“Concomitant” or “sequential” eradication of *Helicobacter pylori*: which regimen comes first?

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**Summary**

“Sequential” or “concomitant” non-bismuth quadruple regimens are currently recommended by the recent updated (Maastricht IV) European guidelines as alternative to bismuth based quadruple regimen first line therapies, in areas with a high rate (over 20%) of clarithromycin resistance [1]. Besides this, there is no trial comparing both regimens in settings with increasing rates of clarithromycin resistance [2]. In a recent prospective, randomized, multicenter, clinical trial, conducted in Spain, McNicholl et al aimed to compare the effectiveness and safety of these therapies for *Helicobacter pylori* (H. pylori) eradication [3].

They included a large number of patients (n=338) with non-investigated/functional dyspepsia (80%) or peptic ulcer disease (20%), naïve to eradication therapy. Mean age was 47 years, 60% were women and 20% smokers. They were randomly assigned to sequential treatment; omeprazole (20 mg/12 h) and amoxicillin (1 g/12 h) for 5 days, followed by 5 days of omeprazole (20 mg/12 h), clarithromycin (500 mg/12 h) and metronidazole (500 mg/12 h) [170 patients (50.3%)] or concomitant treatment; same drugs at the same doses taken concomitantly for 10 days [168 patients (49.7%)]. Eradication was confirmed with 13C-urea breath test or histology (depending on the indication), at least 4 weeks after treatment. Treatment related adverse events and adherence to treatment were also carefully evaluated.

A total of 302 patients completed the follow up and were tested for *H. pylori* eradication. The success rate of either regimen was defined as the primary outcome measure and was expressed both by intention-to-treat and per protocol. Secondary outcomes included the rate of treatment-emergent adverse events (AEs) and patients’ adherence to treatment. Concomitant and sequential eradication rates were respectively, 87% versus 81% by intention-to-treat (P=0.15) and 91% versus 86% (P=0.13%) per protocol. Multivariate analysis showed an odds ratio of 1.5 towards better eradication rate with concomitant regimen of borderline significance (OR 1.5, 95% CI 0.9-2.8). Respective adherences to treatment were satisfactory and comparable between treatments (83% versus 82%). AEs were reported by as many as 59% of their patients but were mostly mild (60%), leading to treatment discontinuation in only 12 patients. In conclusion, the concomitant regimen had a non-significant advantage over sequential therapy and was the only one overcoming the 90% cure rate, per protocol. Both therapies were well tolerated and safe.

**Opinion**

*H. pylori* is a global human pathogen that plays an essential role in the pathogenesis of prevalent diseases, including peptic ulcer disease and gastric malignancy [4]. Therefore, this infection should be cured whenever it is diagnosed [5]. Due to globally increasing prevalence of clarithromycin resistance [6,7], clarithromycin-based standard triple therapies have lost their efficacy [8] and should be abandoned as first line therapies, in several parts of the world, including most European countries and Greece [9,10].

Accordingly, the current European guidelines preclude the use of empiric standard triple therapies in areas with high prevalence of clarithromycin resistance (over 20%) and instead they recommend as first-line treatments, bismuth-based or alternatively non-bismuth quadruple regimens (the so called “concomitant” or “sequential” regimens). As bismuth salts are currently unavailable in several countries the usage of non-bismuth quadruple therapies is becoming inevitable [11]. Up to now, there are only a few head-to-head studies comparing sequential and concomitant regimens but either they took place in low clarithromycin resistance settings [12,13] or the comparison of the two regimens was unfair (i.e. 5 days concomitant versus 10 days sequential) [14]. The trial conducted by McNicholl et al is the first one randomly comparing concomitant and sequential regimens, both of 10 day duration, in a European setting with increasing rates of clarithromycin resistance.
resistance. This is a well-designed study, conducted in a clinical practice setting, thus representing the “real-world” situation (i.e. the effectiveness of treatment regimes in the usual, every day practice). Unfortunately, in routine clinical practice, antibiotic susceptibility testing is neither usually performed nor indicated and this was the major limitation of this study, as acknowledged by the same authors [3]. The absence of culture based estimates limits generalization of study results and their reproducibility in areas exhibiting different patterns of antibiotic resistances [15]. In addition, if we extrapolate the results of the recent European survey on antibiotic resistance concerning Spain (clarithromycin resistance 14% and metronidazole 28%) to the study population, then we refer to a population with moderate and not high (over 20%) rate of clarithromycin resistance [16]. There are many available data in a number of recent studies, showing that bacterial resistance to key antibiotics (clarithromycin and/or metronidazole) adversely affects treatment outcome either with sequential or concomitant therapy [15,17-19]. Up to now, there is no non-bismuth quadruple therapy which totally overcomes bacterial resistance [20] but it is also true that concomitant regimen seems to work better than sequential against dual and possibly metronidazole resistant strains of H. pylori, as we have efficiently shown in an ongoing, randomized, multicenter trial [21]. In contrast, a recent meta-analysis [22] has shown equal efficacy of both regimens but it has been criticized for the inclusion of two studies that unfairly compared concomitant and sequential regimens of different duration [23,14,24]. When both regimens are fairly compared, concomitant shows a significant advantage over sequential [21,23].

The small difference (delta) in eradication success rates among these regimens, recorded in different studies, is expected to get wider and statistically significant as we move from low (i.e. Taiwan, 7%) to moderate (i.e. Spain, 14%) and high (Greece, 26%) clarithromycin resistance areas (delta value = 0%, 5% and 10%, respectively) [12,3,21]. This fact probably reflects the divergent effects of these regimens on antibiotic resistant strains and should properly be addressed in future trials. As there is no size that fits all, the answer to the question: “Which regimen comes first in H. pylori eradication?” is not straightforward and largely depends on the level of bacterial resistances in a defined population [25].

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