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Last Doubts Resolved: Artesunate Is Superior to Quinine for the Treatment of Severe Falciparum Malaria

ABSTRACT & COMMENTARY

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Dr. Blackburn reports no financial relationship to this field of study;
this article originally appeared in the May issue of Infectious Disease Alert.

Synopsis: *African children with severe falciparum malaria were randomized to receive either intravenous artesunate or intravenous quinine. Those who received artesunate died significantly less frequently than those who received quinine. These data, taken together with previous trials, strongly suggest that intravenous artesunate should replace intravenous quinine as the treatment of choice for severe falciparum malaria worldwide.*

Source: Dondorp AM, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): An open-label, randomised trial. *Lancet* 2010;376:1647-1657.

DESPITE THE RECENT GAINS ACHIEVED BY MULTIDISCIPLINARY CONTROL PROGRAMS, malaria still kills nearly 1 million people and causes almost 300 million symptomatic illnesses globally per year, with most of this burden borne by sub-Saharan Africa. Severe malaria, usually caused by *Plasmodium falciparum*, is defined in part by respiratory distress, renal failure, altered mental status/seizures, metabolic acidosis/hypoglycemia, and hyperparasitemia. The mortality rate of severe malaria, even with appropriate treatment, is as high as 15%-20% in some series, and the disease is nearly universally fatal if untreated.

The standard treatment worldwide for severe malaria has been intravenous quinine for many years (given the unavailability of intravenous quinine in the United States, quinidine is used instead, a drug with similar efficacy but more toxicity). Although effective, the mortality rate of severe malaria treated with quinine remains high, and quinine/quinidine are toxic, sometimes causing infusion-related hypotension, cinchonism, blindness, deafness, and hypoglycemia; quinidine adds to these adverse effects an even higher risk of arrhythmias than seen with quinine.

Artemisinins, the most rapidly acting antimalarials available, are potent and well-tolerated, providing a theoretical advantage for this drug class over the quinine derivatives. A major clinical trial performed recently in Southeast Asia showed that the mortality rate in patients with severe falciparum malaria was 22% in patients treated with intravenous quinine, and 15% in those treated with intravenous artesunate.[1] Because few children were included in this trial, the generalizability of these results to children with severe malaria was questioned.[1] In addition, the applicability of these results to malaria acquired in Africa also was unclear. The authors therefore undertook a clinical trial comparing the intravenous formulations of quinine and artesunate in children with severe falciparum malaria in Africa.

More than 5,400 children (age < 15 years) with severe falciparum malaria from nine different sub-Saharan African countries were enrolled in the trial. The median age of enrolled patients was about 3 years. The trial was an open-label, randomized comparison of the standard dosing regimens of intravenous artesunate and intravenous quinine. At trial entry, 30% of patients had severe anemia, about one-third had coma, one-third had seizures, and more than 40% had severe acidosis, with no difference between the study groups. About 6% of those tested (125 of 2,095) were HIV-positive; the case-fatality rate was high (28%) in HIV-infected patients, with no significant mortality difference between treatment groups. The primary outcome measure of the trial was in-hospital mortality.

Overall, 8.5% of patients who received artesunate died, compared with 10.9% of patients who received quinine (P = 0.0022), a relative mortality reduction of 22.5%. Significantly fewer patients in the artesunate-treated group developed worsening neurological status, coma, or seizures than in the quinine-treated group after trial entry, although the frequency of long-term neurological sequelae did not differ between groups. No serious treatment-related adverse effects were seen, and significantly fewer patients in the artesunate-treated group developed hypoglycemia than in the quinine-treated group after enrollment. The authors also performed a meta-analysis of all severe malaria trials that have compared survival between parenteral artesunate and parenteral quinine. The overall odds ratio for death was 0.69 (P < 0.00001) in favor of artesunate, with no significant heterogeneity between results generated in Africa and Asia.

■ COMMENTARY

This large, well-designed trial showed that artesunate significantly reduces mortality among African children with severe falciparum malaria. Despite the findings of the earlier SEAQUAMAT trial in Southeast Asia, which demonstrated a 35% mortality reduction in patients treated with IV artesunate compared to those treated with IV quinine, some questions about the applicability of these results to children or to patients with malaria acquired in Africa were raised.[1] This was in part because of perceived differences in the epidemiology, pathology, and susceptibility of malaria parasites to quinine in Africa, and differences in the natural history of the disease in children as compared to adults. These concerns were not substantiated, based on both the current AQUAMAT trial, and the meta-analysis the authors performed of trials that have compared artesunate to quinine for severe malaria.

