induced acute hepatic failure, different management modalities have been used to reduce its fatality rate. Dengvaxia is the first dengue vaccine, which has a significant effect in patients with the age group of 19–45 years.²⁸ Paracetamol can be taken to control the symptoms of muscle aches and pains, and fever, whereas non-steroidal anti-inflammatory drugs, such as ibuprofen and aspirin should be avoided. This is because anti-inflammatory drugs are associated with severe bleeding. The most common treatment is maintenance of the patient's body fluid volume particularly for patients with critical infection.²⁹ Artificial liver support has also been recently suggested for the treatment of dengue patients with liver failure. This is used to support the liver in the elimination of waste materials from the body and acts as a liver while its transplantation.³⁰

Many drugs (chloroquine, balapiravir, celgosivir, and lovastatin) have been tried to be repurposed for severe dengue infection, which primarily affects the liver a major part of its replication. But, they are not effective in treating the infection.³¹ Since the treatment for dengue virus-induced acute liver failure is non-specific, and many of the more experienced clinicians described the guidelines as only making sense in the light of clinical experience.³² Currently, the concurrent needs of an effective dengue vaccine and an urgent need for an effective antiviral agent against dengue is continuing.³³ Therefore, this review aims to discuss the therapeutic use of NAC for dengue virus-associated acute liver failure as definitive therapy.

Use of N-Acetylcysteine for the Treatment of Dengue Virus-Induced Acute Liver Failure

N-acetylcysteine was used clinically for around 30 years as a mucolytic agent. Nowadays, various studies showed that NAC has an activity against dengue virus-induced acute liver failure as indicated in the table below (Table 1). Various online sources like Google Scholar, PubMed/MEDLINE, ResearchGate, and Science Direct were used to search the articles used for this study.

Potential Benefit of N-Acetylcysteine in Dengue Virus-Induced Acute Liver Failure

Most of the patients receiving NAC during their clinical status showed a positive response to the drug which could encourage the use of NAC for dengue-induced acute liver failure. As indicated in the table, the mechanism of action of NAC in patients who recovered from dengue-induced ALF could be associated with its ability to increase antioxidant defense system, its free radical scavenging activity, and its vasodilatory activity that increases blood flow to the liver.^{40,41}

As reported by Chandrasena et al (2019), the antioxidant enzymes such as glutathione peroxidase and glutathione reductase have been reduced during acute dengue infection. Thus, the antioxidant activity of NAC could be due to increasing plasma antioxidant levels such as glutathione peroxidase and glutathione reductase which results in reducing oxidative stress.²⁴

A mechanistic study was done on mice to assure how NAC completely cures ALF with no sequelae. NAC showed antiviral activity by reducing infectivity in HepG2 cells infected DENV, suppressing DENV replication, and reducing oxidative damage. NAC could also reduce the infectivity of dengue virus at its entry, replication, post translation, RNA synthesis and exocytosis in a dose-dependent manner. Additionally, the drug up-regulates the expressions of pattern recognition receptors including, retinoic acid-inducible gene I and melanoma differentiation-associated gene 5 in DENV-infected mice.⁴²

Conclusion and Future Perspective

Generally, dengue virus infection and its associated complications are now becoming a global burden; and it does not

Table I Clinical and Preclinical Studies of N-Acetylcysteine in Dengue Virus-Induced Hepatitis

