The challenge of *Helicobacter pylori* resistance to antibiotics: the comeback of bismuth-based quadruple therapy

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Abstract: A proton-pump inhibitor (PPI), clarithromycin-based, triple therapy has been the recommended treatment for *Helicobacter pylori* eradication for the past 15 years. Due to a steady increase in *H. pylori* resistance to clarithromycin, this triple clarithromycin-based treatment has become progressively less efficacious. Several approaches are available to address this situation: one is to test for clarithromycin resistance so that this triple clarithromycin-based regimen is given only to those who will benefit; a second is to prescribe the drugs sequentially, beginning with amoxicillin and a PPI followed by clarithromycin and metronidazole, again with a PPI or the four drugs prescribed concomitantly; a third alternative is to use bismuth-based quadruple therapy, PPI plus a standardized three-in-one capsule, bismuth subcitrate potassium, metronidazole, and tetracycline (BMT, sold under licence as Pylera®). The advantages of these different approaches are reviewed, including the relevance of BMT three-in-one capsule in clinical practice.

Keywords: bismuth salts, clarithromycin, BMT (Pylera®), sequential therapy, antimicrobial susceptibility testing

Introduction

Almost 20 years after the establishment of the current clarithromycin-based triple therapy for the eradication of *Helicobacter pylori* [Bazzoli *et al.* 1993; Lamouliatte *et al.* 1993], its efficacy is seriously challenged in many parts of the world. The aim of this first-line therapy to obtain the highest possible eradication rate, at least 80% or more, is no longer being met leading to a large amount of retreatment.

Among the possible causes of failure, which are becoming more important every year, is the decrease in the number of peptic ulcer disease treated given that the eradication rate is always higher in peptic ulcer disease than in nonulcer dyspepsia, and even more, antibiotic resistance to clarithromycin [Megraud and Lamouliatte 2003]. The same is also true for levofloxacin resistance; levofloxacin was proposed a decade ago as an alternative to clarithromycin [Cammarota *et al.* 2000]. There are different ways to circumvent the problem of resistance, the most interesting of which is the use of a combination of drugs for which resistance

does not appear to be a problem. Bismuth-based quadruple therapy is an attractive alternative treatment, especially in its most recent galenic formulation, bismuth subcitrate potassium, metronidazole, and tetracycline (BMT, sold under licence as Pylera®). The current situation in terms of *H. pylori* resistance to antibiotics, alternative treatments and the relevance of BMT three-in-one capsule in clinical practice are presented, 10 years after a previous review on the topic [De Boer, 2001].

Increased resistance of *H. pylori* to clarithromycin and levofloxacin

Antimicrobial resistance in *H. pylori* is the consequence of mutations. In the case of clarithromycin there are essentially three point mutations, which can occur at the two nucleotide positions 2142 (A2142G and A2142C) and 2143 (A2143G) in the peptidyl transferase loop of the 23S rRNA gene; these mutations result in a conformational change leading to a decrease in binding of the drug. These mutations occur by chance, do not have an impact on bacterial fitness and

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can therefore remain for many generations. Furthermore, all macrolides are similarly affected by these mutations resulting in class-wide resistance [Megraud and Lehours, 2007]. Usually a low proportion of these mutants is present in the *H. pylori* population and often remains undetected by current methods. However, when a macrolide is prescribed for any infection, selection for these resistant mutants occurs and these resistant strains become the majority of the bacterial population.

The only efficient remaining drug is the second antibiotic, amoxicillin (or metronidazole), when clarithromycin-based triple therapy is prescribed to patients carrying such resistant strains. The result is a treatment regimen that is essentially an antibiotic monotherapy with limited efficacy.

The same is true for levofloxacin and all fluoroquinolones, except that the mutations occur at different locations, that is, the DNA gyrase, and are more numerous than in macrolides. The presence of these mutations prevents the inhibition of chromosome replication of the bacterium normally observed in the presence of the drug [Megraud and Lehours, 2007].

Antimicrobial resistance due to point mutations is known to increase slowly but steadily in the case of *H. pylori* resistance to clarithromycin and levofloxacin. Limited resistance to clarithromycin was present when the clarithromycin-based triple therapy was initially established in the 1990s and it has increased steadily over the last 20 years. In most European countries, as well as the rest of the world, the prevalence of clarithromycin resistance has reached 20% or more [Megraud *et al.* 2011], and is responsible for a large number of treatment failures. Ten years later, the situation has repeated itself with regard to levofloxacin resistance, and several countries have now reached a resistance prevalence that no longer allows for levofloxacin's empiric use.

