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Haemolysis associated with the treatment of malaria with artemisinin derivatives: a systematic review of current evidence

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SUMMARY

Background: Artemisinin derivatives are the mainstay of antimalarial treatment, both for uncomplicated malaria and for severe disease. Artemisinins are known for their rapid onset of action, good tolerability, and safety. However, besides the sporadic but worrying reports of delayed parasite clearance after treatment with artemisinins, there have been an increasing number of reports of acute haemolytic anaemia following their use and the safety of this class of antimalarials is being questioned.

Methods: In this systematic review, all reports of patients experiencing haemolysis following the use of artemisinins for the treatment of malaria were identified and collated into an electronic database. Summary statistics were calculated to characterize the epidemiology and clinical features of this safety concern related to artemisinin derivatives.

Results: A total of 37 patients were identified suffering from haemolysis following the treatment of severe malaria with artemisinin derivatives. Thirty-one cases had received intravenous artesunate, while the remaining cases were attributed to other parenteral or oral regimens of artemisinin derivatives. The majority of patients were returning travellers (n = 30), and six clinical cases had been reported in paediatric patients. The median onset of haemolysis was 15 (interquartile range (IQR) 13–15) days after the initiation of treatment for the 'delayed-onset' pattern and 17 (IQR 13–22) days for the 'persistent' haemolysis pattern. The median reduction in haemoglobin due to haemolysis was 6 g/dl (IQR 4–8 g/dl). The estimated proportion of patients suffering from severe malaria experiencing haemolysis after treatment with artemisinin derivatives was 13% (95% confidence interval 9–18%), and 73% of these (i.e., 9% of the total population) required blood transfusions. No fatal outcome has been reported in the literature to date.

Conclusions: Haemolysis is commonly associated with the class of artemisinin drugs when used for the treatment of severe malaria. Potential causes of this safety issue are discussed. Although no deaths attributed to haemolysis have been reported so far, this safety issue may lead to life-threatening anaemia and is particularly worrying for regions where safe blood products are not readily available.

1. Introduction

Despite recent progress in rolling back malaria-related morbidity and mortality, the burden of disease remains unacceptably high with an estimated 207 million clinical cases of malaria each year and more than 600 000 malaria-related deaths.[1] Severe malaria therefore remains a serious clinical condition with considerable mortality, even in high-income regions.[2]

The artemisinin class of antimalarials following the spread of drug resistance in *Plasmodium falciparum* isolates to previously used first-line drugs.[3] Artemisinins were demonstrated to show unparalleled rapid parasite clearance, excellent tolerability, and were assumed to be exceptionally safe in the treatment of malaria.[4,5] Due to a high rate of recrudescence when used as monotherapy, the use of artemisinins has been recommended in combination with partner drugs for the treatment of uncomplicated malaria, in the form of artemisinin combination therapies (ACT).[6–8] Artesunate, artemether, and dihydroartemisinin became the most widely employed oral artemisinin derivatives used in ACT.

The intravenous administration of artesunate – a water soluble artemisinin derivative readily hydrolysed to the active metabolite dihydroartemisinin – was demonstrated to lead to improved survival rates compared to standard quinine therapy for severe

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P. falciparum malaria. This was shown both for a predominantly adult Asian patient population, as well as for African children.[9,10] Parenteral artesunate became the treatment of choice for severe *P. falciparum* malaria based on these clinical trials.[11] Besides its efficacy, it was postulated that intravenous artesunate showed good tolerability and superior safety compared to the previous standard drug quinine.

Until recently, the rare occurrence of hypersensitivity reactions was considered the only clinically important safety issue associated with artemisinins. However, since then, the publication of an increasing number of cases and case series of patients experiencing late onset haemolysis following antimalarial treatment with artemisinin derivatives has raised important questions about the safety of this class of antimalarials.[12–19] To date, conclusive evidence about the frequency, clinical implications, pathophysiology, and importance of haemolysis associated with the use of artemisinin derivatives has been lacking. In this systematic review we collate all the available evidence to address these questions and to provide the basis for further discussions on the impact of this finding on our current management of patients with severe *P. falciparum* malaria.

2. Methods

In this systematic review, all reported cases of late onset haemolysis following treatment with artemisinin derivatives were identified. Published reports were sought using the following search terms: 'artemisinin', 'artesunate', and 'artemether' combined with one of the following keywords: 'haemolysis', 'delayed haemolysis', 'anaemia', and 'haemolytic anaemia'. Medline, Thomson Reuters Web of Science, Google Scholar, and conference abstracts were screened to identify further publications. The unpublished grey literature was searched using internet search engines, interviews of experts in the field, and references of published reports. There was no exclusion on the basis of time period or language of publication. All studies were assessed for risk of bias based on study design and the reporting of outcome variables. Data were entered into an electronic database for further analysis.

