A systematic review and meta-analysis of the effectiveness and safety of atovaquone-proguanil (Malarone) for chemoprophylaxis against malaria

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CRD summary
The authors concluded that atovaquone-proguanil (Malarone) is a highly effective agent for malaria prophylaxis, which is well tolerated compared with other antimalarials. This was a generally well-conducted review and, despite considerable clinical differences between the studies, the conclusions are likely to be reliable.

Authors’ objectives
To assess the safety and effectiveness of atovaquone-proguanil (Malarone) as a chemoprophylactic agent against malaria.

Searching
MEDLINE and EMBASE (since the 1950s) and the Cochrane Library (on infectious diseases) were searched to June 2007, and Web of Knowledge up to 2006. Reference articles cited in Annals of Tropical Medicine, references of retrieved articles, and World Health Organization and Centers for Disease Control and Prevention websites (up to 2007) were also searched. The search terms were reported and no language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that assessed the use of atovaquone-proguanil for chemoprophylaxis against malaria were eligible for inclusion. Trials were required to report pre- and post-intervention patient information and outcome measures of either effectiveness or safety. The primary review outcomes were parasitaemia and side-effects.

The participants in the included studies varied: some studies exclusively enrolled children, others only adults. Both non-immune travellers and migrant populations to affected areas and long-term residents of endemic areas were represented in the studies. Where reported, children had a mean age of between 3 and 16 years and weighed between 10 and 50 kg; mean ages of adults were between 18 and 65 years and weights were at least 50 kg. The studies used placebo control, or the alternative prophylaxis comparators chloroquine-proguanil, mefloquine or doxycycline. The included studies excluded patients with co-morbidities such as the human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS), pregnant or lactating women, people with previous malaria, or those receiving alternative prophylaxis at any point during the study period.

Two reviewers assessed papers for inclusion in the review.

Assessment of study quality
The validity of the studies was assessed using the Jadad score, which awards a maximum of 5 points for the criteria of randomisation, allocation concealment, blinding, and the treatment of withdrawals and drop-outs.

Two reviewers independently assessed validity.

Data extraction
Relative risks (RRs) were calculated for key outcomes. One reviewer extracted the data, which were checked by a second reviewer.

Methods of synthesis
The RRs were pooled in fixed-effect meta-analyses for individual comparisons. The protective efficacy of atovaquone-proguanil was calculated from the placebo comparison. Statistical heterogeneity between studies was assessed using the $I^2$ statistic.
Results of the review
Ten RCTs (n=4,539) were included in the review. Sample sizes ranged from 108 to 1083 patients.

Study quality was generally high, with Jadad scores of 4 or 5 where reported.

Atovaquone-proguanil versus placebo (6 RCTs): the pooled RR of malaria was 0.041 (95% confidence interval, CI: 0.020, 0.082). There was no evidence of statistical heterogeneity. The protective efficacy was calculated to be 95.8% (95% CI: 91.5, 97.9). There were some discrepancies between the text and tables.

Atovaquone-proguanil versus alternative prophylaxis (3 RCTs): 2 studies used a comparator of chloroquine-proguanil, while the other used mefloquine. Only one RCT reported any malaria cases; all three were in the chloroquine-proguanil group. Pooling of the 2 studies using chloroquine-proguanil comparator groups revealed no significant difference between the groups in incidence of malaria (p=0.25).

Adverse events (4 RCTs): patients in the atovaquone-proguanil groups had fewer severe adverse effects (RR 0.61, 95% CI: 0.42, 0.90) and showed a trend towards fewer self-reported adverse events (RR 0.82, 95% CI: 0.67, 1.01). There was no significant difference between the atovaquone-proguanil and comparator groups in incidence of neuropsychiatric events or proportion of patients completing their course of medication. Significant heterogeneity was detected in the analyses of self-reported effects and neuropsychiatric effects.

Authors' conclusions
Atovaquone-proguanil is a highly effective prophylactic against malaria infection and is very well tolerated compared with other antimalarial agents.

CRD commentary
The review question and the inclusion criteria were clear. The authors searched a number of databases and other relevant sources without language restrictions, thereby reducing the risk that relevant studies were not included and that language or publication bias was present. An appropriate validity assessment was conducted and review methodology was rigorous at all stages. There was considerable clinical heterogeneity between the included studies, which was reflected in statistical heterogeneity in some instances. As this heterogeneity was not further investigated, it is not completely clear that meta-analysis was appropriate in all instances. However, this was a generally well-conducted review of high-quality RCTs and the conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that atovaquone-proguanil may be of particular value to travellers visiting areas with resistance to other antimalarials, or for whom mefloquine is contraindicated because of the potential for neuropsychiatric adverse effects.

Research: The authors stated that an assessment of the cost-effectiveness of atovaquone-proguanil in long-term travellers and residents of malaria endemic areas, and research on its efficacy in individuals with HIV and AIDS, is warranted.

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