Efficacy and Safety of Ivermectin against Dengue Infection: A Phase III, Randomized, Double-blind, Placebo-controlled Trial

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Background: Results from the previous phase II study (unpublished data) indicated that 3-day treatment with oral ivermectin (400 µg/kg; once daily) is safe in patients with dengue infection.

Objective: We conducted this phase III clinical trial to determine the virological and clinical efficacies and confirm the safety of this treatment regimen in adult patients with dengue infection at Siriraj Hospital.

Methods: This was a randomized, double-blind, placebo-controlled trial of once daily dose of 400 µg/kg of oral ivermectin for three days compared to placebo for treatment of patients with dengue infection, between February 2014 and September 2017. Patients aged 15 years or older, who had fever suspected of dengue infection and positive dengue non-structural protein NS1 rapid test, were recruited. They were randomly assigned (1:1 in block of four) to placebo or three-day of oral ivermectin treatment. The virological outcomes were plasma dengue viremia clearance and dengue nonstructural protein 1 (NS1) antigenemia clearance. Clinical efficacies included fever clearance and the proportion of patients who developed dengue hemorrhagic fever (DHF) after treatment.

Results: Overall 146 patients were enrolled. A number of 131 patients were included in the modified intention analysis (66 patients in the ivermectin group and 65 patients in the placebo group). The median (IQR) plasma dengue viremia clearance were 80.5 (71.7-89.3) hours and 82 (74.2 -89.8) hours in the ivermectin and the placebo groups, respectively (p=0.766). The median (IQR) NS1 clearance times were 90 (70.3-109.8) hours and 102 (76.6-127.4) hours in the ivermectin and the placebo groups, respectively (P=0.027). Nineteen patients (74.47%) and 30 patients (46.15%) had undetectable NS1 at discharge in the ivermectin and the placebo groups respectively (P=0.001). The median (IQR) fever clearance times were 79 (73.1-84.9) hours, 79 (70.7-87.3) hours in the ivermectin and the placebo groups, respectively (P=0.736). There were no serious adverse events observed in this study.

Conclusion: Once daily dose of ivermectin treatment for three days is safe. Virological efficacy is demonstrated by significant difference of NS1 clearance time and proportion of patients with NS1 negative at discharge between the two treatment groups. However there is no clinical efficacy of ivermectin shown in this study. The pharmacokinetic and pharmacodynamics study are needed in order to modify the dosage regimen of ivermectin treatment to improve the clinical efficacy.

Keywords: Ivermectin, Dengue infection, Efficacy, Safety