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Which Therapy for *Helicobacter pylori* Infection?

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Introduction

Clarithromycin-containing triple, sequential, concomitant, and hybrid therapies, bismuth-containing 4 drug therapies, and now a levofloxacin-containing concomitant therapy - what is the clinician to do? This issue of *Gastroenterology* contains a non-inferiority comparison of two newer approaches to 4 drug fluoroquinolone-containing therapies and report good to excellent results¹. The trial is a model of how such studies should be done. Bravo!

H. pylori is an infectious disease and clinicians should expect, and in fact, demand that recommended treatments provide cure rates of at least 90%, preferably 95%. The current report provides essentially all the details one might wish including those regarding patient selection, follow-up, therapy for treatment failures, susceptibility testing, outcome with different patterns of resistance, etc (i.e., the data clinicians need to use in their practices).

There are few mysteries with regard to treatment success with *H. pylori* therapy: one only need know the success rates with susceptible and resistant strains². The calculations are slightly more complicated with multiple antibiotic containing regimens because as the number of antibiotics increases, the combinations of antibiotics still remaining effective when resistance is present to one or more also increases (see below). Where a study is done (e.g., Italy or the U.S.) is not important. What is important is the local pattern of resistance (i.e., if their bugs are like your bugs one should expect the same results). If such data were available for each new therapy, acceptance or rejection for local use could be based on rational grounds.

Until recently, most comparative trials and meta-analyses of anti-*H. pylori* therapies consisted of comparisons of regimens with unacceptably low success (e.g., bismuth 60.9% vs. clari triple 46.5%)³ or a good regimen vs. one with unacceptable results (i.e., a good vs. a bad) (e.g., sequential 91% vs. triple 75.5%)⁴. Randomization to regimens known to be

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inferior is now generally recognized as unethical and should neither be done, published, nor subject to meta-analysis^{5,6}. Hopefully, in the future few such trials will be done and fewer will be published.

What should you expect in your practice?

Here, we will focus on the levofloxacin concomitant regimen as it combined success, simplicity and cost savings compared to the same drugs used as a sequential therapy. Treatment success with levofloxacin susceptible strains (and no other resistances) was about 97% vs. 67% for levofloxacin resistant but metronidazole susceptible strains and 90% for metronidazole resistance but levofloxacin susceptible strains. In the Fredrico et al. trial¹ the number of resistant strains was low, resulting in wide 95% confidence intervals for the results with resistant strains; more clinical experience is required to fully understand and quantify the limitations of this new therapy.

In the presence of fluoroquinolone resistance, the fluoroquinolone effectively drops out leaving a 5 day metronidazole-amoxicillin-PPI triple therapy. Metronidazole resistance alone leaves a 5 day levofloxacin triple therapy. Both triple regimens still have a relatively high dose of PPI. Dual levofloxacin and metronidazole resistance produces a 5 day dual PPI-amoxicillin therapy which should yield a treatment success of around 25%^{7,8}. The formula for treatment outcome based on these study data would be [Outcome = (% with no resistances X 0.97) + (% metronidazole resistant X 0.9) + (% levofloxacin resistant X 0.67) + (% dual resistant X 0.25)]. Figure 1 shows that one would expect the regimen to maintain its effectiveness as long as fluoroquinolone resistance remained below 20% to 25%. Using the formula one would expect a high prevalence of metronidazole resistance alone (e.g., 50%) to be well tolerated (success 90%), however dual levofloxacin and metronidazole resistance alone would compromise success if resistance exceeded approximately 10%.

The ability to extrapolate outcome based on trial data is only possible if the susceptibility data and outcome for each subgroup are presented. Studies without such data should be strongly discouraged and hopefully fewer journals will be willing to accept them. The lack of such data is largely responsible for the ongoing controversy regarding the place of sequential therapy⁹.

The role of fluoroquinolone therapies

Fluoroquinolone resistance is increasing rapidly worldwide as fluoroquinolones have become the antibiotic *de jour* in many countries. It behooves the clinician to take a good history of possible fluoroquinolone use including ciprofloxacin as prior use virtually ensures resistance. Fluoroquinolones also have “black box” warnings and probably should not be considered for first line empiric therapy except where fluoroquinolone resistance is rare and both clarithromycin and metronidazole resistance is high.

As noted above, the results in the presence of resistance changes a 4 drug levofloxacin quadruple therapy into 5 day triple therapies (either a metronidazole or a levofloxacin triple therapies). Of interest, the reported results were higher than one would expect based on experience and published meta-analysis of 7 day regimens (e.g., 7 day fluoroquinolone therapies typically have produced unacceptably low success; 10 day regimens were better but rarely achieve 90% success)¹⁰. This contrasts to 14 day fluoroquinolone triple therapy which appeared to provide excellent results¹¹. Caveats are: most prior studies likely contained a mixture of susceptible and resistant strains and the Etest overestimates the prevalence of metronidazole resistance¹². None-the-less the data are the data and additional experiments to increase the sample sized are needed to provide a more accurate results.

What remains to be done with sequential and concomitant fluoroquinolone therapies

All regimens should be optimized meaning identification of the preferred components including drugs, doses, formulations, number and timing of administrations per day, relation to meals, and duration of therapy that provides the simplest, best accepted, and cheapest regimen at also maintains the effectiveness at 90 or 95%. Those attempting to duplicate the results of Federico et al. should use exactly the same “recipe” including drugs, doses, and relation of taking drugs to meals¹. One would hope to soon see a series of pilot studies exploring whether the results remain unchanged with changes in the PPI or its relative dose, the fluoroquinolone, and whether fluoroquinolone dosing twice a day is needed¹³. It would seem unwise to embark on a large study of a 5 day fluoroquinolone concomitant regimen that differed in possibly important ways from that described by Federico et al. without such pilot data confirming high levels of success with an altered regimen¹.

Our understanding of the numerical effects resistance to levofloxacin and metronidazole on treatment outcome are also based on small numbers and these results need to be firmed up. Small carefully designed studies in populations with previously identified metronidazole or levofloxacin resistance should be considered.

The early history of sequential therapy was not to optimize the regimen and quantify the effects of resistance but instead to repeatedly reconfirm that sequential therapy was superior to triple therapy, a known inferior regimen. This was followed by a meta-analysis consisting largely of these same data⁴. We believe that comparison trials are best reserved for multicenter trials¹⁴. Clinical trials should also have stopping rules to allow inferiorly performing regimens to be stopped as soon as it becomes clear that they can not achieve the prespecified success outcomes¹³. Only regimens that produce good to excellent results should be compared as only regimens that achieve their prespecified outcome (such as 90% or 95% treatment success) should be recommended for clinical practice.

Recommended therapies

Ideally infectious disease therapies are chosen based on culture and susceptibility testing from each patient. The alternative is to choose a regimen based on the pattern of resistance locally and thus the admonition to use the regimens that are most effective locally¹⁵. Clarithromycin-containing triple therapy loses effectiveness (e.g., success below 90%) when resistance is between 7 to 10%. Clarithromycin-containing sequential and concomitant therapies lose effectiveness with moderate clarithromycin resistance (i.e., 15 to 20%) and when metronidazole resistance approaches 40%. We prefer concomitant therapy as it is not complex and it may retain its effectiveness at a slightly higher level of resistance compared to sequential therapy. Hybrid therapy (dual amoxicillin plus a PPI followed by concomitant therapy) is theoretically superior to concomitant alone but that remains to be tested in areas with high resistance or directly against resistant strains¹⁶. Bismuth-containing quadruple therapy is an effective regimen provided the doses are sufficient and the duration is at least 10 and preferable 14 days especially whenever metronidazole resistance is considered likely. Compliance remains an issue for anti-*H. pylori* regimens and special efforts to ensure compliance are always needed.

Conclusion

In the U.S., clarithromycin resistance has undermined clarithromycin-containing therapy and it should be abandoned as an empiric regimen. Fluoroquinolone resistance is also increasing rapidly. We prefer the 4 drug non-bismuth containing concomitant or alternately sequential therapies for treatment of naïve patients. The alternative is a 4 drug bismuth-metronidazole-tetracycline PPI regimen with treatment extended to 14 days if metronidazole resistance is suspected. The new levofloxacin-containing concomitant regimen would be a good choice

for rescue therapy (failed 2 different therapies) provided the doses and drugs are used exactly as described and susceptibility testing is available or at least the patient has no prior history of prior fluoroquinolone use.

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Figure 1.

Effect of fluoroquinolone resistance on treatment success with levofloxacin concomitant therapy.

Results are presented using the formula shown $\pm 5\%$. Using the results from the Federico et al.¹ study one would predict that treatment success with the described 5-day levofloxacin concomitant therapy would not fall below 90% unless the prevalence of fluoroquinolone resistance increased to between 20% and 25%.