Evidence Update

Summary of a Cochrane Review **Malaria Series**

Which artemisinin-based combination therapies (ACTs) are effective for treating uncomplicated *P. falciparum* malaria?

Generally, all of the WHO recommended artemisinin combination treatments were very effective, but trials report true failure rates exceeding 10% in some areas.

Background

The World Health Organization recommends ACTs for the treatment of uncomplicated *P. falciparum* malaria, and state that the first-line ACT adopted in a region or country should have a treatment failure rate of less than 10%. Current available combinations are compared.

Inclusion criteria

Studies:

Randomized controlled trials. Last search date.

Participants:

Adults and children with a microscopically confirmed diagnosis of uncomplicated *P. falciparum* malaria.

Intervention:

A three-day course of: dihydroartemisinin-piperaquine; artesunate plus mefloquine; artemether-lumefantrine (six doses); artesunate plus amodiaquine; artesunate plus sulfadoxine-pyrimethamine or amodiaquine plus sulfadoxine-pyrimethamine (a non-artemisinin-based combination therapy still in use in some African countries).

Outcomes:

Treatment failure at days 28, 42, and 63, gametocytemia, adverse events, serious adverse events.

Results

- Fifty studies were included: 21 with concealed allocation, most conducted in Africa (31) and Asia (17). Pregnant and lactating women and young infants (less than 1 year in Asia and less than 6 months in Africa) were excluded from all trials.
- Dihydroartemisinin-piperaquine, performed well compared to the ACTs in common use (vs. mefloquine in Asia: PCR adjusted treatment failure day 63 relative risk 0.39, 95% confidence interval 0.19 to 0.79; 1062 participants, 3 trials; versus artemether-lumefantrine in Africa: PCR adjusted failure day 42; RR 0.39, 95% CI 0.24 to 0.64; 1136 participants, 3 trials). It did however have a failure rate above 10% in one trial from Papua New Guinea.
- Artemether-lumefantrine and artesunate plus amodiaquine both performed well in most studies which evaluated them, but failure rates above 10% have been reported with both combinations from study sites in Uganda.
- There is very little good quality evidence available comparing artesunate plus sulfadoxine-pyrimethamine to dihydroartemisinin-piperaquine, artesunate plus mefloquine or artemether-lumefantrine but it has performed well in head to head trials with artesunate plus amodiaquine in Africa.
- ACTs were superior to amodiaquine plus sulfadoxine-pyrimethamine in East Africa (PCR adjusted treatment failure day 28: artemether-lumefantrine vs AQ+SP; RR 0.12, 95% CI 0.06 to 0.24; 618 participants, 2 trials; artesunate plus amodiaquine vs AQ+SP; RR 0.44, 95% CI 0.22 to 0.89; 1515 participants, 3 trials).

Adapted from Sinclair D, Zani B, Donegan S, Olliaro P, Garner P. Artemisinin-based combination therapy for treating uncomplicated malaria. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD007483. DOI: 10.1002/14651858.CD007483.pub2. [New search March 2009} *Evidence Update* published in March 2011.

Authors' conclusions

Implications for practice:

In Asia, dihydroartemisinin-piperaquine was at least as effective as artesunate plus mefloquine (HIGH quality evidence), providing a valuable alternative to the ACTs in current use.

In Africa, dihydroartemisinin-piperaquine was at least as effective as artemether-lumefantrine (HIGH quality evidence), and artesunate plus amodiaquine (MODERATE quality evidence), and these combinations continue to perform well in most areas. Artesunate plus mefloquine is also likely to be an effective option in Africa where resistance to mefloquine is rare, although it has been little studied in this context.

Amodiaquine plus sulfadoxine-pyrimethamine is no longer an effective first-line treatment in several East African countries (MODERATE quality evidence). It was, however, still performing well in Senegal in 2003, Madagascar in 2006, and Burkina Faso in 2005.

Evidence of the safety of ACTs is accumulating. Serious adverse events with these drugs appear to be rare. However, these trials are too small to detect rare but clinically important events and so it is imperative that active monitoring continues.

Implications for research:

Examples of treatment failure rates above 10% exist for all ACTs. The local efficacy of the first-line ACT should therefore continue to be monitored after its introduction to detect resistance.

Further trials are necessary to assess the efficacy and safety of these combinations in pregnant women and very young infants.

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