ERADICATION OF HELICOBACTER PYLORI INFECTION IN OUTPATIENT CARE

Doctoral thesis (PhD)

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1. Introduction
The discovery of *Helicobacter pylori* (*H. pylori*) lead to a major paradigmatic change in the second half of the 20th century in our conception and treatment of the acid-related disorders. The discovery made by the Australian researchers was rewarded with the Nobel prize for Medicine in 2005 and thus, it became part of the history of medicine. In this doctoral thesis, the author’s aims is to analyse the possibilities of eradicating the infection in Hungary, in an attempt to obtain an overall view of the results obtained in the country.

2. Aims
The aims of this thesis are:
1. The primary, second- and third-line eradication of *H. pylori* infection on an outpatient care basis: analysis of single-centre, prospective, controlled trials;

3. Primary, second- and third-line eradication of *H. pylori* infection on an outpatient basis
3.1. Patients and methods. Six eradication regimens were evaluated in 3 open, controlled, prospective, single-centre trials between 1995 and 1999. The regimens chosen were those recommended by the HGS and Italian authors before 1996 and then by the Maastricht and HGS consensus. In primary treatment studies, 321 duodenal ulcer (DU) patients were enrolled. The diagnosis of DU was established by upper endoscopy, the *H. pylori* infection was identified by the modified Giemsa stain from 2 antral and 2 corporeal biopsies + rapid urease test. Before 1997, eradication was confirmed by repeated endoscopy and histology. With the advent of the urea breath test (UBT) in 1997 in Hungary, all the controls were performed according to the European protocol 6 weeks after treatment with a $^{13}$C-UBT. One-hundred thirty-four patients resistant to primary regimens were included in a cross-over controlled prospective study between 1998 and 2001. Forty-one patients resistant to the second-line therapy were randomized to receive quadruple therapies between 2001-2003.
3.2. Statistics. The significance between groups was determined by the chi-square test, the value of p=0.05 was taken as significant. 95% confidence intervals were determined. The relationship between the values of $^{13}$C-urea test and rate of eradication was assessed by linear regression. The statistical methods used are those described in the literature.
3.3. Results. The regimens used, the duration of treatment and eradication results on an intention-to-treat (ITT) and per-protocol (PP) basis are given in Table 1. The cumulative results of the three consecutive eradication cycles are presented in Figure 1.
Table 1. First-, second and third-line eradication of H. pylori in duodenal ulcer patients

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of cases</th>
<th>Duration of treatment (days)</th>
<th>Control</th>
<th>Eradication ITT (%)</th>
<th>Eradication PP (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAM</td>
<td>48</td>
<td>7</td>
<td>Histology</td>
<td>51.2</td>
<td>63.5</td>
<td>ITT:0.02</td>
</tr>
<tr>
<td>OAC</td>
<td>52</td>
<td>7</td>
<td>urease test</td>
<td>72.3</td>
<td>80.2</td>
<td>PP:0.03</td>
</tr>
<tr>
<td>PAC</td>
<td>48</td>
<td>7</td>
<td>Histology</td>
<td>80.8</td>
<td>92.1</td>
<td>ITT:0.65</td>
</tr>
<tr>
<td>RBCC</td>
<td>51</td>
<td>7</td>
<td>urease test</td>
<td>80.3</td>
<td>85.4</td>
<td>PP:0.67</td>
</tr>
<tr>
<td>LCM</td>
<td>60</td>
<td>7</td>
<td>^13^C-UBT</td>
<td>78.3</td>
<td>92.1</td>
<td>ITT:0.86</td>
</tr>
<tr>
<td>RBCMC</td>
<td>61</td>
<td>7</td>
<td></td>
<td>78.7</td>
<td>90.2</td>
<td>PP:0.93</td>
</tr>
<tr>
<td>Second-line regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAC</td>
<td>66</td>
<td>7</td>
<td>^13^C-UBT</td>
<td>65.2</td>
<td>60.3</td>
<td>ITT:0.58</td>
</tr>
<tr>
<td>RBCMC</td>
<td>68</td>
<td>7</td>
<td></td>
<td>60.3</td>
<td>65.0</td>
<td>PP:0.57</td>
</tr>
<tr>
<td>Third-line regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PATN</td>
<td>21</td>
<td>7</td>
<td>^13^C-UBT</td>
<td>61.9</td>
<td>65.0</td>
<td>ITT:0.58</td>
</tr>
<tr>
<td>PATBs</td>
<td>20</td>
<td>7</td>
<td></td>
<td>55.0</td>
<td>70.6</td>
<td>PP:0.03</td>
</tr>
</tbody>
</table>

Abbreviations: A=amoxicillin, Bs=bismuth subsalicylate, C=clarithromycin, M=metronidazol, NF=nitrofurantoin, O=omeprazol, P=pantoprazole, RBC=ranitidin bismuth citrate, RUT=rapid urease test, T=tetracyclin, ITT: intention-to-treat, PP=per protocol, ^13^C-UBT: ^13^C- urea breath test

Figure 1. Cumulative rates of eradication after primary, second-line and third-line treatment in duodenal ulcer patients. Results on an ITT and PP basis.

