Failure of optimized dual proton pump inhibitor amoxicillin therapy: What now?

For a decade following the initial description of dual amoxicillin–proton pump inhibitor (PPI) therapy by Unge *et al.*,[1] investigators attempted to optimize the doses and duration of this regimen in an attempt to reliably achieve >90% cure rates (reviewed in Dore *et al.*).[2] When given twice daily PPI and amoxicillin cured approximately 62% patients (range 60–64%),[3] and increasing the omeprazole dosage from 20 to 60 mg b.i.d. did not reliably improve outcome.[4] For example, even amoxicillin 750 mg t.i.d. with omeprazole 40 mg b.i.d. or 40 mg t.i.d. for 14 days cured only approximately 80% of cases.[5] Labenz *et al.*[6] gave 40–80 mg of omeprazole with amoxicillin 500 mg q.i.d. for 2 weeks with 82.8% success. In the USA, dual therapy with 1 g amoxicillin and 30 mg lansoprazole, each given every 8 h produced a 60–70% cure rate[7,8] and even this low cure rate was approved by the Food and Drug Administration (FDA).

By 2000, PPI–amoxicillin dual therapy was largely abandoned as being unable to reliably achieve even 90% cure rates. Failure was in part attributed to antimicrobial dormancy or the persister state.[9] While *Helicobacter pylori* can survive low pH, it can multiply only between pH 6 and 8.[9] Thus, the majority of time amoxicillin is present in the blood, *H. pylori* is not replicating and is able to survive. Traditional attempts to overcome persistence include increasing the duration of therapy, increasing the pH, or both.[9] Increasing the duration of therapy to 6 weeks also proved unreliable in improving the outcome.[10] Beta-lactams are pH dependent and most effective and stable at neutral pH.[11,12] However, even b.i.d. or t.i.d. PPI dosing fails to maintain intragastric pH at 6 for more than 12 h. Most *in vivo* work on PPI and amoxicillin dosing has been done by Furuta *et al.* and has been based on the concept that the bactericidal activity of beta-lactam antibiotics is likely to be dependent on time rather than concentration.[13-15] Studies in Japan and Taiwan (areas of high prevalence of CYP2C19 slow metabolizers) have shown that it is possible to maintain a high pH and a Minimal inhibitory concentration (MIC) within the effective range if amoxicillin and PPI were given at approximately 6-h intervals[14-16] producing high treatment success.[17]

European studies identified the factors predictive of treatment failure with dual therapy which included poor adherence, short duration of therapy, and smoking; in contrast, corpus gastritis was associated with success.[2] Yang *et al.*[16] also reported that prolonged elevated intragastric pH and improved cure rates were associated with slow CYP2C19 metabolizer genotype and corpus gastritis. Repeating dual therapy after failure of PPI–amoxicillin therapy has proved to usually produce lower cure rates.[18,19] Dual therapy has also been relatively unsuccessful as rescue therapy.[20] Both observations are consistent with the treatment failures producing a population enriched with poor pH responders (e.g., CYP2C19 rapid metabolizers or natural hyper secretors).

Optimized dual therapy

In 2015, Yang *et al.*[21] introduced "optimized" dual therapy using a second-generation PPI, rabeprazole, plus 750 mg of amoxicillin four times a day. They also prohibited any acid foods. They achieved relatively high cure rates irrespective of CYP2C19 genotype;[21] for treatment of naïve patients the cure rate was high [intent-to-treat (ITT) = 95.3%; 95% CI = 91–98%; and per protocol (PP) = 96.6%] but was lower among those who had failed previous therapy (ITT = 89.3%; 95% CI = 80–97%, and PP = 89.3%). They suggested this regimen as a possible first line regimen. A similar regimen had been previously examined in Europe, where Miehlke *et al.*[22] gave 40 mg omeprazole q.i.d. with amoxicillin 750 mg every 6 h for 2 weeks. They achieved lower cure rates: only 75.6% ITT (95% CI = 60–88%) and 83.8% PP (95% CI = 68–94%).[22] In that study, *H. pylori* was susceptible to amoxicillin, both pre- and posttreatment. CYP2C19 genotypes were not assessed but in Western countries slow metabolizers are infrequent.