Study Design	Method and Intervention	Treatment Outcome and Possible Mechanism of Action	References
Case report	A patient was presented with dengue-associated hemorrhagic fever complicated with acute liver failure and hepatic encephalopathy. The patient was administered with NAC.	The patient was completely cured after NAC administration. The drug may improve systemic hemodynamics and may increase tissue oxygen delivery.	[40]
Case series	A retrospective analysis of eight consecutive adult patients (5 men and 3 women) was undertaken. Five patients had early-stage pretreatment hepatic encephalopathy (coma grades I–II), and three had advanced encephalopathy (coma grades III–IV). They received NAC 150 mg/kg loading dose intravenously over 15 minutes followed by 12.5 mg/kg/h for 4 h and then 6.25 mg/kg/h for up to 72 h.	The first five patients recovered completely after NAC administration and the three have died. NAC may benefit the acutely injured liver by improving systemic hemodynamics and by increasing tissue oxygen delivery.	[41]
Case report	A 54-year-old mother presented with 3 days history of fever, headache and body ache. Intravenous NAC was administered at 100 mg/kg/day as an infusion and continued for 5 days with liver failure regimen.	She was recovered and marked improvement in liver enzymes was observed. NAC could use as an antidote for the viral oxidative stress, and it could have a vasodilatory effect.	[34]
Case report	A 53-year-old male presented with a history of fever for 4 days. The patient received an intravenous infusion of NAC at a rate of 100 mg/hour.	He recovered after he got treated with NAC. NAC could have free radical scavenging activity, improves antioxidant activity and acts as a vasodilator to improve oxygen delivery and consumption.	[35]
Case series	Seven children developed dengue-induced acute liver failure. NAC was given at 100 mg/kg intravenously over 24 hours. In patients who continued to have hepatic encephalopathy at the end of the first dose, NAC was continued up to 72 hours.	Four patients recovered from encephalopathy. The remaining three responded after the second and third doses. NAC might scavenge free radicals, improves antioxidant defense and acts as a vasodilator to improve oxygen delivery and consumption.	[36]
Case report	A 6-year-old boy was diagnosed with dengue-associated fulminant liver failure. He was treated with intravenous NAC.	A rapid decrease in liver transaminases and normalization of coagulation profile followed by clinical improvement was observed.	[22]
Case report	A 43-year-old woman with serologically confirmed dengue fever presented with acute liver failure. She was managed with intravenously administered NAC.	She has been recovered with no sequelae after she treated with NAC. NAC might scavenge free radicals, improves antioxidant defense system.	[37]
Case report	A 37-year-old admitted with fever, repeated vomiting, body aches, and fatigue for four days. NAC was administered with Recombinant activated clotting factor VII (rFVIIa).	The patient got cured after NAC administration. NAC might improve oxygen delivery and consumption	[38]
Case report	Among one hundred and fifty-five patients with ALF, eight of them were identified to have dengue-induced ALF. Seven patients received NAC infusion at 100–150 mg/kg/day for a minimum of five days.	All the patients were treated and survived. This might be due to NAC's activity to improves systemic hemodynamics and tissue oxygen delivery.	[30]
Case report	A 23-year-old woman presented with fever, nausea, emesis, diffuse abdominal pain, myalgias, and weakness. She was tested positive for dengue fever antibodies immunoglobulin G and immunoglobulin M, and she was treated with platelets and NAC, as well as APAP and external cooling for fever.	She gradually recovered without requiring a liver transplant. NAC could prevent hepatic damage by scavenging free radicals, improving systemic hemodynamics, and optimizing tissue oxygen delivery.	[39]
Preclinical Study	HepG2 cells of mice were seeded and infected with different DENV serotypes, and then treated with vehicle or NAC at concentrations of 5 mM, 10 mM, and 20 mM.	NAC exhibited a significant reduction in DENV E protein expression in a dose-dependent manner. The possible mechanism of NAC could be: Reducing infectivity in HepG2 cells infected with the different serotype of DENV, its antiviral responses to suppress DENV replication, its ability to improve clinical manifestations in DENV-infected mice, reducing virus replication in the livers of DENV infected mice, and reducing oxidative damage in the livers of DENV-infected mice.	[42]

Abbreviations: ALF, acute liver failure; DENV, dengue virus; NAC, N-acetylcysteine; rFVIIa, recombinant activated clotting factor VII; RNA, ribonucleic acid.

have a specific treatment modality. To prevent dengue virus-associated complications and mortality, searching for promising therapeutic options is important. N-acetylcysteine has crucial importance in the treatment of dengue-induced acute liver disease possibly by reducing oxidative stress, by its direct antiviral activity and by increasing blood flow to the liver. It has the potential to be used as a definitive therapy for dengue-associated liver failure.

Various case reports and series; and one animal study showed that NAC has an important role in the treatment of dengue-induced acute liver failure. Large randomized clinical trials and several animal studies are required to confirm the efficacy of NAC in dengue virus-induced acute liver failure. Additionally, further investigations are in need to decide the mechanism of action of NAC in dengue-induced acute liver disease.

Abbreviations

ALT, Alanine Transferase; AST, Aspartate Transferase; DENV, Dengue Virus; IL, Interleukin; NAC, N-acetylcysteine; TNF, Tumor Necrosis Factor; WHO, World Health Organization.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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