The prospective, serial analysis of the UBT results showed that in therapeutic failures, the δ‰ values increase significantly over time after each failed regimen (Table 2) and there is a negative correlation between pre-treatment UBT value and rate of eradication (Figure 2).

Table 2. Values of the ^13^C-urea test after first, second- and third-line eradication in successfully treated and failed cases (mean δ and 95% CI)

<table>
<thead>
<tr>
<th>UBT result</th>
<th>Before 1st Treatment</th>
<th>After 1st Treatment</th>
<th>Before 2nd Treatment</th>
<th>After 2nd Treatment</th>
<th>Before 3rd Treatment</th>
<th>After 3rd treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful</td>
<td>1,3</td>
<td>0.5-2.3</td>
<td>12.4</td>
<td>9.7-15.7</td>
<td>16.2</td>
<td>13.4-19.6</td>
<td>0.031</td>
</tr>
<tr>
<td>Eradication</td>
<td>0.8-1.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>13.3</td>
<td>7.3-19.1</td>
<td>13.2</td>
<td>7.3-19.1</td>
<td>19.2</td>
<td>13.4-25.0</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19.32</td>
<td>16.222.4</td>
<td>25.83</td>
<td>19.8-31.8</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Notes: ^1^Before second-line vs. third-line therapy; ^2^after primary treatment vs after second-line regimen; ^3^after second-line vs after third-line therapy
3.4. Discussion. Primary regimens containing a proton pump inhibitor (PPI) + 2 antimicrobials achieved eradication rates in line with the national and international provisions (80% on an ITT basis). Some regimens, as OAM, had a lower efficacy and therefore, are not recommended. The effectiveness of second-line regimens was by 15-25% lower than that of the same therapies given as primary treatment while the third-line regimens resulted in a further decrease of 5-10%. However, the cumulated eradication rate after 3 consecutive regimens was 98%. The UBT test has a predictive value: the δ > 15-20‰ was associated with low eradication rates. In these cases, prolonging the treatment duration, increasing the dosage, quadruple combinations, using of novel antibiotics or sequential treatment might be considered.

Meta-analysis is an integral part of evidence-based medicine and has become a frequently used method for resolving discordances and uncertainties between randomised controlled trials (RCT). The purpose of a meta-analysis is to combine the results of similar trials statistically and is aimed at improving the estimation of treatment effects whilst minimizing the biases of such estimations. However, RCTs do not cover the complete range of studies, and therefore the inclusion of congress abstracts was also accepted.

A meta-analysis was carried out in the Hungarian full papers and abstracts of the annual meetings of the HGS (1993 and 2002) and that of European abstracts published at the EHPSG, UEGW, DDW and WCOG (1997-2004) was performed. The data were extracted and entered into an Excel database. The quality of the abstract was analysed by a standardised protocol. The treatment arms of the abstracts were classified and groups of similar regimens were constructed (PPI-based triple, RBC-based triple, H₂ blockers-based regimens, double and quadruple therapies and antimicrobial-based analysis). The pooled eradication rates of each group were calculated. The differences between the groups were estimated by using the chi-square test. In comparative trials, the combined odd ratios were estimated.

4.2. Results
The pooled eradication rates in the therapeutic groups mentioned above are given in Table 2.

<table>
<thead>
<tr>
<th>Regimens used</th>
<th>Hungary</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Eradication (%)</td>
</tr>
</tbody>
</table>
### 4.3. Discussion.

Most of the results obtained in Hungary and Europe are in agreement with the provisions of the Maastricht 1 and 2 Consensus Statement (eradication of 80% on an ITT basis) and other meta-analyses published. The results showed, that PPI- or RBC-based one week triple therapies are the regimens of choice in the primary treatment of the infection. There was no difference in the efficacy of all available PPIs. The antimicrobial-based analysis concluded that regimens containing C + either a N or A are more efficient than A+N combinations. Some disagreements between the Hungarian and European results (effectiveness of H2-blockers, double combinations) might be explained by the different study period and study design (open vs. controlled trials).

### 5. The assessment of the quality of life in functional dyspepsia

In the developed world, FD is the most prevalent disease of the upper gastrointestinal tract. This benign, but chronic condition, however, affects adversely the quality of life (QoL) and working productivity of the patients. Besides the RCTs and meta-analyses, the assessment of QoL is an important instrument in the evaluating the natural history of the FD and the effect of different therapies.

#### 5.1. Patients and methods.

The disease-specific Functional Digestive Disorders Quality of Life questionnaire (FDDQoL) prepared by the Mapi Research Institute, Lyon, France was used. The Hungarian version was prepared by the forward-backward translation, Harmonisation, clinical and cognitive debriefing. Permission for use was obtained from the parent institute. The validity of the Hungarian questionnaire was verified on 14 healthy and 22 FD patients by determining its internal consistency, intra-class correlation, convergent, divergent, face and content validity.

