SEQUENTIAL THERAPY FOR ERADICATION OF *HELICOBACTER PYLORI* INFECTION

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Helicobacter pylori (H. pylori) infection habitually causes chronic active gastritis, which significantly enhances the risk for intestinal metaplasia in the stomach, and it is undoubtedly involved in gastric carcinogenesis. Moreover, *H. pylori* also plays a crucial role in the pathogenesis of peptic ulcer and mucosa-associated lymphoid tissue lymphoma, including peptic ulcer complications, such as bleeding or stenosis [1-4]. Therefore, a safe and effective eradication regimen for this infection is imperative [5]. While the prevalence of *H. pylori* infection has been falling in developed countries, difficulties with eradication have been increasing as the prevalence of *H. pylori* strains resistant to the most commonly used antimicrobials increases [6-8].

According to the Maastricht III guidelines, the first-line treatment for *H. pylori* eradication is the so-called standard triple therapy using a proton-pump inhibitor (PPI) standard dose *bid*, amoxicillin (AMO) 1 g *bid*, and clarithromycin (CLA) 500 mg *bid*. In the case of penicillin allergy, metronidazole (MET) 500 mg *bid* is substituted for amoxicillin. After a decade of CLA-based treatment and continued widespread use of long acting macrolides in general practice, 10%-15% of *H. pylori* strains are resistant *de novo* to CLA [3]. As a result, the failure rate is around 30% for the triple therapy (PPI plus AMO plus CLA) [4,9].

When the first-line *H. pylori* eradication treatment fails, a second-line treatment of quadruple therapy, with a PPI standard dose *bid*, colloidal bismuth subcitrate 120 mg *qid*, MET 500 mg *tid*, and tetracycline 500 mg *qid*, is recommended. Some recent studies have compared the efficacy of the triple *vs* quadruple therapy, and a meta-analysis has assessed these studies: eradication rates were not significantly different among patients receiving triple or quadruple therapy [4,10-12].

CLA and MET resistance has increased substantially in recent years, and there has been a corresponding decrease in the eradication rate for *H. pylori* infection in most Western countries [4]. Therefore, antibiotic resistance is the main cause of failure in *H. pylori* eradication and beta-lactamase produced by resistant *H. pylori* strains is a possible mechanism underlying the ineffectiveness of an AMO-based triple or quadruple therapy [1]. CLA resistance is considered crucial as to the success of a therapeutic regimen, because, unlike MET, CLA resistance cannot be overcome by increasing the dose of the drug. The increase in *H. pylori* strains with primary resistance to CLA is becoming a major problem in many western countries and reaches as high as 13% in the US and 24% in some European countries [13,14]. Because of this, Maastricht III consensus suggested that CLA should not be used in areas with CLA resistance rate >15% and indicated bismuth-containing quadruple therapy as first line *H. pylori* eradication regimen in this setting [15].

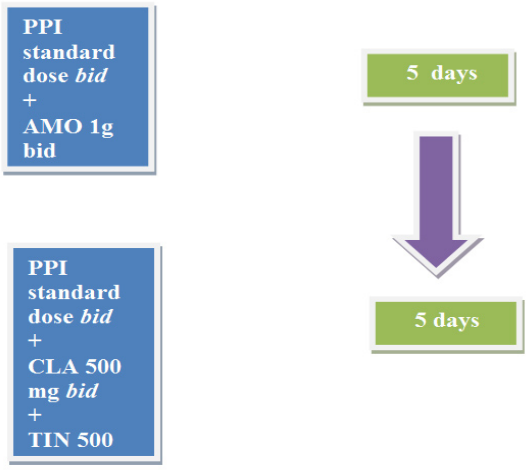

Figure 1: Sequential Therapy.

Recently, a novel 10-day sequential therapy (ST) has been proposed for *H. pylori* eradication by De Francesco *et al.* [16]. Strictly speaking this is not a new approach as it uses well-known drugs with approved indication for *H. pylori* eradication. However, the administration strategy is innovative. The sequential regimen consists in a simple dual therapy including PPI standard dose *bid* plus amoxicillin 1 g *bid* for the first five days followed by a triple therapy including PPI standard dose *bid* plus CLA

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500 mg *bid* plus tinidazole 500 mg *bid* for the remaining 5 days (Figure 1). Several randomized clinical trials have demonstrated that this ST is more effective than standard triple therapy reaching eradication rates of approximately 90%. Interestingly, ST has a high efficacy also in the face of CLA resistance with eradication rates close to 80% in this setting.

The mechanism of action of ST is still unclear, but the initial dual therapy with AMO might reduce the bacterial load in the stomach and this, in turn, may improve the efficacy of the subsequently administered triple therapy [17]. Moreover, it has been suggested that regimens containing AMO prevent the selection of secondary CLA resistance. In fact, it is known that bacteria can develop efflux channels for CLA, which rapidly transfer the drug out of the bacterial cell wall, preventing the binding of the antibiotic to the ribosome. It has been speculated that disruption of the cell wall caused by AMO prevents the development of CLA efflux channels. This may help improving the efficacy of CLA in the second phase of the treatment. However, the improved efficacy of ST compared with standard triple therapy may not be due to the sequential administration of the drugs itself but to the larger number of antibiotics to which the organism is exposed (three *vs* 2, respectively).

