

Helicobacter pylori eradication in nonulcer dyspepsia: Clearing up the controversy

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ARTICLE

Veldhuyzen van Zanten S, Fedorak RN, Lambert J, Cohen L, Vanjaka A. Absence of symptomatic benefit of lansoprazole, clarithromycin, and amoxicillin triple therapy in eradication of *Helicobacter pylori* positive, functional (nonulcer) dyspepsia. *Am J Gastroenterol* 2003;98:1963-9.

ARTICLE SUMMARY

Veldhuyzen van Zanten et al conducted a double-blind, randomized, multicentre study comparing triple therapy for *Helicobacter pylori* eradication to placebo for the treatment of nonulcer dyspepsia (NUD) symptoms in adult patients (1). Patients had moderate to severe epigastric pain on entry (rated at least a three on a five-point scale for at least three of the previous 14 days). The main outcome measure was the Mean Dyspepsia Summary Score (MDSS), which represents the mean severity of eight dyspepsia symptoms (epigastric pain, belching, heartburn, upper abdominal bloating, flatulence, sour taste, nausea and halitosis). Of the 1143 patients who were screened for this study in 27 centres across Canada, 157 were randomized. *H pylori* was eradicated in 82% of the active group compared with 6% in the placebo group. Symptoms improved in both groups over the 12-month study period, but there was no difference between the two groups in MDSS (2.34 in active and 2.30 in placebo groups at baseline, compared with 1.68 and 1.67, respectively, at the last visit). Nor were there differences in any of the individual symptoms, in the proportion of patients who achieved a certain MDSS score or in health care utilization, such as physician visits, need for additional prescriptions or days lost from work. The authors concluded that, compared with placebo, therapy for *H pylori* produced no sustained improvement of NUD symptoms.

COMMENTARY

Dyspepsia is a very prevalent symptom in Canada (2) and a large proportion of individuals experiencing this symptom have

NUD (3). It has been postulated that *H pylori* may play a role in NUD, but studies comparing eradication with placebo therapy have yielded conflicting results. Two recently performed meta-analyses on these studies have come to differing conclusions, with one (4) showing no benefit, while the other (5), which was slightly more complete, reported a small benefit from eradication therapy. These discrepant results may, in part, be due to the underlying ulcer diathesis found in the population being studied, because studies conducted in areas with a high background prevalence of peptic ulcer disease tend to show the best NUD symptom response to *H pylori* eradication (6). Veldhuyzen van Zanten et al designed this study with adequate outcome measures and duration in the Canadian setting (1).

Because it is a functional disorder, designing a trial for NUD is not a simple task. The study adheres to guidelines set forth for functional gastrointestinal disorders by the Rome II working group (7), a committee chaired by Dr Veldhuyzen van Zanten himself. One of the greatest challenges in NUD trials is choosing a suitable outcome measure. Unlike *H pylori* eradication, there is no simple objective parameter that establishes the success or failure of NUD treatment. The fact that NUD is defined by the presence of a cluster of symptoms does not render this task any easier. This was the reason for using the MDSS. In addition, the authors examined other end points, including individual symptoms and health care utilization data. The authors also evaluated the patients who achieved a certain MDSS (less than 1.5, less than 2.0 or less than 2.5) because the percentage of patients responding to treatment can be considered more clinically meaningful than mean changes in symptom severity. Again, there were no differences in any outcome measure between the study groups.

One potential criticism of this study relates to the fact it was slightly underpowered. The sample size calculation was performed to detect a clinically important improvement in the MDSS and required 63 patients per group, but the study was terminated before this was achieved because the study medications reached their expiry dates. This reflects the reality of studies with very stringent inclusion criteria. The per-protocol analysis revealed that only 50 subjects entered the active treatment

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group and 60 were given placebo. None of the outcome measures, however, demonstrated even a trend favouring the treatment arm. Hence, there was no suggestion that increasing patient numbers would have altered any of the conclusions.

On the other hand, this study exhibited several excellent attributes, including randomization, blinding, adequate follow-up duration, multiple assessments over time and the use of validated symptom scores. The multicentre nature of this trial should strengthen the generalizability of the results. However, only an average of 5.8 patients were recruited per centre despite a long recruitment period, raising the possibility of selection bias. The authors themselves wondered which strategy yields more generalizable results: multicentre studies with small numbers of patients enrolled per centre or studies involving only a few centres with high enrolment numbers.

Interestingly, both groups showed similar improvement in symptoms, which persisted throughout the entire year. As

pointed out in the article, this is likely a result of regression toward the mean of the more severe symptoms and, perhaps more importantly, the reassurance provided by normal findings at endoscopy. The latter should not be overlooked when patients do not respond to empirical treatment for uninvestigated dyspepsia.

The results of this study are important because they demonstrate a lack of clinically significant benefit in symptom reduction over one year when testing and treating *H pylori* in NUD patients in the Canadian setting. It did not address, however, other potential benefits of *H pylori* eradication, such as ulcer or gastric cancer prevention. Moreover, these results do not negate the advantage that has been demonstrated by another randomized controlled Canadian study (8) of treating *H pylori* in infected uninvestigated dyspepsia patients. If a proportion of NUD patients respond to *H pylori* eradication, as is suggested by other trials (5), the current study suggests that, in Canada, it is very small.

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