Resistance to clarithromycin and levofloxacin is mostly due to the use of these drugs for infectious diseases other than *H. pylori* infection. This explains why those countries in northern Europe, which have a strict policy for antibiotic use, still have a low prevalence of resistance.

The impact of clarithromycin resistance on eradication rates was proven in clinical trials where antimicrobial susceptibility testing was performed. For example, in a meta-analysis performed by Fischbach

and colleagues, the success of the triple therapy decreased by 66.2% (95% confidence interval [CI] 58.2–74.2), when the *H. pylori* strain was resistant *versus* susceptible [Fischbach and Evans, 2007], and while fewer studies are available, the same trend has been observed with levofloxacin [Perna *et al.* 2007].

Adapting current treatments in areas of high antibiotic resistance

Tailored treatment

A logical approach is to test the antimicrobial susceptibility of *H. pylori*. Even if the prevalence of clarithromycin resistance is 25–30%, the majority of patients could benefit from the standard triple therapy while a significant number receive alternative treatments. The standard methods using culture and antimicrobial susceptibility testing (e.g. Etest, AB bioMerieux, Solna, Sweden) take several days. They can now be replaced by rapid molecular methods that detect both *H. pylori* and its resistance to macrolides. They include a standard polymerase chain reaction (PCR) (Seeflex® ClaR *H. pylori* ACE detection, Seegene, Seoul, South Korea) [Lehours *et al.* 2011], a real-time PCR (Engenex, Vienna, Austria) [Schabereiter-Gurtner *et al.* 2004], or a fluorescence *in situ* hybridization (seaFAST *H. pylori*, SeaPro Theranostics International, Lelystad, The Netherlands) [Russmann *et al.* 2001]. These methods do not require specific transport conditions, are easy to perform, and are reliable and fast. A molecular approach is also possible to test for levofloxacin resistance, which uses a commercially available multiplex PCR followed by strip hybridization (HelicoDR, Hain LifeScience, Nehren, Germany) [Cambau *et al.* 2009].

There are shortcomings in using this approach however, because a number of treatments occur after a noninvasive test, the *H. pylori* antimicrobial susceptibility cannot be known and traditionally, gastroenterologists do not automatically request culture and susceptibility testing for *H. pylori*, while this approach (Culture and Susceptibility testing) is widespread in the general infectious disease specialty practice. We can expect that the availability of molecular methods will be an incentive for development in this domain.

'Sequential' treatment

The impact of resistance can be minimized when drugs are prescribed sequentially instead of

concomitantly. Zullo and colleagues proposed using a proton-pump inhibitor (PPI) and amoxicillin for 5 days followed by a PPI with clarithromycin and metronidazole for the next 5 days [Zullo *et al.* 2000]; this regimen turned out to be effective for *H. pylori* strains resistant to clarithromycin. When susceptibility testing was performed it clearly showed that when clarithromycin-resistant strains were present, the outcome was better with sequential therapy (72%) than with standard therapy (33%) [Gisbert *et al.* 2010].

The hypothesis explaining the better results from administering the drugs sequentially is that during the first phase of the treatment, amoxicillin probably decreases the bacterial load, eliminating most, if not all, of the clarithromycin-resistant mutants, which represent a small proportion of the initial *H. pylori* population. The second phase of the treatment then allows the eradication of the remaining bacteria in the absence of clarithromycin-resistant mutants.

A number of variations in this sequential treatment have been tested, with modifications to the length of treatment (4–7 days for each phase) and/or the drugs used. A levofloxacin sequential treatment has also been tested with variable success; 82.5% eradication in Spain [Molina-Infante *et al.* 2010] and 96% in southern Italy [Romano *et al.* 2010].

The sequential treatment is considered to be a quadruple therapy by some and it was proposed to give the drugs concomitantly instead of sequentially. Hence, the ‘concomitant’ therapy originally proposed by Treiber and colleagues in 1998 [Treiber *et al.* 1998] has been recently re-evaluated [Essa *et al.* 2009]. Although the results are good, the ecological impact of this regimen can be expected to be quite negative with the selection of multiresistant strains despite a heavy antibiotic load received by the patients and, in a number of cases, the use of clarithromycin is not appropriate since it has no beneficial impact on *H. pylori*-resistant strains.

