Author's response to reviews

Title: Genetic polymorphisms in MDR1, CYP3A4 and CYP3A5 genes in a Ghanaian population: a plausible explanation for altered metabolism of ivermectin in humans?

Authors:

William Kudzi (wkudzi@yahoo.com)  
Alexander N.O Dodoo (alexooo@yahoo.com)  
Jeremy J Mills (Jeremy.mills@port.ac.uk)

Version: 3 Date: 16 June 2010

Author's response to reviews:

Dear Editor,

I would like to submit revisions to the manuscript MS: 2123107729263686 titled “Genetic polymorphisms in MDR1, CYP3A4 and CYP3A5 genes in a Ghanaian population and their relevance on response to ivermectin treatment”. Specific response to each reviewer’s comment is shown below;

Reviewer 1 “P-glycoprotein (P-gp), a product of the multidrug resistance”
Response: The sentence has been edited to read “P-glycoprotein (P-gp), a product of multidrug resistance (MDR1) gene”

Reviewer 1: “compared the data with that of those from ivermectin treated patients.”
Response: This has been edited to read “compared the data with that of ivermectin-treated patients with a view to exploring the relationship between suboptimal response to ivermectin and MDR1 and CYP3A allelic frequencies”

Reviewer 1: “CYP3A5*6 alleles were detected at varied varying”
Response: Error corrected

Reviewer 1: “responders in a small size group of 42 patients”
Response: The sentence has been edited to read “In 42 patients treated with ivermectin, difference in MDR1 variant allele frequency was observed between suboptimal responders and responders”

Reviewer 1: “P-glycoprotein (P-gp), a product of the multidrug resistance”
Response: Sentence edited as “P-glycoprotein (P-gp), a product of multidrug resistance gene (MDR1)”

Reviewer 1: “and prevents the accumulation of drugs”
Response: Error corrected
Reviewer 1: “an also be substrates for Ccytochrome P450”
Response: Error corrected

Reviewer 1: “be acting synergistically as a barrier for its oral drug absorption [24].”
Response: Sentence now reads “probably act synergistically to reduce its oral absorption in susceptible individuals [24]”

Reviewer 1: “high microfilariae loads after many years of treatment [26].”
Response: Sentence now reads “high microfilaria load in these patients despite many years of treatment [26].”

Reviewer 1: “To examine the influence of genetic variations within MDR1, CYP3A4 and CYP3A5 genes on response of patients”
Response: “To explore the influence of genetic variations within MDR1, CYP3A4 and CYP3A5 on response to ivermectin treatment by examining genotype frequencies in responders and suboptimal responders.”

Reviewer 1: “Aliquots of the blood sample (500 µL) was were spotted and preserved”
Response: Error corrected

Reviewer 1: “A P-value # 5 was considered significant.” Was this 5%?
Response: Error corrected

Reviewer 1: “Haplotypes 1 (*1B/*1/*1/*1) and 2 (*1/*1/*1/*1) may be associated with normal expression of CYP3A proteins while haplotypes 3, 4 and 5 may be linked to the reduced CYP3A protein expression. This may be due to the presence of CYP3A5*3 variant allele.” These sentences need further explanation.
Response: “Haplotypes 1 (*1B/*1/*1/*1) and 2 (*1/*1/*1/*1) may be associated with normal expression of CYP3A proteins while haplotypes 3, 4 and 5 may be linked to the reduced CYP3A protein expression. The reduced expression of haplotypes 3, 4 and 5 may be associated with reduced CYP3A4 activity.”

Reviewer 1: The authors state “Although the host and the parasite do have MDR1 and CYP3A genes, we anticipated that genetic polymorphisms of MDR1 and CYP3A genes within the host may provide an explanation for the suboptimal response phenotype observed by Awadzi and colleagues in the use of IVM for the control of onchocerciasis [26, 27].” Do they believe that the parasites play a role in the of apparent drug inefficacy? This should be addressed
Response: Yes, we do believe that the parasites may play a role in the apparent drug inefficacy. However, there is also the need to explore the possibility of the host genes contributing to the apparent drug inefficacy.
Reviewer 1: “CYP3A5 allele frequency distribution profiles for”
Response: Sentence now reads “CYP3A5 allele frequency distribution in”

Reviewer 1: “variant was the only allele significantly different allele among”
Response: Error corrected

Reviewer 1: “Although haplotype data for the MDR1 polymorphism did not demonstrate a statistically significant difference between responders and suboptimal responders (p = 0.127, FET), individuals with (C-G-T) haplotype were more likely to be a suboptimal responders.
Response: Error corrected

Reviewer 1: “or suboptimal responders respectively”
Response: Error corrected

Reviewer 1: “However a significant difference was observed between”
Response: Error corrected

Reviewer 1: “This These data is are also similar to the incidence levels”
Response: Error corrected

Reviewer 1: “Whilst some studies have indicated the possibility of the parasite genes being involved in the suboptimal response”. Needs a reference also.
Response: Error corrected

Reviewer 1: “analysed in the Ghanaian population (POP), responders (RES) and suboptimal responder (SOR) subjects”
Response: Sentence now reads “analysed in the random sample from the normal population as well as in responders and suboptimal responders”

Reviewer 1: “in a representative Ghanaian population were comparable”
Response: Error corrected

Reviewer 1: Table 2
Needs Ghanaian population (POP), responders (RES) and suboptimal responder (SOR)
Response: Genotype data on random Ghanaian population is shown in Table 1 while that of responders and suboptimal responder in Table 2

Reviewer 1: Figure 1B
Why do the figures not add up to 100%?
Response: Few SNPs were excluded from the final statistical analysis because their genotype results were unclear leading to the sum total of the haplotype being less than 100%

Reviewer 2: Title – please replace on: …“their relevance to response to
invermectin
treatment

Response: Title has been edited to read “Genetic polymorphisms in MDR1, CYP3A4 and CYP3A5 genes in a Ghanaian population: a plausible explanation for altered metabolism of ivermectin in humans?”

Reviewer 2: p.6: SNPs should be written: c.1236C>T, c.2677G>A, etc
Response: Corrected

Reviewer 2: “p.6: Do you mean a P value </= 0.05? was significant?”
Response: Error corrected

Reviewer 2: “Figures 1A and 1B: can you mark significance levels on the graphs so that one can see what is statistically significant without reading the legend?”
Response: Significant difference between responders and suboptimal responders for haplotype (CGT) and haplotype 4 (*1/*1/*3/*1) has been marked on the graph