Letter: could sequential therapy extended to 14 days replace prolonged triple regimens for *Helicobacter pylori* treatment?

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Sirs, We read with great interest the meta-analysis by Liou *et al.*,[1] which provided a novel insight into a debated topic (i.e. triple vs. sequential regimens for *Helicobacter pylori* eradication). Indeed, despite the authors confirming that 10-day sequential therapy had a similar success rate, compared with prolonged 14-day conventional triple therapy, interestingly they showed that 10-day sequential therapy was superior to 14-day conventional triple therapy in clarithromycin-resistant strains (especially when resistance was due to an A2143G mutation in 23S bacterial rRNA), which is in complete agreement with our 10-year experience.[2–4]

However, the meta-analysis by Liou *et al.* also found that the prolongation of sequential treatment to 14 days achieved better results than 14-day conventional triple therapy. Therefore, it may be argued that the 14-day sequential therapy could be the optimal first-line strategy to optimise *H. pylori* eradication. Unfortunately, the study failed to report a direct comparison between 14 and 10 days of sequential therapy.

To further evaluate this relevant result, we reviewed the most important medicine databases (PubMed, EMBASE, Web-of-Science and Scopus) and found that a 14-day sequential therapy was assessed in four clinical studies.[5–8] As shown in Figure 1a, 14-day sequential therapy eradicated the bacterium in 433 of 479 patients in an intention-to-treat analysis, with a pooled success rate of 90.4% [95% confidence interval (CI) 87.8–93.0%].

This value is higher than the success rate with 10-day sequential therapy, which ranges from 75% to 85%, with a mean of about 80% in most meta-analyses.[2] However, only two studies [5, 6] compared directly 10-day and 14-day