Bismuth-based quadruple therapy

The main concern of this alternative treatment is to avoid the major but problematic antibiotics, that is, clarithromycin and levofloxacin.

Soon after the discovery of *H. pylori*, Marshall and colleagues’ review of past literature showed that

some antimicrobial compounds (e.g. bismuth salts and metronidazole), had been used to treat peptic ulcer disease in the past with some success. He then used this combination in a double-blind trial *versus* cimetidine, observing the eradication of *H. pylori* in most patients treated with the combination and a low relapse rate of duodenal ulcer after 1 year [Marshall *et al.* 1988].

Borody and colleagues proposed the first successful combination to eradicate *H. pylori*, which contained bismuth salts, metronidazole and tetracycline [Borody *et al.* 1987]. This combination was later recommended by a working party at the World Congress of Gastroenterology in Sydney, Australia in 1990 [Tytgat *et al.* 1990], and later by the National Institutes of Health consensus conference in 1994 [NIH, 1994]. A review by Penston in 1994 included 67 studies and 3787 patients and demonstrated a global eradication rate of 89% per protocol and 72% by intention-to-treat (ITT) analysis [Penston, 1994].

In the early days, a PPI was sometimes prescribed with this combination, but the concept of quadruple therapy, that is, omeprazole, bismuth salts, metronidazole and tetracycline (OBMT), emerged in 1994 [de Boer *et al.* 1994]. In 1995, two articles, independently and at the same time, showed that adding PPI to bismuth-based triple therapy increased treatment efficacy [de Boer *et al.* 1995; Borody *et al.* 1995]. This combination had its supporters but remained essentially a rescue treatment during the following 10 years when the PPI-clarithromycin-based triple therapy was the standard treatment [European Helicobacter Pylori Study Group, 1997].

Treatments are changing for several reasons. First, in the context of increased resistance to antibiotics, as seen previously, the quadruple therapy has the advantage of using the following compounds.

1. Bismuth salts is a compound with a short-term effect that acts topically; the mechanism of action is not known but appears to be more like an antiseptic than an antibiotic, and no resistance has been described;
2. Tetracycline is an antibiotic for which resistance is rarely encountered. The reason is that to reach a high level resistance, three adjacent point mutations are required. The change in the nucleotide triplet (AGA-926 to 928→TTC) has been associated with this resistance probably because of a lack of

binding to the h1 loop, which is the binding site of tetracycline on the 30S subunit of the ribosome. The two 16S rRNA copies are both involved. Simple or dual mutations at these positions lead to intermediary minimum inhibitory concentrations. The probability of finding these mutations on the same organism is extremely low and explains why this resistance does not occur. Resistance to tetracycline involving an efflux mechanism has also been described.

3. For the third antimicrobial compound, metronidazole, resistance *in vitro* exists at a high prevalence in most countries around the world, but the clinical impact of this resistance is limited and it can be overcome by increasing the dose and duration of treatment. The meta-analysis of Fischbach and Evans reports a 14% decrease in treatment success when this resistance is present *in vitro* [Fischbach and Evans, 2007].

Secondly, a specific galenic formulation of BMT three-in-one capsule (Pylera®, Aptalis, Mont St Hilaire, QC, Canada) has been developed, which allows standardization of the treatment with a possible positive impact on compliance and hence on eradication rates.

A recent meta-analysis of OBMT in comparison with the PPI-clarithromycin-based triple therapy, which reported the results of 1674 patients included in nine randomized clinical trials, gave a summary eradication rate of 78.3% for OBMT, that was, in fact similar to the 77% obtained with the alternative treatments, with no statistically significant difference in side effects [Luther *et al.* 2010]. However, heterogeneity among the arms receiving quadruple therapy, especially with regard to the dose of metronidazole used, must be acknowledged.

The new formula consists of 40 mg of bismuth subcitrate potassium (equivalent to Bi_2O_3), 125 mg of metronidazole and 125 mg of tetracycline hydrochloride given as a three-in-one capsule four times daily with 20 mg of omeprazole twice daily. It gives the opportunity to standardize the doses of molecular antimicrobials contrary to what occurs when the drugs are administered separately.