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It now appears that for all regions and patient populations, artesunate should be the drug of choice for treating severe malaria, given that it is more rapidly acting, better tolerated, and more effective than quinine (and "by extension," quinidine). Unfortunately, access to the drug remains problematic, and currently no Good Manufacturing Process (GMP) formulation of artesunate is commercially available. Because it is not FDA-approved in the United States, artesunate is only available from the Centers for Disease Control and Prevention (CDC) through an investigational new drug (IND) protocol for severe malaria in patients who meet certain criteria.[2] Although the drug is available on an emergency basis through CDC, delay to administration is inevitable with this mechanism, and rapid therapy clearly matters for severe malaria. Given that there is little doubt that this is the superior drug for a disease with a high mortality rate, artesunate should be approved for widespread use in the United States immediately, and wider supplies of this vital drug ensured worldwide. ■

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2. Centers for Disease Control and Prevention. Notice to Readers: New Medication for Severe Malaria Available Under an Investigational New Drug Protocol. *MMWR Morb Mortal Weekly Rep* 2007;56:769-770.

Fever with Thrombocytopenia Associated with a Novel Bunyavirus in China

ABSTRACT AND COMMENTARY

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Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostic; this article originally appeared in the May issue of Infectious Disease Alert.

Synopsis: *A severe fever with thrombocytopenia syndrome (SFTS) was recognized in China beginning in 2009. A novel virus, SFTS bunyavirus, was isolated from patients meeting the case definition of this syndrome.*

Source: Yu Y-J, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. *N Engl J Med* 2011;364:1523-1532.

Due to heightened surveillance of acute febrile illness in China, a severe illness associated with thrombocytopenia and multi-system organ involvement was recognized beginning in 2009. *Anaplasma phagocytophilium* was originally suggested as a cause but the pathogen was not detected in most patients. Blood samples from patients meeting the case definition were used to inoculate a variety of cells in culture, viral RNA was detected by PCR, and the pathogen was subsequently characterized by electron microscopy and nucleic acid sequencing. Enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence assay (IFA), and neutralization assays were developed and were used to document seroconversion of patients to the novel pathogen.

A novel virus, designated SFTS bunyavirus, was isolated from 171 patients, ages 39-83 years, from six provinces in China. These patients presented with an illness characterized by fever (100%), abdominal pain (49%), thrombocytopenia (95%), leucopenia (86%), and clinical and laboratory evidence of multi-system organ dysfunction in many cases. Eleven of 81 patients who had adequate clinical data available for study died. The cell line tested, which appeared to have the greatest sensitivity for SFTS virus infection, was DH82 (a canine macrophage cell line). Sequence analysis revealed the novel virus was a member of the genus phlebovirus in the Bunyavirus family.

■ COMMENTARY

This is an interesting report from the world's most populous country and is a testament to the first rate epidemiologic and laboratory research that now exists in China. While this newly described SFTS illness, and the novel bunyavirus that is its etiologic agent, appears to define a distinct syndrome, it is not sufficiently distinctive to exclude other infections in the differential diagnosis. Other infections would potentially include rickettsial infections, anaplasmosis, leptospirosis, and several viral infections such as dengue and various hemorrhagic fever with renal syndromes. The vector for SFTS is not yet known, but most phleboviruses are associated with sandflies. Other phleboviruses are known to be transmitted by ticks and Rift Valley fever is transmitted by *Aedes* species mosquitoes. SFTS RNA has been detected in a small number of *Ixodidae* species ticks and this has been proposed as a candidate vector. ■

An old disease — in new immigrants

By Carol A. Kemper, MD, FACP

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Dr. Kemper does research for Abbott Laboratories and Merck; this article originally appeared in the June issue of Infectious Disease Alert.

COCCIDIOIDAL INFECTIONS ARE ALWAYS UNIQUE — THE travel history often provides the right clue for the practitioner — but first you have to think to ask the right question. My practice has recently seen three Asian immigrants hospitalized with what proved to be acute coccidioidomycosis; two of whom had focal pulmonary disease (one with cavities and erythema nodosum) and the third with evidence of dissemination to mediastinal nodes and skin. All three were suspected of having pulmonary tuberculosis until pathology and fungal cultures surprisingly revealed coccidioidomycosis. The first two patients were Asian Indian and the third was Chinese. All three worked in high tech in Silicon Valley, were young (28-40 years of age), were in good health, and had recent, albeit brief, exposure to an endemic area. Two of the patients had traveled down Highway 5 from the Bay Area to Las Vegas for holiday, stopping for gas and food along the way. The third, who was Chinese, had traveled to Phoenix for business for 3 days, and had lunch on the outskirts of the city at an outdoor Mexican restaurant.

