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Efficient Identification and Evaluation of Effective *Helicobacter pylori* Therapies

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Introduction

Helicobacter pylori is an important human pathogen that causes gastroduodenal inflammation resulting in diseases such as duodenal ulcer disease, gastric ulcer disease, iron and/or vitamin B12 deficiency, gastric adenocarcinoma and primary B-cell gastric lymphoma [1–5]. There has been a decline in the effectiveness of recommended therapies resulting in unacceptably low cure rates (ie, below 80%) [6–8]. Much of the decline in effectiveness is attributable to increasing antibiotic resistance.

The problems

Although recent trials primarily done in Italy have identified drug combinations with improved results for empirically administered therapy [9], aannually hundreds if not thousands of patients fail empirical administered *H. pylori* eradication therapy. Physicians have generally remained unaware that the therapy they prescribe has failed in part because post eradication testing is not routinely practiced and is not always recommended by current guidelines [8]. With few exception, (eg, Sweden) worldwide the success rate with legacy triple therapy consisting of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin has fallen to below 80% [6–8, 10]. Despite its increasing ineffectiveness, traditional (ie, legacy) triple therapies are still widely identified as “approved” or “recommended” regimens. In addition, hundreds of patients enter clinical trials designed to either test or compare combination therapies (eg, 7 vs. 10 days) that have either not been identified in pilot studies to be suitable candidates for further evaluation, or studies in which new combinations of proven effectiveness are compared to triple therapies despite the fact that clarithromycin resistance is high in that population leading to poor cure rates. In many instances patients are not made aware that the randomization involves treatments in which cure rates are either known or suspected to be markedly different.

Possible solutions

Solutions possibly include 1) Physician education. Practicing physicians generally have no inkling of the rate of resistance in their population or region such that recommendations based on resistance rates (ie, don’t use if resistance is greater than x%) have little meaning to them. Ideally, clinicians should be provided with direct statements regarding the effectiveness of different therapies in their region (eg, triple therapy is no longer an acceptable choice as empiric therapy and all patients should be considered as having clarithromycin resistant infections unless proven otherwise based on high local success rates) [10]. Unfortunately, this ideal situation, which is generally a standard of care of other infectious diseases, is unlikely to be

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achieved with *H. pylori*, at least in the near future. The other option that is available now is post treatment noninvasive testing (eg, urea breath test or stool antigen testing) and this should be strongly encouraged as it will alert physicians to common presence of unsuccessful results in their patient population; 2) Identify new regimens using a results-based approach designed to be efficient and to minimize patient risks and drug exposure [6]; and 3) Better educate investigators and institutional review bodies regarding the attributes of informed consent. Here, we will focus on items 2 and 3.

Results-based evaluation of new and old therapies

We propose that new or improved regimens be identified and/or evaluated using a standardized RESULTS-BASED approach. This approach begins with pilot studies designed to identify and refine potential therapies that are equal to or better than the best currently available ones. Candidate therapies are identified through experiments whose outcomes are categorized as "go" or "no go" defined on meeting or exceeding predefined threshold cure rates (eg, >90% per protocol).

Initial study parameters (ie, dose, dosing interval, and duration etc) are chosen based on those most likely to succeed (ie, maximum) and thus the ensuring that failure to achieve the defined outcome would signify no further need to expose additional patients to that regimen. Doses and dosing intervals would be based on the pharmodynamics of the drugs used and for practical purposes would probably be limited to dosing no more often than every 6 hours with the duration of 14 days [11–13].

Studies would be powered so as limit patient risk as well as exposure to the drugs using designs such as Simon's optimal two-stage design, Ensign et al.'s three-stage design with restriction, and Chen's three-stage design without restriction [14–18]. An example of a for a pilot study to identify a TENTATIVELY EFFECTIVE therapy might define success as a PER PROTOCOL cure rate of 90% or greater and rates of 80% or less would be considered as unacceptable. In this example, up to 50 completed patients would be the maximum to be entered but the actual enrollment would be based on achieving a lower 90% confidence interval of 80% or greater. Initially the plan would be to evaluate 30 patients and the study would stop if a cure rate of 97% [97% (28 of 30) 90% CI: 80–99%] was achieved or if 6 failures occurred (see below). If the stopping points were not met, 40 patients would be entered. The stopping point would be a 92% cure rate [37 of 40, 90% CI: 82–98%] or 6 failures. If the stopping points were not achieved, 50 patients would be entered success would be defined as a 92% [45 of 50, 95% CI: 80–96%]. If 90% or greater success were not achieved with 50 completed patients, failure would be declared. Identification of a TENTATIVELY EFFECTIVE therapy (eg, 98% cure rate) would then prompt additional and larger studies to confirm the results and could be done as a larger study or as part of a randomized controlled trial (RCT) designed to compare the new combination with a previously identified high success rate therapy or probably most often with a simplification of the new regimen. Such RTCs would be ideal for studying issues such as different durations (eg, 10 days instead of 14 days) but the RCTs would be held to the same standard (eg, 90% cure rates or greater) used to separate acceptable from unacceptable combinations. In most instances one might envision a series of pilot studies designed to explore dose, dosing interval, and duration for a TENTATIVELY EFFECTIVE regimen. This would then be followed by a RCT to identify the best in terms of cost, side effectiveness, etc.

Table 1 shows an example of current often arbitrary choices for comparison therapy. Here a new therapy is compared to legacy triple therapy. While it proved to be significantly better (p = 03), when viewed alone it had a relative low cure rate (ie, 82%) that does not allow one to make a "go" of "no go" decision regarding further development. Thus, at the end of the day, 300 patients would had been studied with a relatively poor result and one would not know

whether the regimen might be improved by increasing the dose, duration, frequency of administration etc. The table also shows two examples of the series of pilot studies approach based on starting with the "best shot" with high doses and long durations. In the first example, the initial pilot study identified a tentative effective therapy and the investigator could then attempt to simplify it while maintaining efficacy. The 4th pilot study identified that b.i.d. was not an effective approach. One could then make a decision about whether to continue to explore other simplifications such as t.i.d, or do a RCT to compare the preferred choices such as series B with series C. Importantly only 200 patients have been used and the total number of treatment failures was low. The third example, shows a high dose long duration new regimen whose upper 95% CI was below 90%. It would likely be abandoned as the best shot in terms of dose and duration had been taken.

An actual example of the arbitrary approach (in terms of dose, durations, and criteria of success) are the studies in which levofloxacin was substituted for clarithromycin in triple therapy. These were done with different doses and durations and meta-analyses showed that the cure rate was 68% (95% CI 62–74%) with 7 days increasing to 87% (95% CI 82–92%) with 10 days [19]. Clearly many patients received ineffective therapy and neither the 7 nor 10 day trials told the investigators whether to abandon the therapy, increase the doses, durations or both. This approach also likely resulted in some patients unnecessarily developing fluoroquinolone resistant *H. pylori*. Another common approach has been start with a RCT that tests different parameters such as dose or duration which is subject to all the problems of arbitrarily choosing treatment parameters and almost always puts some patients at a high and unnecessary risk of receiving an ineffective regimen.

Comparisons of highly effective with less effective therapies

Studies which compare new highly effective therapies with triple therapies already proven to provide low cure rates in the same population with the goal of showing statistically that the new therapy is superior should no longer be done. *H. pylori* is fundamentally an infectious disease and there is no compelling reason to treat it any differently from other infectious diseases [20]. Typically, increasing failures in a population is related to the increasing prevalence of resistant organisms. As antibiotic resistance erodes the effectiveness of current antibiotics in other infections (eg, urinary tract infection, pneumonia, or tuberculosis) few would consider it necessary or prudent to compare a new regimen proven to be effective in pilot studies with the previous best choice whose effectiveness was now known to be impaired becaue of resistance and yet this is commonly done for *H. pylori*. We propose that gastroenterologists reconsider our focus on "better than" some other therapy and instead focus on results based outcomes as is typical for other infectious diseases.

If one is required to compare a new highly successful therapy with a legacy therapy whose success rate has declined (eg, required by a regulatory body for approval) one must deal with potential ethical issues especially those related to confirming that patients received full and appropriate disclosures regarding what the investigators knew about the differences between regimens as well as whether entering the trial would possibly would decrease the chance of subsequent successful therapy (ie, by development of resistance). Such disclosures relate to the fact that informed consent must include all relevant data that might affect the patient's decision to enter or to continue in a trial and the fact that comparator was less effective (eg, a twice a day standard dose dual therapy) or failure often resulted in development of resistance would need to be fully disclosed to the institutional review board (IRB) and to the patients [21]. One can not be simply describe the older regimen as "approved" or "recommended" even if both statements were true. In addition, any new information discovered during the study must be provided to the IRB and the consents documents revised for both ongoing as well as new patients irrespective of their potential effects on recruitment or retention [21]. Clearly patient

rights always trump all other considerations; physicians can not withhold information before or at any time during the trial [21].

With few exceptions, results are expected to be provided in terms both of overall cure rates and separately for susceptible and resistant strains. Failure of clarithromycin-containing triple therapy is most often due to the presence of clarithromycin resistance such that a new therapies superiority is generally predictably due to the fact that it provides higher cure rates with clarithromycin resistant *H. pylori* [22, 23]. If one wishes to study the effect of resistance to one component of a therapy, patients with known resistance should be studied directly rather than in the context of treating populations with known high rates of resistance only serves confirm that the inferior therapy was a poor choice in areas with a high prevalence of resistance to one or more components.

What to do now

traditional triple therapy should not be used empirically unless it has been proven to be effective based on local susceptibility or outcome data. Physicians have generally not been aware that the effectiveness of triple therapy had waned in part because the success or failure was rarely confirmed routinely. Post treatment testing provides an early warning of increasing antibiotic resistance should become routine until therapies that reliably cure 95% of patients are available. Alternative empiric approaches include sequential therapy which as originally described is the sequential administration of a dual therapy (a PPI plus amoxicillin for 5 days) followed by a PPI plus clarithromycin and tinidazole for 5 days and it is a poor choice in regions where both clarithromycin and metronidazole/tinidazole resistance are common. Intention to treat cure rates have typically been <95% (or Grade B based on the scale of A = >95%, B = 90–94%, C = 85 to 89%, D = 81–84%, and F = ≥80%) [6] and can likely be further improved by changes in dose, duration or administration (eg, by continuing the amoxicillin into the triple therapy arm) [24].

Other alternatives include 1) giving all four drugs (PPI, amoxicillin, clarithromycin, metronidazole/tinidazole) concomitantly (concomitant therapy) [24]. Concomitant therapy is less complicated than sequential therapy (ie, simply add two metronidazole/tinidazole tablets to traditional twice a day triple therapy) but has the same concerns in terms of effectiveness in the presence dual resistance. 2) Bismuth-containing quadruple therapy (a PPI, bismuth, tetracycline, metronidazole/tinidazole). Importantly, with quadruple therapy, the dose of metronidazole (1500 mg) and duration (14 days) are important in areas where metronidazole resistance is more than trivial [10, 25, 26] .3). A triple therapy substituting a fluoroquinolone (eg, levofloxacin) for clarithromycin. However, as mentioned above duration is important and the rapid increase in quinolone resistance has already markedly undermined the effectiveness of this combination such that it is probably a poor choice for empiric therapy [10]. 4) High dose PPI – amoxicillin dual therapy [10]. This approach is being reconsidered and should be watched closely as it may offer either a good initial therapy or it can be used as a base for new triple or quadruple therapies [24].

Conclusions

Future studies of *H. pylori* treatments would be more efficient if investigators and IRBs recognized that comparisons against known ineffective regimes are generally unnecessary, sometimes inappropriate, and always require documentation of appropriate and extensive disclosures to the patients. Comparisons should largely be limited to identifying the better of two or more highly successful regimens. For example, 10 RCTs showed that sequential therapy reliably yielded relatively high cure rates (grade A or B). One can ask what was actually gained by inclusion of triple therapy which repeatedly confirmed the results expected in that region

(ie, legacy triple therapy was no longer an effective choice in that population)? [9] In those studies, triple therapy reliably produced a Grade F results which would also be considered as unacceptable even using the low criteria proposed by the Maastricht consensus conference more than a decade ago. Our proposal is to change the focus from showing that therapy A is superior to therapy B to show that therapy A is reliably effective. The "A vs. B" approach has generally resulted in at least one of the therapies having unacceptably low cure rates and such studies should be very difficult to do if one provides appropriate informed consent. It also will avoid the confusing declaration of equivalence when both therapies actually produce results that are equally ineffective [27].

We propose instead that new therapies be scored using a results-based approach using predefined criteria to separate acceptable from unacceptable results. RTCs are only utilized to compare good or excellent therapies such as to simplify a regimen and deal with issues such as cost and side effects with effectiveness being maintained. If effective therapy is available, the is little if any justification for continuing to use or comparison them with ineffective regimens.

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References

1. Graham, DY.; Sung, JY. Helicobacter pylori. In: Feldman, M.; Friedman, LS.; Brandt, LJ., editors. Sleisenger & Fordtran's Gastrointestinal and liver disease. Pathophysiology, diagnosis, management. 7. Philadelphia: WB Saunders Co; 2006. p. 1049-1066.
2. Cardenas VM, Mulla ZD, Ortiz M, Graham DY. Iron deficiency and *Helicobacter pylori* infection in the United States. Am J Epidemiol 2006;163:127–134. [PubMed: 16306309]
3. Dholakia KR, Dharmarajan TS, Yadav D, Oiseth S, Norkus EP, Pitchumoni CS. Vitamin B12 deficiency and gastric histopathology in older patients. World J Gastroenterol 2005;11:7078–7083. [PubMed: 16437651]
4. DuBois S, Kearney DJ. Iron-deficiency anemia and *Helicobacter pylori* infection: a review of the evidence. Am J Gastroenterol 2005;100:453–459. [PubMed: 15667507]
5. Hershko C, Lahad A, Kereth D. Gastropathic sideropenia. Best Pract Res Clin Haematol 2005;18:363–380. [PubMed: 15737896]
6. Graham DY, Lu H, Yamaoka Y. A report card to grade *Helicobacter pylori* therapy. Helicobacter 2007;12:275–278. [PubMed: 17669098]
7. Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. Aliment Pharmacol Ther 2007;26:343–357. [PubMed: 17635369]
8. Chey WD, Wong BC. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. Am J Gastroenterol 2007;102:1808–1825. [PubMed: 17608775]

9. Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. Ann Intern Med 2008;148:923–931. [PubMed: 18490667]
10. Graham DY, Shiotani A. New concepts of resistance in the treatment of *Helicobacter pylori* infections. Nat Clin Pract Gastroenterol Hepatol 2008;5:331.
11. Furuta T, Shirai N, Kodaira M, Sugimoto M, Nogaki A, Kuriyama S, Iwaizumi M, Yamade M, Terakawa I, Ohashi K, Ishizaki T, Hishida A. Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of H. pylori. Clin Pharmacol Ther 2007;81:521–528. [PubMed: 17215846]
12. Treiber G, Malfertheiner P, Klotz U. Treatment and dosing of *Helicobacter pylori* infection: when pharmacology meets clinic. Expert Opin Pharmacother 2007;8:329–350. [PubMed: 17266468]
13. Klotz U. Pharmacokinetic considerations in the eradication of Helicobacter pylori. Clin Pharmacokinet 2000;38:243–270. [PubMed: 10749519]
14. Chow, S-C.; Liu, J. Design and analysis of clinical trials: Concepts and methodologies. Hoboken: John Wiley & Sons, Inc; 2004.
15. Fleming TR. One-sample multiple testing procedure for phase II clinical trials. Biometrics 1982;38:143–151. [PubMed: 7082756]
16. Chen TT. Optimal three-stage designs for phase II cancer clinical trials. Stat Med 1997;16:2701–2711. [PubMed: 9421870]
17. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1–10. [PubMed: 2702835]
18. Ensign LG, Gehan EA, Kamen DS, Thall PF. An optimal three-stage design for phase II clinical trials. Stat Med 1994;13:1727–1736. [PubMed: 7997706]
19. Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent *Helicobacter pylori* infection: a meta-analysis. Am J Gastroenterol 2006;101:488–496. [PubMed: 16542284]
20. Graham, D. Conceptual evolution from gastritis, to peptic ulcer and gastritis, to ‘cystitisof the stomach’ and finally, to a smallpox equivalent. In: Notthfield, TC.; Mendall, M.; Coggin, PM., editors. Helicobacter pylori infection. Pathophysiology, Epidemiology, and Management. Dordrecht: Kluwer Academic Publishers; 1993. p. 170-174.
21. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES PART 50--PROTECTION OF HUMAN SUBJECTS (21 CFR Part 50). http://www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html.extra1. need to add reference. AAA 1996..
22. Moayyedi P. Sequential regimens for *Helicobacter pylori* eradication. Lancet 2007;370:1010–1012. [PubMed: 17889226]
23. Zullo A, De FV, Hassan C, Morini S, Vaira D. The sequential therapy regimen for *Helicobacter pylori* eradication: a pooled-data analysis. Gut 2007;56:1353–1357. [PubMed: 17566020]
24. Graham DY, Lu H, Yamaoka Y. Therapy for *Helicobacter pylori* infection can be improved: sequential therapy and beyond. Drugs 2008;68:725–736. [PubMed: 18416582]
25. Bardhan K, Bayerdorffer E, Veldhuyzen van Zanten SJ, Lind T, Megraud F, Delchier JC, Hellblom M, Stubberod A, Burman CF, Gromark P, Zeijlon L. The HOMER Study: the effect of increasing the dose of metronidazole when given with omeprazole and amoxicillin to cure *Helicobacter pylori* infection. Helicobacter 2000;5:196–201. [PubMed: 11179983]
26. de Boer WA. Bismuth triple therapy: still a very important drug regimen for curing *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 1999;11:697–700. [PubMed: 10445785]
27. Graham DY, Yamaoka Y. One- or two-week triple therapy for *Helicobacter pylori*: questions of efficacy and inclusion of a dual therapy treatment arm. Gut 2007;56:1021–1023. [PubMed: 17566035]

Table 1

Examples of current and series of pilot studies to identify a tentatively effective new therapy

The "arbitrary" approach of identifying a new therapy

Arbitrary approach: RCT comparison of 300 patients

7 day PPI, clarithromycin 500 mg, amoxicillin 1 gram all bid. (70% 95% CI = 62–77)

7 days: PPI, Drug A 500 mg, Drug B, 500 mg, Bismuth 2 tabs (82% 95% CI = 73–83)

Use of a series of pilot studies to choose therapies for randomized controlled trials.

A. Initial therapy: long duration – high dose (all with a PPI b.i.d.) with 50 patients per group

Drug A 500 mg, Drug B 500 mg, Bismuth 2 tabs q.i.d. for 14 days (96% 95% CI = 86–99)

B. First simplification 10 days instead of 14 days

Drug A 500 mg, Drug B 500 mg, Bismuth 2 tabs q.i.d. for 10 days (94% 95% CI = 83–98)

C. Second simplification 7 days instead of 10 day

Drug A 500 mg, Drug B 500 mg, Bismuth 2 tabs q.i.d. for 7 days (94% 95% CI = 83–98)

D. Third simplification try bid instead of q.i.d.

Drug A 500 mg, Drug B 500 mg, Bismuth 2 tabs b.i.d. for 14 days (80% 95% CI = 66–89)

Pilot study where the decision to stop development would be made after the first study

A. Initial therapy: long duration – high dose (all with a PPI b.i.d.) with 50 patients

Drug C 500 mg, Drug D 500 mg, Bismuth 2 tabs q.i.d. for 14 days (78% 95% CI = 64–88)