The value of this regimen is based on two randomized clinical trials: one performed in North America [Laine *et al.* 2003] and the other in Europe [Malfertheiner *et al.* 2011], where the

BMT three-in-one capsule was compared with the standard regimen of omeprazole, amoxicillin and clarithromycin (OAC). The main differences between the two trials were the type of patients, for example, ulcer patients only in the American study, and the length of OAC treatment. Indeed, because the recommended length of treatment was 7 days in Europe, OAC was given for 7 days in the European trial; for the same reason, it was given for 10 days in North America. Pooled data from these two trials have been submitted [Moayyedi *et al.* 2011].

The ITT results in the North American trial ($n = 299$) were 86% (95% CI 79–91%) for OBMT and 80% (95% CI 73–86%) for OAC; for the European trial ($n = 440$), they were 80% (95% CI 74–85%) and 55% (95% CI 49–62%), respectively.

The apparent lower success rate in the European trial can be linked to protocol violations. In contrast to many other trials, the protocol was very stringent in requesting two negative urea breath tests (UBTs) at a 1-month interval. Unfortunately, some missing second UBT results led these cases to be considered as failures. Considering one UBT result instead of two, the eradication rate was 93% for OBMT *versus* 68% for OAC.

It is interesting to look at the difference between the eradication rates of a clarithromycin-based regimen *versus* OBMT in the two trials: 6% in the North American trial and 25% in the European one. One possible explanation may be the difference in length of treatment. However, a meta-analysis comparing the length of OAC treatment showed that extending therapy beyond 7 days provided a modest increase in success (5%) [Fuccio *et al.* 2007]. The most likely reason appears to be the higher resistance to clarithromycin in Europe than in North America between the two trials carried out 10 years apart.

Indeed, the resistance rate was in the range of 10% in North America during 1994–2000 while it was 21% in Europe in 2008–2009. The resistance rate was an independent predictor of treatment failure ($p = 0.004$) as well as suffering from nonulcer dyspepsia *versus* peptic ulcer disease ($p = 0.003$) in the multivariate analysis [Moayyedi *et al.* 2011].

In contrast, no predictor of treatment failure could be found for OBMT. Despite the high level

of metronidazole resistance in both trials, it did not influence the results significantly.

Another international multicentre study, which was not a comparative trial, was carried out to evaluate the impact of metronidazole *in vitro* resistance on the efficacy of BMT three-in-one capsule *in vivo* [O'Morain *et al.* 2003]. A total of 170 patients were included and the metronidazole resistance rate was 33%. The overall eradication rate by modified ITT was 93% with no difference between metronidazole-resistant cases, 93% (95% CI 85.4–100%), and metronidazole-susceptible cases, 95% (95% CI 90.9–99.8%).

The other important point concerns the safety issue of bismuth regimens. While bismuth salts are reputed not to be absorbed systematically (< 1%), high doses and long-term consumption of certain salts may lead to high blood levels and potential toxicity. In the 1970s in France, high doses of bismuth salts were associated with encephalopathy and sometimes a fatal issue, which led to a ban on bismuth salts [Bader, 1987].

In the context of *H. pylori* eradication, the doses of bismuth currently employed in this version of OBMT are lower than previously and administered for a short time period leading to blood levels lower than 50 mg/l, considered to be on the threshold for potential bismuth toxicity [Hillemand *et al.* 1977].

A systematic review and meta-analysis on all randomized clinical trials comparing bismuth-based treatments with other treatments were conducted by Ford and colleagues [Ford *et al.* 2008]; 35 randomized clinical trials totalling 4763 patients were identified, and 2435 were treated with bismuth salts. No serious adverse event was reported with the bismuth therapy. There was also no statistically significant difference in the total number of adverse events between those receiving bismuth salts and other regimens or in the individual adverse events, that is, abdominal pain, diarrhoea, dizziness, headache, metallic taste, nausea or vomiting. The number of patients stopping the treatment because of adverse events was also not statistically different. The only significant difference concerned the occurrence of dark stools, with a relative risk of five.

In conclusion, we are now at a crossroads. With the exception of a limited number of countries or

regions that have shown a prudent use of antibiotics, *H. pylori* resistance to the main antibiotics included in eradication regimens now necessitates the abandonment of the empiric prescription of PPI-clarithromycin-amoxicillin. The problem can be solved by including testing in the treatment strategy, using the components of triple therapy in different ways, or by using an OBMT regimen, such as the single BMT three-in-one capsule (Pylera®) plus omeprazole, which does not have the limitations of the legacy triple therapy and appears to provide the rationale for empiric first-line use.

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