Tafenoquine for the prevention of *Plasmodium vivax* malaria relapse

Tafenoquine (Krintafel) is the first new drug to be approved for the treatment of relapsing *Plasmodium vivax* malaria in 70 years. Tafenoquine was engineered to be a metabolically stable and thus slowly eliminated version of the 8-aminoquinoline, primaquine, providing relapse prevention with a single dose as compared to 1–2 weeks of daily primaquine. Although it also causes protracted haemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency, it has the potential to accelerate *P vivax* elimination.[1]

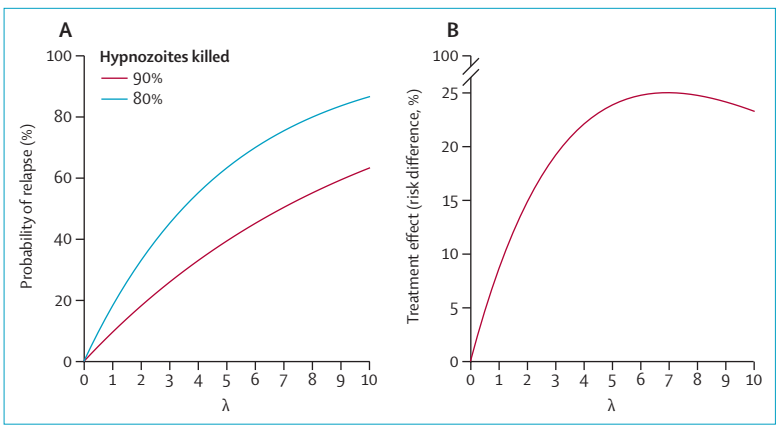

Figure: **Poisson-binomial model of the effect of the latent hypnozoite load on treatment effect estimates**

The model assumes that the number of hypnozoites is Poisson distributed and that activation is a binomial random event per hypnozoite. Drug efficacy is defined as the average percentage of hypnozoites cleared. (A) The probability of relapse after treatment (defined as the probability that at least one hypnozoite remains) for two drugs with different efficacies depends on the mean number of hypnozoites in the liver (Poisson parameter λ). (B) The risk difference (shown here on the percentage scale) comparing the two drugs varies non-linearly as a function of the mean hypnozoite load λ.

The initial US Food and Drug Administration approval recommended tafenoquine combination therapy using any antimalarial appropriate for the treatment of *P vivax* malaria. This recommendation was changed in 2020 to restrict tafenoquine radical cure to co-administration with chloroquine only, following unpublished results from a randomised trial of tafenoquine versus low-dose primaquine versus placebo in Indonesian soldiers returning from Papua (NCT02802501).[2] The recommended blood-stage treatment in Indonesia is dihydroartemisinin–piperaquine. The INSPECTOR trial showed overlapping confidence intervals for tafenoquine and placebo for the 6-month recurrence-free primary endpoint.[3] Fewer recurrent infections were observed after low-dose primaquine although recurrence rates were high (48%). These results were framed as inconsistent with previous phase 2 and 3 trials of tafenoquine. The Krintafel label change is also based on evidence for synergy in radical curative efficacy between 8-aminoquinolines, quinine, and chloroquine. However, dihydroartemisinin–piperaquine has been effective in combination with primaquine[4] so the specificity and importance of synergy are unclear. A simpler explanation is that the recommended dose of tafenoquine is too low.

There are three reasons why it is incorrect to assume that the phase 2 and 3 trials and INSPECTOR are comparable. First, the phase 2 and 3 randomised trials showing non-inferiority of tafenoquine compared to low-dose primaquine were carried out in endemic areas where recurrent infection can be caused by reinfection and relapse or recrudescence. In non-inferiority trials, reinfection will bias treatment effects towards the null by diluting the endpoint. This is not the case for soldiers returning to the Indonesian island of Java where reinfection was not possible. Second, tafenoquine has non-negligible blood stage activity.[5] Suppressive blood concentrations last for weeks after treatment, slowing parasite growth after the release of mature hepatic schizonts. Primaquine does not provide blood stage prophylaxis after treatment because it is rapidly eliminated, which confounds the interpretation of treatment effect estimates. Finally, primaquine and tafenoquine each have a dose–response relationship that, in theory, is dependent on the latent hypnozoite burden. Heavily inoculated individuals (eg, non-immune soldiers deployed to high-transmission areas) will probably need higher doses. Because relapse can be caused by a single hypnozoite, there is a non-linear treatment effect modification as a function of the latent burden (figure). These three factors are crucial for understanding why treatment effect estimates cannot be directly compared between randomised trials carried out in different contexts.

Although synergistic interactions with chloroquine might contribute, underdosing is a simpler alternative that can explain both the non-inferiority of tafenoquine to low-dose primaquine in the phase 2 and 3 trials, and the disappointing results from the INSPECTOR study. Studies with higher tafenoquine doses are needed urgently.

We declare no competing interests.

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