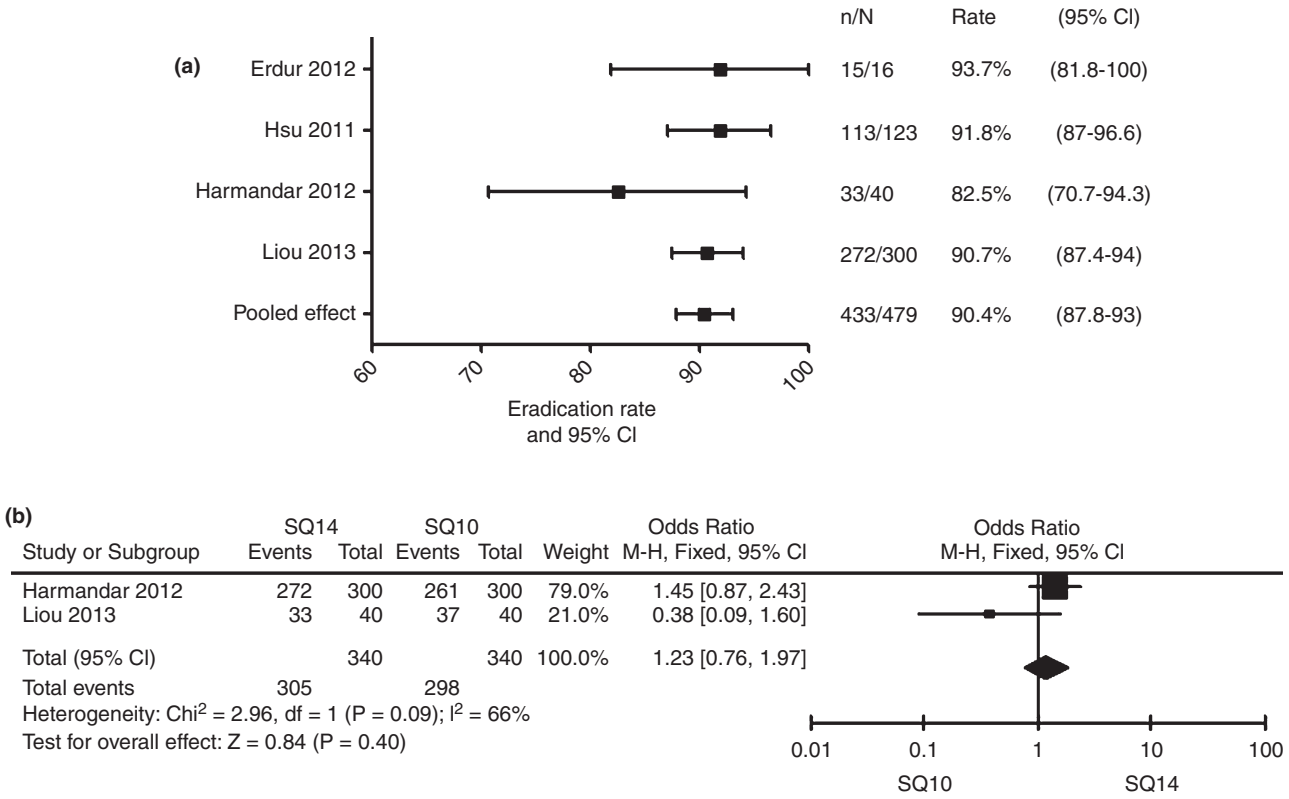

Figure 1 | Pooled-data analysis of eradication rates of prolonged 14-day sequential therapy (SQ14) (a), and meta-analysis comparing the effectiveness of SQ14 vs. traditional 10-day sequential therapy (SQ10) (b).

sequential therapy directly, and, in this case, no significant difference was found (odds ratio = 1.23, 95% CI 0.76–1.97, $P = 0.40$; see Figure 1b), using a fixed-effects model.

In conclusion, this meta-analytic approach underlines that, although 14-day sequential therapy may achieve better results than classical 10-day sequential therapy, a strong and evidence-based proof for implementation of 14-day sequential therapy in clinical practice does not exist at the moment. Nonetheless, we believe that sequential therapy remains a very good first-line treatment,[9] and optimising its duration could afford some benefits in the future, when novel trials on the topic become available.

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Letter: could sequential therapy extended to 14 days replace prolonged triple regimens for *Helicobacter pylori* treatment? Authors' reply

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Sirs, We greatly appreciate the interest of Losurdo *et al.* in our study,[1, 2] and agree with their viewpoint about the lack of direct evidence to support the superiority of 14-day sequential therapy over 10-day sequential therapy.[3–5] We did a systemic review of randomised control trials comparing 10 and 14 days as first-line treatment in adults, and identified four randomised trials comparing the efficacy of 10-day and 14/15-day sequential therapies.[4, 6–8]

Meta-analysis of the four studies showed that 14/15-day sequential therapy was not significantly superior to 10-day sequential therapy [risk ratio 1.03, 95% confidence interval (CI) 0.96–1.12, $P = 0.418$; heterogeneity: $Q = 4.2$, $I^2 = 28.6\%$, $P = 0.241$, Figure 1] using a random effects model. The risk difference was 3% (95% CI −3% to 9.1%, $P = 0.369$).

We also agree with their viewpoint that more trials are needed to assess the efficacy of 14-day sequential therapy as first-line treatment of *Helicobacter pylori* infection. However, it is estimated that more than 1500 patients in each arm would be needed to test that hypothesis that 14 days is superior to 10 days. However, the risk difference between 10 and 14 days might vary in regions with a different prevalence of antibiotic resistance.[4, 5] The risk difference might be greater in regions with higher clarithromycin and higher metronidazole resistance and vice the versa.[4]

For example, the predicted efficacy of 10 and 14 days would be 82.0% and 86.6%, respectively, in a region with clarithromycin resistance of 20% and metronidazole resistance of 40% according to our prediction model (http://hp-therapy.biomed.org.tw).[4] It is therefore estimated that only about 450 patients in each arm would be needed to test the hypothesis that 14 days is superior to 10 days in a region such as this.

In summary, our meta-analysis showed that 14-day, but not 10-day, sequential therapy was superior to 14-day triple therapy.[2] Although 14 days was numerically superior to 10 days, the difference was not statistically significant. More trials that include suscepti-