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

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Objectives: A systematic review and meta-analysis of the effectiveness of atovaquone–proguanil (Malarone) as a chemoprophylactic agent against malaria.

Methods: The data sources searched for this study included Cochrane systematic reviews (on infectious diseases), MEDLINE and EMBASE, Web of Knowledge and Annals of Tropical Medicine. All unconfounded randomized controlled trials assessing the chemoprophylaxis against malaria with atovaquone–proguanil were included in the review. Data on study design, study sample, inclusion and exclusion criteria, allocation, blinding, primary and secondary study end points were all extracted by one reviewer and independently rechecked by the second reviewer.

Results: In general, all 10 studies identified had excellent quality with total scores of ≥4 using the Jadad criteria. Ten controlled trials comprising 4539 participants were included for this review. A meta-analysis of six of the ten studies found chemoprophylaxis with atovaquone–proguanil, with a prophylaxis efficacy of 95.8% (95% CI = 91.5–97.9), to be superior to placebo. It was also considered safe and better tolerated with fewer treatment-related adverse events that could lead to premature discontinuation of prophylaxis than in controls. Comparison with alternative chemoprophylaxis also showed atovaquone–proguanil to be better tolerated with fewer treatment-related self-reported adverse events (RR = 0.8234; 95% CI = 0.6731–1.01) or severe adverse events (RR = 0.6140; 95% CI = 0.4200–0.8975). Atovaquone–proguanil is well tolerated with no difference in non-compliance with placebo (RR = 0.8804; 95% CI = 0.6964–1.113; I² = 31.4%).

Conclusions: Evidence from this review shows that atovaquone–proguanil is highly efficacious as a prophylactic agent against malaria infection and is very well tolerated compared with other antimalarial agents.

Keywords: travel, tropical medicine, Plasmodium falciparum, randomized controlled trial

Introduction

Approximately 10 000 North Americans and Europeans acquire malaria each year while travelling abroad and there has been a noted increase in the reported cases in travellers over the years.1,2 Chemoprophylaxis is one of the most important measures, along with avoidance of mosquito bites, in reducing risk in travellers to malaria endemic areas.3 Reliance on chloroquine or mefloquine is no longer possible because of increased drug resistance and is also problematic because of reported neuropsychiatric adverse events.1 Atovaquone–proguanil (Malarone) is the most recent recommended regimen for prophylaxis in areas with chloroquine resistance, but so far there has been no systematic review of its efficacy or tolerability and safety.

As far as we know, this is the first systematic review of chemoprophylaxis with atovaquone–proguanil against malaria.

Methods

The objective was to evaluate all existing data, using randomized trials, on the efficacy, safety and tolerance of atovaquone–proguanil as a chemoprophylaxis agent against malaria infection.

Search strategy and selection process

The search strategy used these sources to identify relevant data in the following electronic databases: Ovid MEDLINE and EMBASE

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Systematic review

(Risks through meta-analysis if the effects. A fixed effect model was used to estimate pooled relative tic efficacy, the primary outcome was parasitaemia. For measures of involved paediatric subjects, whereas the remaining six Demographic characteristics varied, for example, three studies compared atovaquone–proguanil as a chemoprophylaxis agent with placebo or atovaquone–proguanil with another chemoprophylaxis agent. The final 10 reports for this review included data on 4539 participants. Table 1 summarizes the characteristics of these 10 studies. Type of participants

Data extraction: inclusion/exclusion criteria

Types of participants

Quantitative data analysis

Results

Data were extracted by one reviewer and cross-checked by another. In case of any suggestion that the study could be relevant, it was retrieved for further assessment by both the reviewers. Criteria for inclusion were use of randomization, reporting on pre- and post-intervention patient information and either effectiveness or safety outcome measures.

Quality assessment of the included studies

The same reviewers independently reviewed all trials included in the review. The quality of the methodology of each selected trial was rated using the Jadad 1996 criteria score and the QUORUM statement checklist.

Quantitative data analysis

All analyses were done using StatsDirect. For studies of prophylactic efficacy, the primary outcome was parasitaemia. For measures of safety, the principal outcome measure was reporting of any side effects. A fixed effect model was used to estimate pooled relative risks through meta-analysis if the I^2 statistic was low.

Type of interventions

Six studies compared atovaquone–proguanil with placebo, whereas the remaining studies compared it with an alternative type of antimalarial chemoprophylaxis. Only 5 out of the 10 studies had a pre-study radical treatment phase, to ensure that subjects who were randomized had identical outcomes.

