World Health Organization

GLOBAL MALARIA PROGRAMME

WHO Information Note on Delayed Haemolytic Anaemia following Treatment with Artesunate

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Injectable artesunate is a life-saving therapy for patients with severe *Plasmodium falciparum* malaria, providing a substantial reduction of mortality. In the two largest randomized controlled trials conducted in patients with severe malaria, parenteral artesunate treatment reduced deaths by 34.7% (in the Asian SEAQUAMAT trial) and by 22.5% (in the African AQUAMAT trial) compared with parenteral quinine.[1,2] WHO currently recommends artesunate (intravenous or intramuscular) as the first line treatment for the initial management of severe malaria.[3]

A number of cases of delayed haemolytic anaemia have been identified following treatment of severe malaria with injectable artesunate. The Medicines for Malaria Venture (MMV), in March 2013, convened a meeting of experts to review the available evidence on delayed haemolytic anaemia following treatment with injectable artesunate. The full report of the MMV convened expert meeting is available on the MMV webpage (http://www.mmv.org/newsroom/events/expert-group-meeting-safety-profile-injectable-artesunate).

This information note reflects the current WHO position based on the outcome of the review meeting and consultation with the Co-Chairs of the GMP Technical Expert Group on Malaria Chemotherapy.

Summary

Delayed haemolytic anaemia following treatment with injectable artesunate has been observed in non-immune travelers presenting with severe falciparum malaria and particularly in patients presenting with hyperparasitaemia. Post-treatment haemolytic anaemia is not specific to a particular injectable artesunate formulations, and has been described following use of injectable artesunate, intra-muscular artemether and, also, oral artemether-lumefantrine.

Available data are mainly from case reports and retrospective studies, conducted with different study designs, case definitions and study endpoints, with delayed anaemia defined differently across the various studies. Definitions of severe malaria have also varied across studies. As a result the incidence and predisposing factors (other than hyperparasitaemia) remain uncertain.

The mechanisms of delayed haemolytic anaemia following the treatment of severe malaria are multiple, and are not fully understood. Conditions such as blackwater fever (sudden massive haemolysis and haemoglobinuria associated with malaria), and severe haemolysis caused by malaria itself, may overlap with delayed haemolytic anaemia. Other mechanisms, such as delayed auto-

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[1] Dondorp A, Nosten F, Stepniewska K, Day N, White N, 2005. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* 366: 717-25.

[2] Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, Chhaganlal KD, Bojang K, Olaosebikan R, Anunobi N, Maitland K, Kivaya E, Agbenyega T, Nguah SB, Evans J, Gesase S, Kahabuka C, Mtove G, Nadjm B, Deen J, Mwanga-Amumpaire J, Nansumba M, Karema C, Umulisa N, Uwimana A, Mokuolu OA, Adedoyin OT, Johnson WB, Tshefu AK, Onyamboko MA, Sakulthaew T, Ngum WP, Silamut K, Stepniewska K, Woodrow CJ, Bethell D, Wills B, Oneko M, Peto TE, von Seidlein L, Day NP, White NJ, 2010. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 376: 1647-57.

[3] *Guidelines for the treatment of malaria, Second Edition*. Geneva, World Health Organization, 2011, (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf.

immune haemolysis may contribute in some cases. Preliminary evidence suggests that the key pharmacodynamic advantage of artesunate over quinine, that it kills young circulating ring stage parasites before they sequester in the microcirculation, could explain the delayed haemolysis. This mechanism explains the rapid action of artesunate and its beneficial effect on mortality and other clinical outcomes. Most of the killed ring stage parasites are cleared rapidly by the spleen by 'pitting' of erythrocytes whereby the dead parasite is removed from within the erythrocyte. These 'once infected' erythrocytes are returned to the circulation but they have a reduced lifespan of about 7–15 days: the delayed destruction of 'once infected' erythrocytes corresponds with the time course of post-treatment delayed anaemia seen clinically. The patients saved by artesunate, who might have died had they received quinine, are particularly those with high parasitaemias. All reported cases of delayed haemolytic anaemia after injectable artesunate have been managed successfully. Some patients have required transfusions, but there have been no reports of fatal outcome.

Conclusions

There is overwhelming evidence that artesunate (intravenous or intramuscular) is a generally well tolerated and life-saving therapy in severe *Plasmodium falciparum* malaria, providing a significant reduction of mortality compared to quinine. The therapeutic benefits far outweigh the risk of artemisinin-related adverse events, including post-treatment delayed haemolytic anaemia.

Recommendations

WHO strongly recommends the continued use of injectable artesunate in the treatment of severe malaria. The need for continued use and further adoption of injectable artesunate as a life-saving treatment by malaria endemic countries should be emphasized and supported.

However, healthcare professionals should be made aware of the potential for delayed haemolytic anaemia for up to one month post treatment. Pharmacovigilance systems should be strengthened at country level with strong involvement of the national pharmacovigilance centres and the WHO Programme for International Drug Monitoring, to better detect adverse events following the use of artesunate, as well as all other medicines.

For data to be comparable across clinical studies, a consistent definition of delayed haemolytic anaemia and of severe malaria is required. Similarly there is the need for standardization of methods for safety reporting systems to enable/ improve data collection.

Recommended Next Steps

- Pathophysiology studies should be conducted to characterize mechanisms of haemolysis and delayed haematological recovery following severe malaria, and thus interventions which may prevent or ameliorate it.
- Prospective clinical trials are needed
  - to define the frequency, magnitude and time course of delayed post-treatment haemolytic anaemia.
  - to identify predictors /prognostic factors for post-treatment haemolytic anaemia,
- Harmonization of Phase IV studies is recommended, particularly for those proposing web-based spontaneous reporting systems by pharmaceutical companies.
- The role of severe malaria patient registries as an additional approach for monitoring and obtaining data /information needs to be explored further.