Pharmacokinetic-Pharmacodynamic Modelling for the Prediction of the Mosquitocidal Effect Duration of High-Dose Ivermectin (IVERMAL Trial, Kenya)

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Abstract:

- High-dose ivermectin, co-administered for 3-days with dihydroartemisinin-piperazine, was recently shown to kill malaria mosquitoes feeding on individuals for at least 28 days post-treatment, while only 7 days was predicted.^{1,2}
- The current pharmacokinetic and pharmacodynamic analysis aimed to determine whether a drug interaction or an unidentified ivermectin metabolite could be contributing to the prolonged mosquitocidal effect of ivermectin.
- The PK/PD model accurately predicted mosquitocidal activity for the entire study duration (28 days) without the need to invoke unidentified variables such as an active metabolite or a drug-drug interaction. Pediatric studies are now needed.

Background:

- Ivermectin is being considered for mass drug administration for malaria due to its ability to kill mosquitoes feeding on recently treated individuals.
- Used widely for onchocerciasis and lymphatic filariasis control at single doses of 150-200 mcg/kg.
- Mosquitocidal effect is short-lived (<7 days).
- Ivermectin has a wide therapeutic index and doses of 2,000 mcg/kg are well tolerated.
- High-dose ivermectin could generate longer effect-durations required for malaria elimination.

Hypothesis:

- A 3-day course of ivermectin 600 mcg/kg/day will kill mosquitoes fed patients' blood for up to 7 days after the start of treatment (Figure 2).¹

Methods:

- Randomized, double-blind, placebo-controlled trial comparing the safety, efficacy and pharmacokinetics of 3 days ivermectin 0, 300, or 600 mcg/kg/day, co-administered with dihydroartemisinin-piperazine (DP).
- Adults with uncomplicated malaria in Kenya.
- Efficacy outcome: The survival of laboratory-reared *Anopheles gambiae* s.s. fed on patients' blood taken 0, 2+4h (Cmax), 7, 10, 14, 21, and 28 days post-treatment was assessed daily for 28 days (see Figure 1).
- Pharmacokinetics: plasma ivermectin concentrations were determined at each blood-feed and as per a PK sampling schedule.

Figure 1: Mosquito feeding

Blood from a participant is fed to 3 cups of 50 mosquitoes (n=150) using an artificial membrane feeding system (heated to 37°C).

Figure 2: Pre-trial simulation

Simulated plasma concentrations of ivermectin 800 mcg/kg/day single-dose and 600 mcg/kg/day 3-day regimen. Maximum concentrations are similar, although mosquitocidal effect-duration (time above the LC50) increases from 1 day 22 hours to 6 days 18 hours.

Results:

- Between July 2015 and May 2016, 141 patients were randomized.
- Outcome data: mosquito mortality rates (n=850, from 91,109 mosquitoes), plasma concentrations (n=534, from 95 patients receiving ivermectin).
- Compared to placebo, ivermectin was associated with increased mosquito mortality for 28 days post-treatment (see Figure 3).²
- Population pharmacokinetics of ivermectin were best described by a two-compartment, oral absorption model (Figure 4).
- Using predicted concentrations instead of observed concentrations had near to no effect on the dose-response curve; it is unlikely that a metabolite or drug interaction are contributing to the prolonged mosquitocidal effect (Figure 5).
- The PK/PD model accurately predicted mosquitocidal activity for the entire 28-day study duration (Figure 6).

Figure 3: Trial results

Hazard ratios for mosquito mortality, by study arm relative to placebo, remained increased for 28 days. While pre-trial simulation predicted <7 days (Figure 2).

Figure 4: Ivermectin concentrations over time

Pharmacokinetic model shows a good fit for each ivermectin regimen (black line= median; dashed lines= 5% and 95% percentiles; shaded area= 95% CI for the percentiles) to the observed concentrations (circles), above the lower limit of quantification (5 ng/mL, horz. line). Kinetics are similar to previous studies.

Figure 5: Relationship between ivermectin concentration and mosquitocidal effect

Left: Dose-response curve using only observed ivermectin concentrations (≥5 ng/mL). Right: The same, now overlaid with PK model predicted concentrations (squares) and corresponding curve (dashed), showing near to no shift in the dose-response curve. An active metabolite or drug-drug interaction would have caused a leftward-shift (red curve).

Figure 6: Mosquitocidal effect over time

The PK/PD model shows a good fit for each ivermectin regimen (black line= median; dashed lines= 5% and 95% percentiles; shaded area= 95% CI for the percentiles) to the observed effects (empty circles), in comparison with baseline mortality (horz. line= 4.2 deaths/100 days). Mosquitocidal activity is accurately predicted for the entire study duration (28 days), and for each study visit (ball-whiskers= median, IQR).

Conclusion:

- High-dose ivermectin increases mosquito mortality for at least 28 days post-treatment, making it a promising new tool for malaria elimination.²
- Its long effect-duration can be explained by the PK/PD of the parent compound, without the need to invoke unidentified variables such as an active metabolite or a drug-drug interaction.
- Pediatric safety and PK studies are now needed.

References:

1. Smit MR, et al. Efficacy and Safety of High-Dose Ivermectin for Reducing Malaria Transmission (IVERMAL): Protocol for a Double-Blind, Randomized, Placebo-Controlled, Dose-Finding Trial in Western Kenya. JMIR Res Protoc 2016;5:e213.
2. Smit MR, Ochomo E, Aljayoussi G, et al. Safety and mosquitocidal efficacy of high-dose ivermectin when co-administered with dihydroartemisinin-piperazine in Kenyan adults with uncomplicated malaria (IVERMAL): a randomised, double-blind, placebo-controlled trial. The Lancet Infectious Diseases. Published online: March 27th, 2018.