Pharmacoeconomics in HP-related diseases : more questions than answers

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The infection of gastric mucosa by Helicobacter pylori (HP) is the commonest infection in human beings. The huge financial burden of HP infection's complications (direct and indirect costs of peptic ulcer disease and gastric malignancies, medical fees and cost of drugs in functional dyspepsia) is very difficult to evaluate. Pharmacoeconomics is at its very beginning in that field. In developing countries, many data are lacking to approach cost/benefit ratio in HP infection. The very high prevalence of HP infection is established but the true incidence of HP-associated diseases, peptic ulcer disease (PUD) and gastric cancer (GC) is not known. There is just no idea of the current (and affordable) fees for management. In developed countries, the necessity of pharmaeconomic approaches is born because of the rapid increase of longevity and costs of medical investigations and therapies, along with economic recession and growing unemployment. Besides some real-time studies, economic models are built on historical data : prevalence and incidence of PUD and GC, direct-indirect costs and impact of HP eradication on the evolution of upper GI tract diseases. Nevertheless, most data about the relationship between HP-associated gastritis and complaints of "functional dyspepsia", often called non-ulcer dyspepsia (NUD) remain unknown.

Simplistic cost minimalisation must be avoided : it does not take on account a possible gain of productivity in the future through the introduction of new, often expensive, technologies to day (1,2). Better approaches should be (2,3), the cost/effectiveness ratio that evaluates the consequences of expenses on one aspect of the clinical prognosis (for instance, additional life-years), the multidimensional cost/utility ratio (impact of the intervention on survival rate and quality of life), and *cost/benefit studies* (monetary evaluation of medical intervention). Economic models (Markov's model, decisional trees) are obviously very sensitive to the injected data and must define clear endpoints.

What has been achieved so far in pharmacoeconomics for the management of PUD, GC and NUD in relation with HP infection ? Can we already define a rational economic approach of dyspeptic patients ?

Pharmacoeconomics data in PUD

In western countries, the yearly incidence of PUD ranges from 0.1 to 0.3% of adult population (above 15 yr. old-4). 10% of adults suffered, suffers or will suffer from duodenal ulcer (4,5). Smoking, low educational and socioeconomic level are risk factors for DU (5). The true natural history of the disease remains unknown since diagnosis criteria and therapies greatly varied during the last decade's (6). Nevertheless, one fact is certain : PUD is a relapsing disease. Without maintenance treatment by acid-suppressors, 80% of the patients will relapse within one year (4) and almost 100% within four years. PUD persists for around 15 years (but might be a life-long disorder) (7) : the economic impact of such chronically relapsing disease is obviously enormous. Since the introduction of potent acid-suppressive drugs in the late seventies, the mortality and the need for hospitalization significantly decreased (8) but while indirect fees (disability, early retirement ...) were declining, direct costs (medical procedures, drugs expenses) concomitantly increased (8,9,10). In United States, the expenses for acid-suppressive drugs have been multiplied by fifty between 1977 and 1989 (11). In HP positive PUD, eradication reduces the yearly relapse rate of DU to 6-7% (4), opening a very attractive new field for pharmacoeconomics approach. Theoretically, one may speculate that systematic HP eradication in the population would reduce the future incidence of PUD. No surprise that most pharmacoeconomics studies in relation with HP have been performed in duodenal ulcer disease.

Real-time pharmacoeconomics studies in DU

Two studies carried out in United Kingdom general practice (12,13), concluded that, in patients with known DU, the direct prescription of an eradicating treatment (PPI plus Amoxycillin) without any investigation allows significant savings during the first year through the decrease of antacids or acid-suppressors intake. Eradication prevents also severe morbidity : during a mean three-year follow-up of 175 patients after eradicating treatment, Powell *et al.* (14) showed that eradication reduces the risk for acute upper GI bleeding by a 18-

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fold factor while expenses for anti-ulcer drugs were three times higher in still HP positive patients.

