Reviewer's report

Title: Genetic polymorphisms in MDR1, CYP3A4 and CYP3A5 genes and its impact on Ivermectin Therapy in Onchocerciasis

Version: 1 Date: 17 July 2009

Reviewer: Dave Bartley

Reviewer's report:

Please find attached the referees report generated by both myself and Dr P. Skuce. The points raised are agreed by both persons.

The manuscript entitled “Genetic polymorphisms in MDR1, CYP3A4 and CYP3A5 genes and its impact on ivermectin therapy in Onchocerciasis” presents some interesting findings about the variation in host response to the treatment with ivermectin and provides information on the non specific mechanism used by humans in the clearance of xenobiotics, in particular ivermectin, from the body. Unfortunately the overall message and overall findings of the manuscript is unclear and is frequently lost in the complexity and weight of material. Also throughout the manuscript, including the title, the authors lapse into the use jargon which at first look is unclear to those not directly in the field.

Reviewer's report

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Please number your comments and divide them into

- Major Compulsory Revisions

The author must respond to these before a decision on publication can be reached. For example, additional necessary experiments or controls, statistical mistakes, errors in interpretation.

- Objectives of the trials and work need to be clearly defined, explained and discussed.

- The paper would benefit from pharmacokinetic data from the various groups to correlate with any impact of genotype on ivermectin therapy.

- Minor Essential Revisions
The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

• The title needs to be clear that the genetic polymorphisms occur in the host and not the parasite. Other minor points “their” impact rather than “its” impact, no capital letters require for “ivermectin” or “therapy” and “against” rather than “in” onchocerciasis.

• Throughout the document abbreviations such as MDR1, CYP3A4 and CYP3A4*1B are used without ever being defined or explained. It is useful for a global audience to describe these in more detail for example the cytochrome P-450 monooxygenase 3A4 (CYP3A4).

• The abstract is full of jargon and a huge amount of specific detail, it would help the flow of the abstract if it provided information on the general theme and findings.

• Within the background section a large section is dedicated to the description of P-gps which forms part of the multi drug resistance family but it may be worth defining the relationship between P-gp and MDR.

• More information may be required for the cytochrome P450 section.

• More discussion on what human mechanisms may be involved in variability in ivermectin treatment efficacy if it is not ABC or CYP is required. If it is believed to be a parasite driven phenomenon then it may be useful to include more details relating to this.

• It may be useful to suggest where the research may go in the future.

• The paper would benefit from the addition of clearly defined aims within the background section of the manuscript and finish in the discussion with whether they were achieved.

• Diagrams and/or graphics would help clarify the results section.

- Discretionary Revisions

These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential.

Through out there are a large number of grammatical errors. A large number are listed below but the manuscript would benefit greatly by being thoroughly proof read.