Type of outcomes

Parasitaemia was the primary outcome in all of the studies, except for one. This trial was concerned with comparing safety and tolerability of atovaquone–proguanil with three other anti-malarials (mefloquine, doxycycline and chloroquine–proguanil). All trials reported adverse effects and tolerability.

Methodological quality

The studies differed in sample size, two studies had 1013 and 1083 subjects randomized, respectively. The remaining eight studies had varied sample sizes ranging between 180 and 320 subjects. Randomization was well described by all ten studies. Eight of the 10 studies used double-blind, placebo-controlled methods, and one study was an open-label study. Most of the studies described their measures to ensure that confounding factors were avoided, i.e. exclusion of subjects that were immune to malaria or those who were taking other antimalarial therapies. Assessment of data collection revealed that most studies reported adequate allocation concealment, i.e. tablets were identical in appearance and taste and neither staff nor subjects were aware of treatment allocation and double-blind data collection by the investigators. All ten trials carried out intention-to-treat analyses with varied losses to follow-up.

All studies complied with the appropriate ethical considerations by obtaining written consent from each adult subject (for children consent was obtained from their parents or legal representative) and ethical approval from the appropriate Ethics Committees.

Efficacy

Five studies included in this meta-analysis compared the efficacy of atovaquone–proguanil with placebo in preventing malaria (Figure 1). The pooled relative risk of malaria in the intervention arm was 0.0423 (95% CI = 0.021–0.0853; I^2 = 0%). Therefore, the protective efficacy of atovaquone–proguanil was 95.8% (95% CI = 91.5–97.9).

Three studies compared atovaquone–proguanil with alternative antimalarial prophylactic agents, two with chloroquine–proguanil and one with mefloquine. In only one of these...
Table 1. Characteristics of the randomized controlled trials (RCTs) assessing the effectiveness of current antimalarial prophylaxis treatments

<table>
<thead>
<tr>
<th>Study year (and reference)</th>
<th>Country</th>
<th>Studied antimalarial agent</th>
<th>Number of cases</th>
<th>Characteristics of participants (inclusion and exclusion criteria)</th>
<th>Jadad score Max (5/5)</th>
<th>Outcomes, efficacy and safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camus et al.6</td>
<td>13 travel clinics and infectious disease units in Canada, Denmark, France, Germany, The Netherlands and UK</td>
<td>Atovaquone–proguanil versus chloroquine–proguanil</td>
<td>221 non-immune paediatrics travellers aged 3–16 years with a weight of 11–50 kg and in good general health</td>
<td>International randomized open label study. 7, 28 active Rx 60 days follow-up</td>
<td>≥4</td>
<td>Blood smear/self-report adverse events assessed by an investigator during visits. No subjects were diagnosed with malaria at any time during the study. Over the treatment period, less atovaquone–proguanil subjects experienced drug-related adverse events (8% versus 14%, between group difference in proportion, −0.06 95% CI, −0.15 to 0.02)</td>
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<tr>
<td>Faucher et al.,14 Financial support obtained from GlaxoSmithKline</td>
<td>Gabon</td>
<td>Atovaquone–proguanil hydrochloride versus placebo</td>
<td>330 school children aged between 4 and 16 years living in a malaria endemic area. Stratified according to their weight: groups 1–4, respectively, 11–20, 21–30, 31–40 and &gt;40 kg</td>
<td>Randomized placebo-controlled study. 12 weeks duration 4 week follow-up</td>
<td>5</td>
<td>Blood smear/self-report adverse events assessed by an investigator during visits 31 of the 144 children in the placebo group developed parasitaemia with an incidence density of 1.01 cases per person per year, and 1 of 150 in the atovaquone–proguanil group with and incidence density of 0.03 (P &lt; 0.001). Prophylactic efficacy of A/P was 97% [(95% CI) = 79–100]. No differences in adverse events</td>
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<tr>
<td>Hogh et al.,7 MAL30011 study Financial funding obtained from Glaxo Wellcome, Inc.</td>
<td>21 travel clinics in Denmark, UK, France, Germany, Netherlands, South Africa and Canada</td>
<td>Atovaquone–proguanil versus chloroquine–proguanil</td>
<td>1083 (adults) non-immune travellers to malaria endemic areas. Both sexes and at least 14 years old and weighed &gt;50 kg</td>
<td>Randomized double-blind study. 7, 28 active, 60 days follow-up after travel</td>
<td>5</td>
<td>Blood smear and ELISA/self-report adverse events assessed by an investigator during visits. Subjects receiving atovaquone–proguanil had lower frequency of adverse events 59 (12%) versus 100 (20%), [P = 0.001]. Estimated minimum efficacy for prevention of P. falciparum malaria was 100% [95% CI] = 59–100 in the atovaquone–proguanil group and 70% [95% CI] = 35–93 in the chloroquine–proguanil group</td>
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<tr>
<td>Lell et al.8 Financial support received from Glaxo Wellcome, Inc.</td>
<td>Gabon</td>
<td>Atovaquone–proguanil hydrochloride versus placebo</td>
<td>320 school children aged between 4–16 years living in a malaria endemic area. Stratified according to their weight: groups 1–4,</td>
<td>Randomized placebo-controlled study, 12 weeks duration 4 weeks follow-up</td>
<td>5</td>
<td>Blood smear/self-reported adverse events discuss at each weekly visit. 25 of the 140 children in the placebo group developed Parasitaemia with an incidence density of 0.9 cases per person per year, and none in the atovaquone–proguanil group (P &lt; 0.001). Prophylactic efficacy of A/P was</td>
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<tbody>
<tr>
<td>Ling et al.,⁹</td>
<td>Papua, Indonesia</td>
<td>Atovaquone–proguanil hydrochloride</td>
<td>297 (adults)</td>
<td>Non-immune volunteers living in non-endemic areas. Aged between 12 and 65 years and weighed ≥40 kg</td>
<td>5</td>
<td>Blood smear/self-report adverse events assessed by an investigator during daily visits. Protective efficacy of atovaquone–proguanil was 84% [95% CI] = 44–95 for <em>P. vivax</em> malaria, 96% [95% CI] = 72–99 for <em>P. falciparum</em> malaria and 93% [95% CI] = 77–98 for mixed vivax and falciparum malaria. Atovaquone–proguanil was reported to be more well tolerated and effective against <em>P. falciparum</em> and <em>P. vivax</em> malaria. Most adverse events were mild (77.0%) or moderate (22.6%) in intensity</td>
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<tr>
<td>Overbosch et al.,¹⁰</td>
<td>15 travel clinics in Netherlands, Germany, UK, Canada and South Africa</td>
<td>Atovaquone–proguanil hydrochloride versus mefloquine</td>
<td>1013 (adults)</td>
<td>Non-immune travellers to malaria endemic areas. Subjects were of a mixed group: 33 were ≤12 years old and 23 were ≥65 years old. Weight of ≥11 kg</td>
<td>5</td>
<td>Self-reported adverse events assessed by an investigator atovaquone–proguanil was better tolerated than mefloquine. However, equal reporting of adverse events in both groups (71.4% versus 67%, difference 4.1% [95% CI] = −1.71 to 9.9). Subjects in the A/P group had lower treat-related neuropsychiatric adverse events (14% versus 29%, <em>P</em> = 0.001), fewer moderate to severe adverse events (10% versus 19%; <em>P</em> = 0.001) and fewer adverse events causing prophylaxis discontinuation (1.2% versus 5.0%; <em>P</em> = 0.001) compared with mefloquine group. Both drugs had similar prophylaxis efficacy as there were no confirmed diagnoses of malaria in either group</td>
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<td>Shacks et al.,¹¹</td>
<td>Western Kenya</td>
<td>Atovaquone–proguanil hydrochloride</td>
<td>198 (adults)</td>
<td>Semi-immune Kenyan volunteers, both sexes. Aged between 18–65 years</td>
<td>≥4</td>
<td>Blood smear/self-reported adverse events assessed by an investigator during weekly visits. Prophylactic efficacy and success rates of in both the high and low doses of atovaquone–proguanil treatment groups were 100%. The differences in success rates between placebo and atovaquone–</td>
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<tr>
<td>Study</td>
<td>Location</td>
<td>Atovaquone–proguanil hydrochloride versus placebo</td>
<td>Participants</td>
<td>Study Design</td>
<td>Adverse Events</td>
<td>Results</td>
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<tr>
<td>Soto et al.</td>
<td>Colombia</td>
<td>180 (adults) non-immune Colombian Soldiers. All male, mean age of 19 years, mean weight of 63 kg</td>
<td>Phase IV, randomized, ≥4 double-blind, placebo-controlled study. 10–16 weeks of residence and 7 days after leaving endemic area 4 weeks follow-up</td>
<td>Proguanil treatments were highly significant (P &lt; 0.001). Both regimens were well tolerated, the type and frequency of drug-related adverse events with each regimen were not different from those in the placebo group. Blood smear/history and physical examination during weekly visits. In total, 47 of 120 (39%) subjects in the atovaquone–proguanil group and 24 of 60 (40%) subjects in the placebo reported one/more adverse events. The protective efficacy of atovaquone–proguanil for all malaria was 100% (LL 95% CI = 63) and 100% (LL 95% CI = 58), respectively.</td>
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<tr>
<td>Sukwa et al.</td>
<td>Zambia</td>
<td>274 (adults) non-immune both female and male volunteers, aged (18–65 years)</td>
<td>Double-blind, placebo-controlled randomized, two-arm parallel study. 10 week duration up to 4 weeks follow-up</td>
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<td>Schlagenhauf et al.</td>
<td>Travel clinics in Switzerland, Germany and Israel</td>
<td>623 (adult) non-immune female and male travellers to sub-Saharan Africa</td>
<td>Randomized, double-blind, four-arm parallel study 17 days before travel, 1–3 weeks during travel and 28 days after travel 28 days follow-up</td>
<td>Self-reported adverse events assessed by and investigator during visits. The incidence of mild adverse events was 82% (95% CI = 75–88), moderate 32% (95% CI = 25–40) and severe 7% (95% CI = 2–11). No statistically significant differences were found with other forms of chemoprophylaxis.</td>
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Financial support was received from GlaxoWellcome, Inc.

Financial support was reported to be an employee of GlaxoSmithKline. His disclosure was not identified to be a conflict of interest.

Financial support was received from GlaxoSmithKline and Roche; Pfizer and Zeneca also provided drugs free of charge.
three studies were any subjects diagnosed with malaria. In this one study, three subjects in the chloroquine–proguanil group developed *Plasmodium falciparum* malaria compared with none in the atovaquone–proguanil group. As only one study reported any malarial infections, no meta-analysis was done comparing the efficacy of atovaquone–proguanil with alternatives. However, the data from the two studies that compared atovaquone–proguanil with chloroquine–proguanil were combined. Although all three malaria cases were in the chloroquine–proguanil group, this was not statistically significant ($P = 0.25$; Fisher’s exact test).

**Adverse events and tolerability**

There was no greater reporting of adverse effects in those taking atovaquone–proguanil compared with those taking placebo. Serious adverse events were rare. Only one adverse event related to atovaquone–proguanil was reported, and this was repeated...
vomiting requiring hospitalization.\textsuperscript{11} Three meta-analyses were done comparing tolerability compared with other antimalarial prophylactic agents; whether participants reported any adverse effects (Figure 2), severe adverse effects and for non-completion of the course. Patients on atovaquone–proguanil had fewer self-reported adverse effects (RR = 0.8234; 95% CI = 0.673164–1.01; \( I^2 = 80.6\% \)) and severe adverse effects (RR = 0.6140; 95% CI = 0.420055–0.8975; \( I^2 = 0\% \)) than those using other antimalarials, whereas neuropsychiatric adverse effects were similar (RR = 0.741928; 95% CI = 0.4787–1.1499; \( I^2 = 86.7\% \)). There was no significant difference in the proportion of study participants who completed their prescribed course (RR = 0.8804; 95% CI = 0.6964–1.113; \( I^2 = 31.4\% \)).

**Discussion**

The issue of prophylaxis efficacy has previously been reviewed.\textsuperscript{16,17} The six studies identified here comparing atovaquone–proguanil with placebo demonstrated a pooled protected efficacy and success rate of 95.5% (95% CI = 90.5–97.9). Also atovaquone–proguanil is very well tolerated with no more adverse effects being reported in people receiving the drug than in the placebo group. Assessment of safety revealed that atovaquone–proguanil was safe at the standard adult dose of 250 mg of atovaquone and 100 mg of proguanil hydrochloride.

The safe dose for children was dependent on the weight of the child using a standard dose of 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride, this review found no comparative studies for analysis.

One study assessing whether atovaquone–proguanil was safe at a higher dose found that there were no statistically significant differences in terms of adverse events between subjects taking the standard dose and a higher dose of 500 mg of atovaquone and 200 mg of proguanil hydrochloride.\textsuperscript{11} It should be noted that there were no significant differences between atovaquone–proguanil and placebo on the number of subjects discontinuing prophylaxis due to adverse events.