Pharmacoeconomics models in DU

All the models comparing HP eradication with intermittent or continuous treatment by acid-suppressors show an indisputable superiority of the eradication policy. In Belgium (15), the fate of 100 DU patients in five strategies has been simulated through a Markov's model (16) on a five-year period. The model took on account direct fees for medical visits and procedures, cost of drugs and probabilities of remission, relapse and cure according to the different strategies. The eradication strategy was shown to have the best cost-benefit ratio when compared to maintenance and intermittent treatments, either with Ranitidine or Omeprazole (see Table I). The expense for one symptom-free day was is three-four times lower in eradication strategy when compared to other managements. Taking on account a yearly incidence of DU around 2400 cases per year per million inhabitants, the eradication strategy would save yearly between 750.000 and 1.000.000 US$ per million inhabitants in our country. A study from Canada (17) reported significant savings at one year. In United Kingdom (18), eradication strategy would reduce the cost of PUD to one tenth of current expenses provided patients who become HP negative should stop acid suppressive treatment : the possible development of reflux esophagitis after HP eradication (19) would be a significant drawback in this respect and deserves prospective real-time studies. Nevertheless, the benefit of HP eradication is probably underestimated in most studies that ignored indirect fees (20). In the 15-year prospective simulation by Sonnenberg and Townsend (21), indirect costs have been evaluated through the mean annual income. Patients receiving anti-HP treatment (assumed eradication rate : 80%) will remain ulcer-free for 99.7% of the time during the 15-year period, compared to 96.6% for patients under maintenance treatment with H2-antagonists and 82.8% for untreated patients. Total cost is US$ 995 for eradication strategy (US$ 2426 if a follow-up endoscopy is performed), US$ 11186 for maintenance therapy and US$ 10350 for intermittent treatment. Should the eradication drop to 50%, the eradication strategy remains cost beneficial, probably because of the very high cost of endoscopy and diagnosis procedures in United States.

Models are very sensitive to the eradication rates. Vakil and Fennerty (22) compared, over a 2-year period, three strategies : H2-antagonist maintenance treatment, Omeprazole-based bitherapies (either with Amoxycillin or Clarithromycin) and triple therapy (Bismuth, Imidazole, Tetracycline) plus an H2-antagonist. The latter scheme is the most cost-beneficial provided two conditions are furfilled : acceptable compliance (60% of the patients must take at least 60% of prescribed tablets) and local resistance rate to Imidazole compounds must be below 36%.

What is the best eradication therapy ?

According to Jönsson (23), the one-week, low-dose, PPI-based triple therapy described by Bazzoli (24) is more effective and cheaper than the standard two-week oral triple therapy (Bismuth, Tetracyclin, Metronidazole-OTT). Treiber (25) also reported the Bazzoli's triple therapy was economically speaking, the best choice. Taylor *et al.* (26) recently reported similar costs for standard OTT, 7-day quadruple therapy and Bazzoli triple therapy with respective recurrence rates of the disease of 18%, 14% and 15%. All eradicating schemes are superior to maintenance treatment with H2-antagonists (72% remission rate at, roughly, double cost). Finally, the therapy with the best eradication rate will be the cheaper strategy. In that respect, the recent assessment of currently available therapies by Penston and Mc Coll (27) clearly concludes in favor of low-dose, one-week, triple therapies.

Unfortunately, the poor results of Bazzoli or Bazzoli-like low-dose therapies in Belgium (28,29,30) and a mean primary resistance rate to Imidazoles around 30% in our country, lead us to propose the formula PPI bid-Clarithromycin 500 mg bid-Amoxycillin 1000 mg bid for seven days as our first choice. In Belgium, the

Table I. — **Results of the 5-year simulation of the five therapeutic strategies expressed as a mean (range) from (15)**

Strategy	Mean n relapses/year	Mean n of symptom-free days/year	Mean yearly cost (Belgian F)	Cost for one symptom-free day (US$)
Intermittent Rx with Omeprazole	1.56 (0.8-2.1)	320 (318-338)	12208 (7634-17015)	1.25
Intermittent Rx with Ranitidine	1.22 (0.8-2.0)	309 (284-334)	12908 (6418-21212)	1.36
Maintenance Rx with Omeprazole	1.10 (0.6-1.8)	330 (324-335)	18068 (10112-32258)	1.77
Maintenance Rx with Ranitidine	1.06 (0.4-2.0)	320 (285-338)	12667 (7393-30390)	1.39
Eradication	0.3	358 (342-364)	4531 (10-20726)	0.41

cost of drugs for one course of eradication attempt (ITT eradication rate well documented and above 80%) ranges from BF 3536 to BF 4813. Adjusted delivery of the necessary and sufficient number of tablets would reduce the cost of one treatment course to a range from BF 1813 to BF 3865.

The differences between the different schemes (both global and adjusted) are not significant when compared to the huge savings from definite cure of PUD but could be relevant if a policy of systematic eradication is decided. The cost for one HP-eradicated patient varies from BF 5729 (RBC-Clari-Amoxy bid) to BF 4224 (PPI-Clari-Imi bid) but the latter could be much higher because of the high rate of Imi-resistance in Belgium. The figure for quadruple therapy is BF 4260/HP-eradicated patient (cost of adverse events not included).

What about gastric malignancies ?

HP-associated chronic gastritis might be the trigger of gastric carcinogenesis. Besides the correlation between the prevalence of HP infection and the incidence of GC, we know HP-related gastritis is recognized in preneoplastic conditions and precedes the development of gastric cancer (31). Chronic inflammation increases mucosal cell proliferation (32). Gastric lymphoma is also associated with HP to a similar extent (33) and prolonged remission of maltomas has been reported after the eradication of HP (34). Nevertheless, environmental and genetic factors (and virulence of the strain ?) are obviously playing roles. Therefore, no firm data are currently available about the possible impact of HP eradication on the prevention of gastric malignancies, let alone the economic consequences of such a strategy.

In United States, the expense for management of one patient with GC reaches US$ 52000 and systematic screening plus eradication (when indicated) at the age of ten would cost US$ 869000 for one life saved (35). The threshold of a favorable cost/benefit ratio depends also on the local incidence of GC. In high-risk population (for instance in Japan), to prevent 5% of GC through HP eradication would be beneficial. In countries with a lower risk for gastric cancers, systematic HP eradication would have to prevent 20 to 30% of GC to reach an acceptable cost benefit ratio (35). Recently, a model of systematic screening and eradication at the age of 50 in order to prevent GC cancer has been reported (36) : assuming eradication would prevent 30% of GC, the expense would be US$ 25000 by life-year saved. The model is obviously very sensitive to the true impact of HP infection on the incidence of GC and, again, there is so far no definite proof that HP eradication could reduce GC risk. The true benefit of a screening-eradication program is unknown and must be balanced with adverse events of drugs and possible harm related to anxiety induced in the population (37).

And functional dyspepsia (NUD) ?

The true relationship between HP-associated superficial gastritis and functional dyspepsia is even more complex and needs to be clarified for both scientific and economic reasons. In Ireland (38), the most various and expensive prescriptions in general practice are established to treat dyspepsia and according to Jones (39), the prevalence of dyspeptic symptoms would be around 40% in the general population (one third of dyspeptic individuals will visit their GP because of this complaints). HP eradication is not the unequivocal solution for treatment of chronic dyspepsia : in a study including 1802 individuals from 20 to 69-year-old (40), striking differences between dyspeptics with or without ulcer were evidenced : demographic features, life-style and psychological background were significantly different. Dyspepsia might be related to other factors than HP infection : the study by Verdu *et al.* (41) confirmed the well-known difference in the prevalence of HP infection among immigrants from developing countries (63%) when compared with natives from industrialized regions (11%). But, despite this difference, they found no significant difference in the prevalence of dyspeptic symptoms between the two populations. There is, so far, no definite argument to assume that HP eradication is able to cure NUD (42) and systematic eradication in HP positive NUD cannot be recommended. Nevertheless, there is some tendency in routine practice to screen dyspeptic patients for HP and, when positive, to treat. Patients are demanding for symptom relief and, because of the fear of long-term severe complications such as GC, doctors are lead to investigate and treat without any certitude of durable success. One key point might be : are there "good" and "bad" HP strains ? Do we need to kill all the HP strains or only some specifically virulent strains ? Should systematic eradication be applied in, let's say, populations at risk because of dietary or genetic background ? The economic impact of the debate is enormous : what's the most cost/effective policy ? To eradicate HP only in PUD, maltomas and chronic atrophying gastritis after full (and expensive) investigation ? Or to prescribe expensive drugs in all HP carriers screened by a cheap method without any clear proof of long-term benefit for public health ?