• Page 2 line 3 Remove “;” after Ghana;.
• Page 2 line 4 Insert “host” prior to MDR1.
• Page 2 line 6 Insert “the” prior to “Ghanaian”.
• Page 2 line 9 Replace “this data was” with “these data were”.
• Page 2 line 10 and 12 Could consider using “RES” as abbreviation for responder and (POP) for general population throughout manuscript.
• Page 2 line 12 Insert “The” prior to “MDR1 (3435T)”.
• Page 2 line 13 “Haplotypes CGC were” rather than “Haplotypes CGC was”.
• Page 2 line 14 Insert “respectively” after 21%.
• Page 2 line 14 “twice as likely” rather than “twice more likely”.
• Page 2 line 18 Need to expand on the “Haplotype (*1/*1/*3/*1) was determined to be significantly different between responders and SORs” sentence to make the meaning better understood in a stand alone abstract.
• Page 2 line 20 Insert “The” prior to “pharmacogenetic”.
• Page 2 line 21 Replace “disease” with “patients”.
• Page 2 line 22 and throughout the manuscript it may be useful to reinforce the fact that the responses are being measured in humans.
• Page 2 line 23 Replace “use” with “treatment”.
• Page 3 line 3 Remove “s” from end of “transporters”.
• Page 3 line 6 “d” missing from dependent efflux.
• Page 3 line 6 Insert “the” prior to “inside of cells”.
• Page 3 line 12 Insert “human” prior to “MDR1 gene”.
• Page 3 lines 15-16 The sentence “The 3435C>T polymorphism which does not result in a change in amino acid sequence” may read better as “The silent/synonymous polymorphism has…..”.
• Page 3 line 21 insert “are ambiguous with some…” after “ethnically different populations”.
• Page 3 line 24 Remove “a” from before “a linkage disequilibrium”.
• Page 4 line 1 Replace “are also substrates for…” with “can also be substrates for…”
• Page 4 line 7 Replace “adults” with “adult humans”.
• Page 4 line 11 should read “identified in the CYP3A4 gene”.
• Page 4 line 20 should read “reported in the CYP3A5 gene,.”
• Page 4 line 25 “reduced” rather than “diminished” levels.
• Page 4 line 26 Insert “the” prior to “CYP3A5”.
• Page 5 line 3 “heterozygous” rather than “heterozygote”.
• Page 5 line 7 “anthelmintic” rather than “antihelmintic”.
• Page 5 line 10 Onchocerciasis doesn’t need to be italicised.
• Page 5 line 12 Remove “the” from “the severity of lesion…”
• Page 5 line 12 Replace “caused by the disease” with “caused by the parasite”
• Page 5 line 13 Replace “problems” with “impact”.
• Page 5 line 15 Remove “onchocerciasis” from “onchocerciasis disease…”.
• Page 5 line 18 “genetic polymorphisms in the MDR1…” rather than “genetic polymorphisms of the MDR1 “.
• Page 5 line 18 Remove “we investigated” from “In this study we investigated the potential”. 
• Page 5 line 24 the sentence would read more fluently as “Ghanaian population with a known IVM treatment history was investigated” rather than “Ghanaian population and in IVM characterised patients.”.
• Page 5 paragraph 2 This section would be better at the start of the section. 
• Page 7 line 24 “SORs were significant (p<0.01, FET)” should read “SORs were statistically significant (p<0.01, FET)”
• Page 7 line 18 Remove second “allele” from “variant allele was the only allele significantly different allele among…”.
• Page 8 line 15 The sentence “compared with data from normal Ghanaian population” would be more accurate if it read “compared with data from a representative sample of the normal Ghanaian population.
• Page 8 line 26 the sentence “(32). It was detected in only 11%……” could read “(32), it was detected in only 11%”.
• Page 8 line 27 Remove “d” from “included“.
• Page 8 line 27 change “1236C to T” should read “1236C the T”.
• Page 9 line 16 Replace “This data is” with “These data are”.
• Page 9 line 26 Insert “the” before “CYP3A5*6 variant”.
• Page 9 paragraph 2 and page 10 paragraphs 3 and 4 would be better suited for the background section of the manuscript.

• Page 10 line 10 Remove the from “being of the people living in the onchocerciasis affected areas”.

• Page 10 line 20 “resistance to IVM” rather than “resistance of IVM”

• Page 10 line 26 Insert “the” into the sentence “as well as the general population”.

• Page 11 line 6 “The SORs were twice more likely” “The SORs were twice as likely”

• Page 13 line 12 “MgCl2” rather than “MgCL2”

• Page 13 line 17 “patterns visualised using a U.V” rather than “patterns visualised with U.V”

• Page 15 table 1 needs a key for (F) and (R).

General points –

• Table legends do not inform the reader about the data held within the tables. A couple of extra lines of description would improve the readers understanding of the data.

• The title states that the manuscript will detail the impact of MDR etc on ivermectin therapy against onchocerciasis, though the disease and its treatment appears to be secondary within the manuscript.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests