Comments regarding use of rifabutin for *Helicobacter pylori* eradication

David Y. Graham

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Correspondence to:
David Y. Graham
Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, RM 3C-190 (111D), 2002 Holcombe Boulevard, Houston, TX 77030, USA.
dgraham@bcm.edu

Dear Editor:

I read the recent progress report on first line *Helicobacter pylori* therapy by Liu and colleagues.[1] Overall, in my opinion, the article is first rate, well thought out, well referenced, and complete. However, I do have a few comments regarding their analysis of our recent rifabutin triple therapy (Talicia®) studies.[2,3] The antibiotics associated with a low prevalence of resistance to *H pylori* are amoxicillin, tetracycline, furazolidone, and rifabutin making these the best candidates for empiric therapy with the expectation of acceptable to high cure rates. As rifabutin triple therapy is experiencing increased interest and use, I would like to clarify and extend several of their points. For example, they pointed out that our recent trial did not include Asian participants. Importantly, the approved product label for this triple therapy does not restrict use in Asian patients. Persons of Asian descent were excluded from the Talicia clinical studies because of their higher prevalence of poor CYP2C19 metabolizers and the potential for study bias considering the small sample size of the study. Non-Asian participants were evaluated based on the CYP2C19 genotype and there were no concerns with respect to safety or efficacy in poor metabolizing participants. Rifabutin has been used successfully for *H pylori* in Asians (Japan, Korea, and China),[4] and their exclusion in the trial should not be considered a reason not to use it in Asians. A second issue regarding rifabutin was that serious adverse reactions may occur, such as myelosuppression. The key to limiting side effects with rifabutin, as with many antibiotics, is not prescribing high doses of unnecessary antibiotics. The experience with rifabutin for other diseases has confirmed that serious adverse events are most associated with higher doses and for longer durations than used for treatment of *H pylori* (e.g. 50 mg Q8 H; 150 mg/daily for 14 days with Talicia). While neutropenia or myelosuppression have been associated with rifabutin use, these side effects have not been seen with *H pylori* treatment trials that use lower doses and shorter durations. The key factors related to rifabutin-associated myelosuppression include higher doses of rifabutin (~600 mg/day) and a prolonged duration of therapy (i.e. several months).[5]

Finally, they noted that with increased usage, the global resistance to rifabutin may be increased. *H pylori* resistance to rifabutin very rarely occurs *in vitro* at an extremely low rate of ~1 in 10^9, and only after multiple serial passages.[6] Resistance among *H pylori* is unlikely, as rifabutin is coupled with the resistance mutation rate of amoxicillin (~1 in 10^5) leading to the likelihood of 1 in 10^{45} for developing resistance to rifabutin. In a recent review evaluating the onset of resistance, no correlation was reported between short-term use of rifabutin (e.g. for *H pylori* treatment) and the emergence of rifabutin resistant TB.[4] Rifabutin is indicated for *Mycobacterium avian intracellulare* (MAI), which is an atypical bacterium and a rare disease associated with HIV-infected and immunocompromised hosts. Importantly, rifabutin is not a first line treatment for *Mycobacterium tuberculosis* (TB), but rather, is reserved for patients who cannot tolerate rifampicin or those with concerns of potential drug–drug interactions.[7] Furthermore, despite prolonged use of rifabutin for the treatment of TB, there have been negligible increases in TB resistance rates to rifabutin.[8] As with treating any infection, it is important to follow the principles of antibiotic stewardship by using the minimal number of effective antibiotics at the lowest doses needed.

Again, I congratulate the authors on an outstanding update.

Conflict of interest statement

The author declared the following potential conflicts of interest with respect to the research,

authorship, and/or publication of this article: Dr Graham is a consultant for RedHill Biopharma and Phathom Pharmaceuticals regarding novel *H pylori* therapies and has received research support for culture of *H pylori*. He is also a consultant for DiaSorin regarding *H pylori* diagnostics and with Otsuka Japan regarding novel breath tests. He has ongoing collaborative research projects with American Molecular regarding molecular diagnostics for *H pylori*. He was the PI of an international study of the use of antimycobacterial therapy for Crohn's disease.

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ORCID iD

David Y. Graham https://orcid.org/0000-0002-6908-8317

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