The current study[23] tested the Yang *et al.* hypothesis that "optimized" PPI–amoxicillin dual anti-*H. pylori* therapy would achieve high cure rates. The study was done in China, which like Taiwan, has a high prevalence of slow CYP2C19 metabolizers. The authors used rabeprazole (10 or 20 mg) and amoxicillin (750 mg) given q.i.d. (before and after meals and bedtime) for 14 days in two groups of approximately 90 subjects each. The cure rates were low with ITT cure rates of 78.1%; 95% CI = 68–86%, and 81.6%; 95% CI = 73–89%, and PP cure rates of 79.1%; 95% CI = 70–87%, and 83.5%; 95% CI = 71–87% for

the 10 and 20 mg rabeprazole doses, respectively. The CYP2C19 genotypes were not assessed although the use of a relatively CYP2C19-independent PPI makes this important. The difference between this study and the Yang *et al*. study included possibly a slight difference in the timing of dosing and the non-restriction on acidic foods; though none has been shown to be critical.

Where do we go from here?

The success of dual therapy is based on two untested hypotheses: First, it is possible to reliably achieve an intragastric pH of 6 or greater using antisecretory therapy alone; and second, maintaining a high amoxicillin MIC is necessary throughout most or all of the 24-h period. The PPIs are imperfect antisecretory drugs as the full effect requires 3–5 days of therapy and the results in terms of pH control in individual patients are highly variable.[24] It is also unknown whether it is critical to maintain the MIC during the entire 24-h period, as only during this period the pH is between 6 and 8, or can this period differ. There There are many infections effectively treated with pulse rather than continuous penicillin therapy, showing that high continuous MIC level is not always a prerequisite for success.[25,26]

It seems likely that the current "optimized" regimen does not reliably maintain the pH at 6 or greater, over the entire 24-h period. In our experience in the USA, dual PPI–amoxicillin therapy using 40 mg of esomeprazole and 500 mg of amoxicillin every 6-h for 14 days results in unacceptable low cure rate when used as rescue therapy, after treatment failures with other regimens. Reliable success in the general population probably requires use of a more potent and reliable long-acting antisecretory agent such as vonoprazan. Possibly, the combination of a PPI and an antacid to help maintain pH might also be effective. Vonoprazan (20 mg) with amoxicillin b.i.d., reliably achieved a cure rate of approximately 80% in Japan. There were several abstracts presented at the US DDW using t.i.d. amoxicillin and b.i.d. vonoprazan with relatively high cure rates, but to the best of the author's knowledge, none has achieved 95% or greater treatment success. The traditional answer for an infectious disease in which antimicrobial therapy fails although the infection remains susceptible after treatment failure (e.g., tuberculosis) is that the duration of therapy was insufficient (i.e., failure is often because of dormancy or persistence). The dosage and duration of vonoprazan remains unknown, but considering the presence of dormancy, longer duration is probably better. Optimal doses and duration of any regimen can only be identified through experimentation; thus it is always prudent to start with longer durations (e.g., 14 days) so that one does not need to repeat the study if the initial results are below expectation.[28] We believe that dual therapy will ultimately prove successful. The current study shows that the future remains in the future.

Disclosures

Dr. Graham is a consultant for RedHill Biopharma and does research on novel Helicobacter pylori therapies, and has received research support for culture of *H. pylori* and is the PI of an international study on the use of antimycobacterial therapy for Crohn's disease. He is also a consultant for BioGaia in relation to probiotic therapy for *H. pylori* infection and for Takeda in relation to *H. pylori* therapies. Dr. Shiotani has received research grants from AstraZeneca Co. Ltd., Astellas Pharmaceutical, Otsuka Pharmaceutical, Daiichi Sankyo Co. Ltd., and Eisai Co. Ltd.

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Conflicts of interest

There are no conflicts of interest.

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