We have recently shown that, in our region of Southern Italy, the prevalence of CLA-resistant *H. pylori* strains was approximately 18% in patients naïve to treatment and reached up to 45% in patients with multiple unsuccessful eradication therapies [18,19]. On the other hand, primary resistance to levofloxacin (LEV) was about 3% [19]. Fluorchinolones such as LEV have been used successfully in combination with PPI and AMO in the treatment of *H. pylori* infection both as first-line [20,21] and second-line [21,22] therapy. We have therefore hypothesized that a LEV-containing ST (LEV-ST) might be superior to CLA-containing ST (CLA-ST) in this clinical setting and designed a study with the primary end-point of assessing whether LEV-ST was more efficient than CLA-ST in eradication of *H. pylori* infection in an area with high prevalence of CLA-resistant *H. pylori* strains. Secondary end-points were to assess the influence of anti-microbial resistance on the outcome of eradication treatments, the incidence of adverse events**,** and the cost-effectiveness of either regimen.

Our randomized, controlled, multicentre study involving 375 patients, demonstrates that in an area of high prevalence (i.e. 15-20%) of CLA resistant *H. pylori* strains, LEV-containing sequential therapy is more effective, equally safe, and cost-saving compared with CLA-containing sequential therapy (Figure 2). In fact, LEV-STs achieved eradication rates higher than 95% both in the ITT and PP analysis compared with approximately 82% eradication rate achieved with CLA-containing ST. The rate and severity of adverse events were low in LEV-STs group and comparable to those in the CLA-ST group.

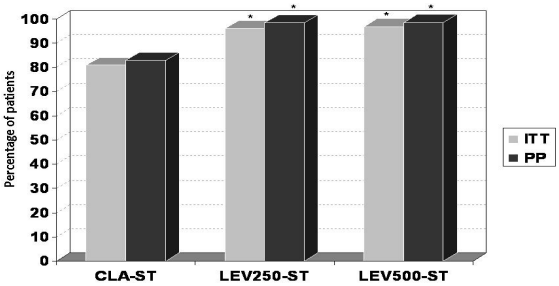

Figure 2: Eradication rates with CLA- containing ST and LEV-containing STs. * p<0.001 vs CLA-ST. ITT: intention-to-treat; PP: per protocol.

In our study, the efficacy of CLA-ST was somewhat lower than expected based on the results of original studies and subsequent metanalyses showing overall eradication rates of approximately 90% [23-26]. This may, at least in part, be contributed to by the higher prevalence of CLA resistant (i.e. approximately 20%) and dual (i.e CLA+MET) resistant (i.e. approximately 6%) *H. pylori* strains in our study population compared with that observed in those studies showing higher eradication rates with CLA-ST [23,26]. Moreover, the efficacy achieved by CLA-ST in our study, i.e. 80.8% in the ITT analysis, is comparable to that described in more recent studies from Korea, Italy, and Spain showing eradication rates of approximately 78%, 86%, and 77% respectively [27-29]. This suggests that the efficacy of ST as indicated by original studies is declining.

Cost is an important consideration for any therapy. However, cost cannot be considered separately from effectiveness. LEV-containing STs were more expensive than CLA-ST, but, when considering the difference in effectiveness, the cost per eradication with LEV250-ST was almost 15 Euros (i.e. 25 US dollars) lower than the cost per eradication with CLA-ST. This was due to the costs of additional office visit, new eradication regimen and new ^{13}C UBT following treatment failure. The difference in cost-effectiveness between the two regimens might even be higher if we consider indirect costs of eradication failure such as unfavorable clinical outcomes, including gastric atrophy, peptic ulcer or gastric cancer, lost time from work and quality of life, variables which are difficult to measure and, thus, often ignored. However, this information cannot be completely generalized to other countries which might have different costs per each of the item evaluated in our study.

Functional dyspepsia and H. pylori

The most widely used definition for dyspepsia is a recurrent pain or discomfort around midline in the upper abdomen. Once any organic disease causing the dyspeptic

symptoms has been ruled out a patient is considered to be suffering from functional dyspepsia (FD). As defined by the Rome III criteria (2006) symptoms in FD must have began at least 6 months before diagnosis and be active for the last 3 months. Besides abdominal pain or discomfort, the symptom complex may include postprandial fullness, nausea, vomiting, bloating, early satiety, belching and epigastric burning. The Rome III System classifies functional dyspepsia (category B1) into two conditions (subtypes): postprandial distress syndrome (B1a) and epigastric pain syndrome (B1b); these are similar to dysmotility-like and ulcer-like dyspepsia of the former Roma II classification [30,31].