The QoL was then assessed in 123 healthy people. 101 *H. pylori* positive and 98 uninfected FD patients. The healthy cases were referred to our institution by the DIMENZIO Kft Insurance Company. The FD was diagnosed based on the Rome II criteria, negative upper endoscopy and abdominal ultrasound.

*H. pylori* positive FD patients received one-week triple regimen consisting in 2x40 mg pantoprazole + 2x1000 mg A + 2x500 mg C. A control UBT was performed 6 weeks after eradication. The patients were allowed to take 1-2x150 mg ranitidin/day as maintenance treatment. *H. pylori* negative patients received 3x10 mg cisapride for 6 weeks and then 1-2x10 mg cisparide on demand for 1 years.
The QoL assessment was performed at baseline, after a short-term (6 weeks) and long-term (1 year) follow-up. The statistical processing of the questionnaires was performed using the specific methods described in the literature. 

5.2. Results

The QoL scores of the FD patients were significantly lower (i.e. worse) than in healthy subjects, regardless of the *H. pylori* status (Figure 3). There were no significant differences between the symptomatic subgroups of FD patients (ulcer-like, dysmotility-like and mixed form). An analysis of the 8 dimensions of the FDDQoL showed that the impairment of the QoL was due to the decrease of daily activity, eating, anxiety level, sleep, discomfort, coping with the symptoms and stress scores.

The triple regimen used was efficient in 76.4% on an ITT and 82.6% of the cases on a PP basis. The QoL improved significantly (p=0.0001) 6 weeks after successful eradication and after 1 year of follow-up (p=0.05) (Figure 4). Prokinetic treatment lead to a similar, significant improvement after 6 weeks (p=0.0001). During the 1 year follow-up of the cases a further slight, but unsignificant improvement occurred (p=0.06) (Figure 4). The effect size was large in both groups after 6 weeks and moderate after 1 year; there was no significant differences in the QoL scores between the treatment arms either at 6 weeks (p=0.11) or after 1 year (p=0.43).

**Figure 3.** Quality of life in *H. pylori* positive and negative functional dyspepsia patients and healthy controls. Box-and-whisker plot of the standardized scores after linear transformation

**Figure 4.** The effect of *H. pylori* eradication or cisapride treatment on the quality of life in functional dyspepsia patients

5.1. Discussions
The translated and validated FDDQoL was useful in the assessment of QoL in FD patients because a) it has the ability to differentiate normal persons from diseased patients; b) it has the ability to capture the changes over time induced by the given therapies. The impairment of the QoL could be overcome either by successfully eradicating the *H. pylori* infection or under prokinetic treatment at least for a period of 1 year. The usefulness and cost-efficiency of the eradication is debated; however, according to our results, it improves the short-term and 1-year QoL of the cases. Other arguments which favour an eradication policy in FD are: prevention of peptic ulcer and gastric cancer as well as reduction of the populational infection reservoir which are highly warranted in Hungary, where the prevalence of the infection is 55-60%. Prokinetic therapy was equally efficient in *H. pylori* negative FD, but the favourable results are overshadowed by the withdrawal of cisapride. Nevertheless, a QoL assessment remains an useful instrument in the evaluation of the new forthcoming prokinetic drugs. FD is a benign, but long-lasting condition: a follow-up of 3-5 years with repeated QoL measurements is desirable to establish the long-term effectiveness of any therapy.

6. Summary of the doctoral thesis
a) The eradication regimens given by us on a single-centre outpatient basis revealed that PPI + 2 antimicrobials achieve eradication rates about 80% on an ITT basis; however. second-and third-line therapies are less efficient.

b) The meta-analysis of the Hungarian and European studies showed that adhering to the recommendations of the 1st Maastricht Consensus will consistently result eradication rates of around 80%, thus underlining the validity of these statements. The effectiveness of double regimens and H2-blockers based therapies is debatable and some contradictions between European and Hungarian results. Second- and third-line quadruple therapies are less efficient than primary regimens. Nevertheless, the ideal regimen for eradication has not been found; especially. re-treatment of patients with resistant *H. pylori* strains still constitutes a problem. as it is stressed by recent expert opinions and guidelines.

c) A serial analysis of the UBT test values showed that they could be a useful predictor of eradication success or failure.

d) QoL is impaired in FD regardless of the *H. pylori* status. Eradicating the infection or prokinetic therapy lead to a short-term and 1-year improvement of the QoL in this condition.

7. List of own publication related to the topic of the doctoral thesis:

7. 1. Books and chapters

7. 2. Journal articles


8. Acknowledgments

I would like to express my warmest thanks and gratitude to all the following people who have helped me during the years of doctoral school and compiling this thesis:

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