The two studies that compared atovaquone–proguanil with chloroquine–proguanil also found that atovaquone–proguanil was better tolerated, with fewer severe adverse events that could cause discontinuation of prophylaxis. For example, one study reported 10 subjects in the chloroquine–proguanil arm and only 1 subject in the atovaquone–proguanil group who had prematurely discontinued chemoprophylaxis due to adverse events.\textsuperscript{2} Two studies found a significantly greater number of gastrointestinal adverse events in the chloroquine–proguanil group than in the atovaquone–proguanil group.\textsuperscript{6,7} These findings are in accordance with the known side effects of chloroquine–proguanil.\textsuperscript{18–20}

Although in the studies identified there were more male participants, there is no reason to believe that atovaquone–proguanil would be less effective in females. None of the studies included pregnant women, and as a result we have not been able to assess its safety as malaria chemoprophylaxis during pregnancy. None of the studies identified in this review assessed long-term use safety, although evidence from observational studies suggest that atovaquone–proguanil is well tolerated long-term.\textsuperscript{21,22}

Although atovaquone–proguanil appears to be safe and well tolerated, the results of this meta-analysis are only based on a relatively small sample, compared with the number of people that could be prescribed antimalarial prophylaxis, and as a result, rarer adverse effects are difficult to ascertain. Two anecdotal case reports of more serious side effects have appeared in the literature, one of hepatitis and one of Stevens–Johnson syndrome.\textsuperscript{23,24} However, it is still not possible to be definitive about the incidence of rarer adverse effects, especially following long-term use. There is a continued need for post-marketing surveillance to determine these issues.

When compared with mefloquine, atovaquone–proguanil was again better tolerated and had fewer severe adverse events reported. Although we have not found a significant difference in the reporting of neuropsychiatric adverse effects when compared with alternate therapies or with mefloquine alone, those that were reported tended to be less severe. Furthermore, fewer subjects discontinued the study drug prematurely in the atovaquone–proguanil group (64; 13.0%) compared with the mefloquine group (76; 15.7%), though this was not statistically significant (\( P = 0.236 \)).\textsuperscript{10} However, given that there were no cases of malaria diagnosed in either study arm, it is not possible to comment on the protective efficacy between the two groups.

Overall all the 10 studies in this review were well designed and showed excellent quality by scoring more than four points on the Jadad criteria.

There were concerns about compliance with prophylaxis therapy among travellers to endemic areas. The lack of compliance with prescribed prophylaxis has been reported to be associated with the development of some cases of malaria.\textsuperscript{3,25} Although none of the studies in this review reported development of malaria due to poor compliance, this is an important issue that needs to be addressed by physicians prescribing chemoprophylaxis therapies.

However, there are some concerns (although not voiced in this review) about the cost implications of newer combination therapies like atovaquone–proguanil. Advocates of atovaquone–proguanil argue that the standard regimen is cost-effective because travellers take it for a shorter duration for prophylaxis and it is better tolerated with fewer adverse events compared with other chemoprophylaxis agents. In addition, atovaquone–proguanil is effective against liver stages of the parasite cycle, shortening the time medication needs to be taken as it does not need to continue post-travel.

All the 10 studies in this review excluded patients with co-morbidities e.g. HIV and AIDS; it would be interesting to assess the efficacy of atovaquone–proguanil in these groups of patients as they are highly vulnerable to malarial infections and may benefit from the protection that atovaquone–proguanil could provide.

One may argue that the use of atovaquone–proguanil in short-term travellers to endemic areas is justifiable but its use in long-term travellers and among residents in malaria endemic areas warrants assessment of its cost-effectiveness. Atovaquone–proguanil is an expensive agent and many individuals in endemic areas may not be able to afford it and so will keep taking less-effective but cheaper therapies.\textsuperscript{26} Addressing this issue needs the involvement of not only drug companies and researchers but the involvement of governments of those countries with high endemicity.

In conclusion, it can be stated that atovaquone–proguanil has demonstrated very good efficacy, safety and tolerability and is a good choice for travellers to endemic areas. It will find
particular value in travellers to areas where there is resistance to other antimalarials. It is also a very good alternative for people for whom mefloquine is contraindicated due to concerns about the potential for neuropsychiatric side effects.

Funding
This systematic review and meta-analysis were conducted as part of a medical student’s selected study. No funding was required.

Transparency declarations
None to declare.

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