These cases are reflective of some of the people acquiring coccidioidal infection around the United States — young, healthy Asian or Latin American immigrants who happen to be exposed while vacationing or working in higher risk areas of California and Arizona. None of my patients had ever heard of cocci before.

Increases in coccidioidomycosis are occurring in both California and Arizona (approximately 60% of cases in the United States are reported from Arizona).[1] From 2000 to 2006, California cases increased from 816 to 2,981. The estimated average annual incidence in California is highest among 40- to 49-year-olds, while hospitalizations are highest among persons aged 60-79 (5.8 hospitalizations per 100,000). Two-thirds of cases (65%) were reported in males. Hospitalizations were highest among non-Hispanic blacks (7.5 per 100,000), followed by Hispanics (3.6 per 100,000), non-Hispanic whites (3.5 per 100,000), and Asians/Pacific Islanders (1.9 per 100,000). From 2000 to 2007, 752 (8.7%) of those 8,657 persons in California requiring hospitalization died. About three-fourths of California cases are acquired in the San Joaquin Valley area, where *C. immitis* is endemic, with the hot spot being Kern County.

The reason for this apparent increase is not well understood. Mandatory reporting requirements for coccidioidomycosis in California have not changed. Climatic changes and increases in rainfall may impact disease incidence (so this coming year should see an increase in cases in California with the bonanza of winter rain). Increasing numbers of non-immune immigrants from Latin America or Asia and elderly persons who travel for business or pleasure may provide an explanation. My theory is that the booming housing industry in the 2000s and expansion of urban residential areas in both Arizona and California probably played a significant role. Interestingly, based on preliminary data for 2008-2009, cases in Arizona and California may have modestly decreased in 2008. Perhaps the downturn in the housing economy and negative impact on new construction in endemic areas, as well as a decrease in business and vacation travel, had a positive effect on total numbers of coccidioidal infections. ■

Reference

1. Centers for Disease Control and Prevention. Increase in coccidioidomycosis — California, 2000-2007. *MMWR Morb Mortal Wkly Rep* 2009;58:105-109.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Two New Drugs Approved for Treatment of Hepatitis C

In this issue: Two new drugs for treatment of hepatitis C; NSAIDs and myocardial infarction risk; AIM-HIGH clinical trial stopped; and FDA actions.

Two new drugs for hepatitis C

The FDA has approved two new drugs for the treatment of hepatitis C — the first new drugs to be approved in years. The approvals came within days of each other, pitting the two drugs (and their companies' marketing departments) against each other in this multibillion dollar market. Both drugs are protease inhibitors and both have similar indications. First to be approved was Merck's boceprevir (Victrelis), which is indicated for adults with hepatitis C who still have some liver function and who either have not been treated previously with drug therapy or who have failed drug therapy. Boceprevir is approved for use in combination with peginterferon alpha and ribavirin. The approval was based on two phase 3 clinical trials of 1500 adults in which two-thirds of patients in the boceprevir, interferon, and ribavirin treatment group experienced a significantly increased sustained virologic response at 24 weeks compared to 38% with interferon and ribavirin alone. Boceprevir is taken orally three times a day with food. The second drug approved was Vertex Pharmaceutical's telaprevir (Incivek), which also was approved for patients with hepatitis C who either have not received interferon-based drug therapy or who have not responded adequately to prior therapies. Telaprevir is also approved for use with peginterferon alpha and ribavirin. Approval was based on three phase 3 clinical trials of over 2000 adults. In previously untreated patients, 79% of patients in the telaprevir group experienced a sustained viral response compared to 46% for standard treatment. Most patients experienced virologic response at 24 weeks suggesting that treatment times may be reduced from 48 weeks to 24 weeks. Telaprevir is also taken orally three times a day with food. Both drugs are approved to treat genotype-1, the most common form of hepatitis C and the most difficult to treat. The drugs have similar side effects, which include anemia and serious rashes. Several other drug manufacturers have similar drugs in the pipeline with approval expected within the next year or two. It is estimated that about 170 million people worldwide and 3.2 million Americans are infected with chronic hepatitis C, which is the most common cause of progressive liver disease leading to liver transplant. Telaprevir is expected to cost nearly $50,000 per treatment course, while bocepavir is expected to cost between $26,000 to $48,000 per treatment course depending on the duration. ■

NSAID use in patients with prior MI

A new study points out the risk of nonsteroidal anti-inflammatory drug (NSAID) use in patients who have had a myocardial infarction (MI) — suggesting that even brief use increases the risk for death and recurrent MI. Researchers from Denmark reviewed the records of nearly 84,000 patients who were admitted with first time MI and their subsequent NSAID use. The risk of death and recurrent MI was correlated to the duration of NSAID treatment. From 1997-2006, 42.3% of patients received NSAIDs. There