The so-called post-infectious FD occurring after acute gastrointestinal infection postulates that inflammation may cause alterations in the enteric nervous system and visceral sensation by modifying signalling in the brain-gut axis. *H. pylori*-induced inflammation of the gastric mucosa in FD falls into the same logic, suggesting that acute and chronic inflammation seem to play some role in the FD pathogenesis. However, so far, FD following acute enteric infection accounts for about 1/3 of FD cases indicating that active inflammation including the one caused by *H. pylori* infection needs to be interpreted and treated on the basis of selected cases [32-34]. Therefore, the controversy involving the benefit of eradication of *H. pylori* in the treatment of FD is related to the mistake of looking at all patients in the same way.

Literature reviews, including several meta-analysis studies published over the last 15 years, have shown that less than 4 out of 10 patients with FD will experience complete relief from dyspeptic symptoms following successful *H. pylori* eradication [35-38]. A systematic review of randomised controlled trials comparing H. pylori eradication with placebo or a different drug treatment has been published [39]. In this analysis, twelve trials were included in the systematic review, nine of which evaluated dyspepsia at 3-12 months in 2541 patients. H. pylori eradication treatment was significantly superior to placebo in treating non-ulcer dyspepsia with relative risk reduction 9% (95% confidence interval). One case of dyspepsia being cured for every 15 people treated. Ang et al. [40] compared in a prospective, randomized controlled study the efficacy of H. pylori eradication against prokinetics in the treatment of FD. Altogether 130 patients were enrolled (H. pylori eradication, 71; prokinetics, 59). In terms of achieving complete symptom resolution, there was a non significant trend favouring H. pylori eradication (31.0% had complete symptom resolution at 12 months compared with 23.7% with prokinetics). Nonetheless, both eradication of H. pylori infection and prokinetic therapy resulted in a reduction of the mean Glasgow Dyspepsia Severity Score (GDSS) and in overall symptom improvement in two-thirds of dyspeptic patients at 1 year.

While the benefits of *H. pylori* eradication in FD are still under debate, it prevents duodenal ulcer (DU) recurrence and complications and leads to a clear symptomatic advantage [41-43]. A few studies evaluating the long-term outcome of *H. pylori* eradication in FD patients, showed a symptomatic benefit and reduced health care needs in favour of *H. pylori*-cured patients [44]. Recently, Maconi *et al.* [45] investigated and compared, in a retrospective 6–7-year follow-up study, the long-term outcome, namely presence of dyspeptic symptoms, need for visits, upper GI endoscopy and use of antidyspeptic drugs, in DU and FD patients after successful *H. pylori* eradication. One hundred four patients (49 DU and 55 FD patients) were included in this investigation. Dyspeptic symptoms disappeared, after *H. pylori* eradication, more rapidly in DU patients than in FD patients. The proportion of patients, however, with sustained resolution of symptoms at 3 and 6 month visits reached 43.6 and 32.7% in FD and 75.5 and 61.2% in DU, respectively. Long-term persistence of dyspeptic symptoms was reported by 60 patients (58%), namely in 25 DU patients (51%) and 35 FD patients (64%). During the 6–7-year follow-up, 29 patients (28%) complained of mild symptoms [13 DU patients (27%) and 16 FD patients (29%)] and 31 patients (30%) complained of moderate-to-severe dyspeptic symptoms [12 DU patients (24%) and 19 FD patients (35%)] (P=0.384). Therefore, altogether, in patients with FD, only 33.9% of *H. pylori* cured patients were symptom-free after 6–7 years. This is in keeping with the results of the latest Cochrane review, where the mean *H. pylori* treatment response rate at 3–12 months was 36%, and almost identical (34%) to that reported by McNamara *et al.* [44] in a 5-year follow-up study after successful *H. pylori* eradication [46].

Conclusions

The practice of using standard PPI triple therapy with CLA and AMO as a primary empirical therapy needs to be reassessed and ST is a novel promising treatment that deserves consideration as a first line treatment strategy for *H. pylori* infection. While robust assessment across a much broader range of patients is required before ST can supplant existing treatment regimens, we suggest he use of ST in settings where the efficacy of triple therapy is unacceptably low. In particular, in areas with CLA resistance >15%, a LEV-containing ST might be recommended as first line empiric choice. However, one must keep in mind that the main disadvantage with use of LEV-containing therapies is the rapid emergence of resistance to this antimicrobial and that in some part of Europe high prevalence of LEV-resistant strains has been described [47]. Therefore, before recommending LEV-containing therapies as first line empiric choice, one must be confident that the local prevalence of LEV-resistant strains is low.

Whether *H. pylori* contributes to functional dyspepsia is still unclear even though growing evidence indicates that the inflammation of the gastric mucosa

induced by the infection and/or the bacterium itself may alter the homeostasis of the stomach thus causing altered gastric function. In this regard, it is well known that *H. pylori* infection is associated with hypergastrinemia and, in a limited number of cases, increased gastric acid secretion or hypochlorydria and alteration of gastric motility [48]. Based on most published studies, *H. pylori* eradication leads to a long lasting symptomatic benefit in about 40% of subjects. Therefore, taking into account that there is no absolute marker capable of predicting the outcome of *H. pylori* infection, eradication of the infection in FD patients is strongly advisable even though the patient must be aware of the possibility that his symptoms will persist after treatment.

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