Short-Course Oral Corticosteroid Therapy Is Not Effective in Early Dengue Infection

Alan D. T. Barrett
Department of Pathology, Sealy Center for Vaccine Development, Center for Biodefense and Emerging Infectious Diseases, Center for Tropical Diseases, and Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston

(See the Major Article by Tam et al on pages 1216–24.)

Dengue is the most important mosquito-borne viral disease worldwide [1]. More than 3 billion people in >120 countries are at risk from dengue with 50–100 million infections each year, of which >2 million will have severe dengue infection, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue is a disease with great morbidity, but fortunately only <25 000 die of the disease. Clinical manifestations vary from asymptomatic, to febrile illness, to severe dengue involving systemic plasma leakage with thrombocytopenia and coagulopathy [2]. Severe disease is usually seen at a time after viremia has reduced to low or undetectable levels, suggesting that it is an immunopathologically mediated disease [3]. Although it is clear that cells of the mononuclear phagocytic lineage are infected, our understanding of the cell and tissue tropism of dengue virus (DENV) is limited. The disease is caused by 4 serologically and genetically related viruses, called DENV-1, DENV-2, DENV-3, and DENV-4, which are members of the flavivirus genus, whose prototype species is yellow fever virus [1, 4]. The 4 DENVs are often considered serotypes, like the 3 poliovirus serotypes; however, the 4 DENVs are distinct viral species and have the same relationships to each other as 4 members of the Japanese encephalitis complex of viruses (Japanese encephalitis, Murray Valley encephalitis, St Louis encephalitis, and West Nile virus).

Taking the above-mentioned together, it is not surprising that the development of vaccines or antiviral drugs against dengue has been and continues to be a complex issue. Currently, there are no licensed drugs or vaccines to treat or prevent dengue, although there are candidate vaccines in phase 2/3 clinical trials [5]. Even if a vaccine were available tomorrow, there would be still a need for antiviral drugs.

Antiviral drug development has focused on 2 approaches: identifying candidate drugs that act specifically against virus-encoded proteins, and drug regimens that can provide supportive therapy and augment the patient’s response to the virus infection [6]. A number of candidate antiviral drugs are in advanced preclinical development and a few are in early clinical development, but none are in clinical efficacy studies. Thus, supportive therapy regimens are an area of keen interest.

The study by Dong et al in this issue of Clinical Infectious Diseases, "A Randomized Placebo-Controlled Trial to Investigate the Effects of Short-Course Oral Corticosteroid Therapy in Early Dengue Infection in Vietnamese Patients," investigates an important area of potential supportive therapy, namely, the use of oral corticosteroid therapy to combat clinical dengue disease. There have been a number of suggestions in the literature that corticosteroids may have a beneficial effect on patients following infection by viral and bacterial agents where the host immune response contributes to clinical disease. Clearly, dengue is a disease for which corticosteroids could be considered as an intervention, in particular a short course of oral steroid therapy to suppress the inflammatory response early in the disease course to reduce the potential of severe dengue disease, but this has not been studied systematically until now.

Dong et al investigated the effects of short-term oral corticosteroid therapy given early in dengue infection with a randomized, placebo-controlled, blinded trial of clinical outcomes of serologically and virologically documented dengue disease in 225 children who were given either 2 days of low or high doses of oral...
prednisolone starting on day 3 after onset of fever, or around 2 days prior to the development of peak vascular permeability and, in some cases, shock. Significantly, neither the low-dose (0.5 mg/kg/day) nor high-dose (2 mg/kg/day) regimen altered major abnormal dengue-related host responses except to reduce alanine aminotransferase responses and heparan sulfate blood levels. Hypoglycemia was observed as evidence of the pharmacological action of steroids in these children. However, hyperglycemia was observed in 5 of 75 (7%) and 9 of 75 (12%) patients given the low dose and high dose of prednisolone, respectively. Although the difference was not statistically significant ($P = .07$, trend test), the increased frequency of raised random sugar levels in the high-dose group raises questions about the dosage of corticosteroids to be used in at least short-term treatment regimens in children.

The study is very well performed and the results provide conclusive evidence that this therapy does not work to diminish dengue disease, at least as a short-term regimen, at the dosages investigated, early in the dengue disease course. As the authors point out, higher dosage and/or longer duration of prednisolone may influence the dengue disease course, but hyperglycemia would suggest that such a regimen would probably have potential safety concerns.

How does dengue treatment research thus go forward? Clearly, we need treatments that can be given early in the disease course, and the study of Dong et al strongly supports this approach. But how do we achieve this? First, severe dengue is normally seen after viremia and second, patients do not normally seek medical advice until they have significant clinical symptoms, even for a febrile disease. Accordingly, early diagnostics are a very important part of a dengue treatment strategy. The last 5 years has seen a major improvement in dengue diagnostics based on quantitative reverse-transcription polymerase chain reaction and assays that detect the nonstructural protein 1 (NS1), which is secreted from virus-infected cells, and this has been adapted to a rapid diagnostic format [7, 8]. Nonetheless, we still need improved rapid diagnostics, which can be utilized early in the dengue infection process and can be used to predict whether or not a patient will progress to severe dengue disease, and if this will include DHF or DSS. Furthermore, basic scientific studies focused on a better understanding of the cells and tissues involved in replication of the virus and a systems biology approach to understanding the host response to dengue virus infection will also be very beneficial to the development of viral and host immune response diagnostic tools and treatments [9].

Finally, the last 10 years has seen huge advances in our knowledge of the molecular virology of flaviviruses, in particular dengue and West Nile viruses. We have structural information for many, but not all, of the 10 flavivirus-encoded proteins, which is leading to detailed structure-function studies of the proteins [10]. This in turn is leading to the design of candidate compounds as potential antiviral agents that are being tested in cell culture and mouse models [11, 12]. This is an exciting time for dengue antiviral research and it is likely that we will see antiviral drug treatments in human efficacy studies in the next 3–5 years.

**Note**

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**References**