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

were more than 35,000 deaths or recurrent MIs in the cohort of whom 43% had filled a prescription for an NSAID. Use of an NSAID was significantly associated with an increased risk of death or recurrent MI at the beginning of treatment (hazard ratio [HR] 1.45; 95% confidence interval [CI], 1.29 to 1.62) and persisted throughout the NSAID treatment course (HR 1.55; 95% CI, 1.46 to 1.64 after 90 days), returning to baseline soon after stopping the drug. The risk of death or recurrent MI varied with different drugs and was somewhat higher with increased COX-2 selectivity. Diclofenac was associated with the highest risk (HR 3.26; 95% CI, 2.57 to 3.86). Duration of therapy was also reviewed with diclofenac causing an increased risk from the beginning of treatment and persisting throughout the treatment course. Ibuprofen showed an increased risk when used for more than one week, whereas celecoxib showed an increased risk after 14-30 days of treatment. Naproxen was not associated with a statistically significant increased risk of death or MI for the entire treatment duration. The authors conclude that short-term treatment with most NSAIDs is associated with increased cardiovascular risk. This suggests that there is no apparent safe therapeutic window for NSAIDs in patients with prior MI and "challenge the current recommendations of low-dose and short-term use of NSAIDs as being safe" (*Circulation* 2011;123:2226-2235). One interesting aspect of this study was the use of rofecoxib (Vioxx) prior to its withdrawal in 2004. While rofecoxib was found to increase cardiovascular risk (the reason for its withdrawal from the market), it appeared to be no more dangerous than other commonly used NSAIDs and was apparently safer than diclofenac. ■

NHLBI stops AIM-HIGH trial

Niacin may not be effective in preventing cardiovascular disease. The National Heart Lung and Blood Institute (NHLBI) has prematurely stopped the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) clinical trial 18 months earlier than planned. Analysis of the data found that adding high-dose, extended-release niacin to statin treatment in people with heart and vascular disease did not reduce the risk of cardiovascular events. AIM-HIGH participants had well-controlled low-density lipoprotein levels on a statin, however they were at risk of cardiovascular disease due to previous history of cardiovascular disease and a combination of low high-density lipoprotein (HDL) cholesterol and high triglycerides. During the nearly 3 years of the study, patients who took high-dose, extended-release niacin with a statin had increased HDL cholesterol and lower triglyceride levels compared to those who took a statin alone; however, the combination was not effective at reducing fatal or nonfatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures. There also was a "small and unexplained increase in ischemic stroke rates in the high-dose, extended-release niacin group" that contributed to the decision to halt the trial. Termination of the AIM-HIGH trial was announced by press release from the NHLBI on May 26. ■

FDA actions

The FDA has approved linagliptin for the treatment of type 2 diabetes in adults. The drug is an inhibitor of DPP-4, an enzyme that degrades incretin hormones (GLP-1 and GIP). It is approved for use as a stand-alone therapy or in combination with other drugs for type 2 diabetes including metformin. The approval was based on eight double-blind, placebo-controlled trials of nearly 4000 patients that showed improved blood glucose control compared to placebo. Linagliptin is marketed by Boehringer Ingelheim Pharmaceuticals as Tradjenta.

The FDA has approved rilpivirine, a new non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of adults with HIV-1 infections who are treatment naïve. Rilpivirine is to be used as part of a highly active antiretroviral therapy (HAART). The approval was based on two phase 3 trials of nearly 1400 adults with HIV who were observed for 48 weeks, and an additional 96-week trial in which the drug was compared to efavirenz as part of multidrug combinations. Rilpivirine was found to be comparable to efavirenz with regard to percentage of patients with undetectable HIV viral load. Patients who failed rilpivirine are more likely to develop drug resistance than patients who failed efavirenz. Rilpivirine is marketed by Tibotec Therapeutics as Edurant.

Rosiglitazone (Avandia) remains on the U.S. market, but its days may be numbered. In a new step to restrict use of the drug, the FDA has updated the Risk Evaluation and Mitigation Strategy to include a restricted access in distribution plan. Physicians and patients must enroll in the distribution program in order to receive the drug. Rosiglitazone will no longer be available in commercial pharmacies after mid-November and will only be available by mail order through certified pharmacies. Use of the drug is limited to patients who are currently on rosiglitazone and whose diabetes is not controlled by other treatments and who are unwilling to change to pioglitazone (Actos). ■