3. Definitions

'Returning traveller' was defined as anyone native to a non-malaria endemic region, visiting an endemic region and returning from there to his/her native non-endemic region. Consequently, a Nigerian man who was diagnosed and treated in Japan was not classified as a returning traveller as he was a native of an endemic region.[15] 'Haemolysis' is the destruction of red cells with subsequent release of haemoglobin. Published studies did not use uniform definitions for haemolysis. In this study, haemolysis associated with the use of artemisinin derivatives was therefore defined as the onset of haemolysis evidenced by a decrease in haemoglobin and an increase in lactate dehydrogenase (LDH) after the complete clearance of asexual parasitaemia from peripheral blood.

Two distinct patterns of haemolysis after the use of artemisinin therapy have been described and classified. These encompass a delayed onset and a persistent pattern of haemolysis (Figure 1).[14,16–19] 'Delayed haemolysis' was defined as the occurrence of a decrease in haemoglobin associated with low haptoglobin or increased LDH at >7 days following the initiation of artemisinin treatment.[19] 'Persistent haemolysis' was defined as continuing haemolysis starting from or around day 7 of artemisinin treatment and persisting beyond day 14. 'Severe malaria' was defined by the authors of the published reports in accordance with the World Health Organization (WHO) recommendations,[20] a modification of this as summarized in the German national guidelines,[13] or based on a definition used by the 'Severe Malaria in African Children Network' (SMAC).[19] Data were extracted by the investigators from the original reports and were entered into a purpose built database. The statistical analysis encompassed descriptive statistics (JMP 10.0; SAS Institute, NC, USA). Median and interquartile ranges were used to describe distributions.

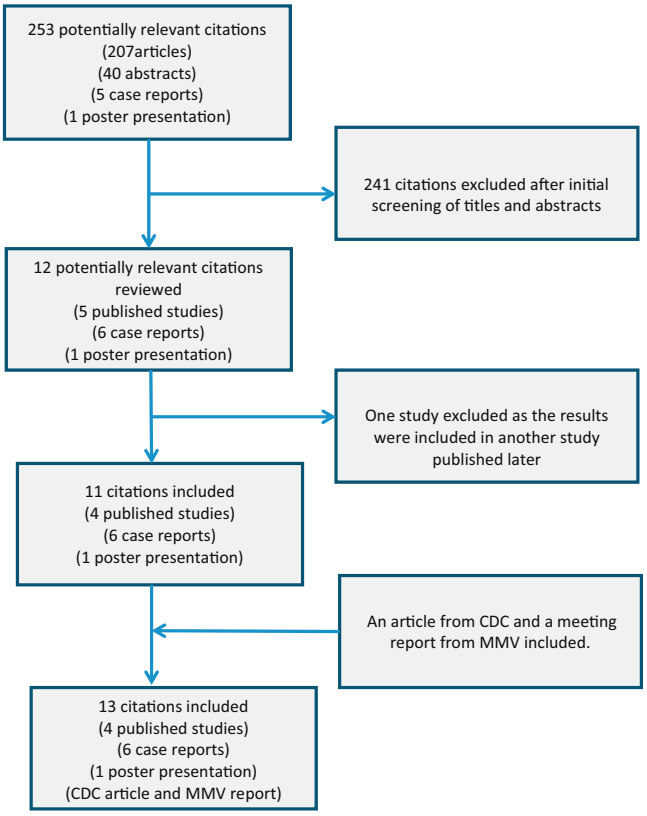

Figure 1. Identification of clinical reports of haemolysis associated with the use of artemisinins.

4. Results

A total of 11 published studies and one poster presentation reporting artemisinin-associated haemolysis were identified and included in this review.[12–19,21–24] One study was excluded from further analysis,[12] since the reported patients were part of a second publication, which was used for the purpose of this systematic review.[13] In addition to the above-mentioned scientific papers, reports by the Centers for Disease Control and Prevention (CDC, Atlanta, USA)[25] and by the Medicines for Malaria Venture (Geneva, Switzerland) were identified and included in this analysis[26] (Figure 1). All published cases were reported from non-malaria endemic regions except for one paper investigating paediatric patients in Africa.[19] Details of patient characteristics, the treatment given, and laboratory findings are summarized in the **Supplementary Material** (Supplementary File 1).

4.1. Description of study characteristics

A total of 37 cases of haemolysis associated with the use of artemisinin derivatives in the treatment of malaria have been reported so far.[12–19,21,23,24,26] Thirty-three cases have been published in research papers and four cases are referred to in a meeting report (one from China, one from the USA, and two from Canada).[26] In addition, surveillance data from France were discussed in that report but have not yet been published and were therefore not available for the purpose of this review. The reports are mainly retrospective studies ($n = 5$) and case reports