The need for invasive approach of dyspepsia addressed by Olson *et al.* (43). In a model, the authors compared five strategies : 1. Endoscopy and biopsy, then eradicating treatment when HP positive ; 2. Endoscopy without biopsy ; 3. HP serology then eradication if positive ; 4. Acid suppressive drugs without any investigation ; 5. Eradicating treatment without any investigation. As attempted and confirmed by others (44), non-invasive approaches are the best choice from a pure economic point of view but the model is very sensitive to the cost of endoscopy and to the probability of symptomatic relapse. If the cost for

endoscopy is below US$ 950 or if 65% of patients without ulcer would ultimately undergo endoscopy, the benefit of the non-invasive approaches vanishes. In Europe, the cost for endoscopy is much lower than in United States : around US$ 200 in Belgium and in Sweden and US$ 300 in United Kingdom (20). No wonder that a Danish study (45) showed that initial endoscopy was more cost effective : when endoscopy rules out peptic ulcer or esophagitis, it avoids the empirical prescription of expensive drugs. Waiting for real-time prospective studies for correct evaluation of the medical and economical consequences of invasive versus non-invasive approaches, an index endoscopy remains the best strategy for dyspeptic patients with no proven antecedent of PUD, at least by European standards.

Finally, when endoscopy discloses an active ulcer, is it necessary to test for HP ? The mean accuracy of all HP detection tests (histology, rapid urease tests, serology and breath tests) is above 90% and more than 95% of DU are HP positive. Greenberg *et al.* (46) showed that additional HP testing during endoscopy increases the cost by 25%. In a retrospective study of 565 consecutive PUD patients they confirmed that these expenses were useless. Nevertheless, the need for careful monitoring of ever-growing HP resistance to antimicrobials (mainly macrolides) and the risk of prescribing antibiotics in patients with HP negative PUD ulcer must be considered. In routine practice, one should follow the recommendation of Kolts *et al.* (47) and use a cheap and accurate rapid urease test.

Conclusions

Systematic eradication of HP in patients with PUD would obviously save a tremendous amount of money. Nevertheless, the different models postulate PUD has been correctly diagnosed : at least, one endoscopic investigation is then required. On the other hand, systematic eradication in all dyspeptic patients testing positive for HP infection by a simple screening method would be at high cost with no proven long-term benefit for individual and public health. The direct prescription of eradicating treatment in patients with a well-documented PUD seems reasonable. The economic impact of the eradication in patients under 45 year, without any alarm symptoms and tested positive for the first time as recommended by the Maastricht guidelines (48) remains unknown. Finally, eradication of HP is perhaps not the end of the story in PUD : gastroesophageal reflux may appear (19) and the cost of adverse events from the treatment must be considered (49). So far, little is known about the possible impact of HP eradication in the prevention of gastric malignancies : a more precise knowledge of the features of individuals who are at high risk because of genetic or environmental background or strains virulence is necessary. Similarly the medical and economic benefit of HP eradication in NUD (the diagnosis of which, by definition, necessitates again endoscopic and echographic investigations) must be evaluated in real-time, well-designed studies, to discriminate between potential responders and non-responders.

Models might not be exported anywhere without further consideration of crucial local data : cost of procedures and therapies, local resistance to antimicrobials, cultural relationship with therapeutic drugs, compliance, dietary habits, local incidence and prevalence of HP-related diseases and, last but not least, local efficiency of the therapeutic scheme. Cost differences between the various therapeutic schemes are low and the regimen with the best eradication rate (on an intent-to-treat basis) will probably have the best cost-effectiveness ratio. Finally, once a well-designed model has been on accurate national or regional data, one must remind that a model remains only a model : computerized simulations must be tested in real-time intervention studies.

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