Chronic dyspepsia in general practice. Tapering the use of acid suppressant drugs

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Chapter 5

Prevalence of CagA status, its relation with disease and influence on the efficacy of *H. pylori* treatment in chronic dyspeptic primary care patients.

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Submitted
Background
CagA+ *H. pylori* has been found associated with peptic ulcer disease (PUD) in Western populations and may affect the efficacy of *H. pylori* treatment. The aim is to determine the prevalence of CagA status and its relationship with disease and treatment outcome in chronic dyspeptic primary care patients.

Methods
In 202/207 *H. pylori* positive patients, CagA status was assessed by determining anti-CagA antibodies in patients’ sera by ID Blot *H. pylori* IgG. Microbial resistance (R) was assessed by the E-test. Ninety patients (25 PUD and 65 non ulcer disease (NUD)) were randomised for 7-day omeprazole, metronidazole, clarithromycin therapy (OMC7).

Results
Anti-CagA antibodies were detected in the sera of 68/74 (92%) PUD patients and of 93/128 (73%) NUD patients (p<0.05). In the sera of 23/25 (92%) immigrant PUD patients and of 44/50 (88%) immigrant NUD patients, anti-CagA antibodies were detected (n.s.)

Intention-to-treat eradication rate was 88% (95%CI:81-95) and per protocol eradication rate was 95% (95%CI:88-99). Eradication rates of OMC7 were similar in PUD patients and NUD patients, irrespective their CagA status and the microbial susceptibility of *H. pylori*.

Conclusion
Prevalence of CagA+ *H. pylori* and its relation with PUD is influenced by patient’s origin. Neither disease status, nor CagA status or MTZ-R affected the efficacy of OMC7.
Introduction

It is generally accepted that *H. pylori* is the major cause of chronic superficial gastritis in humans and an important etiologic factor in the pathogenesis of peptic ulcer disease and some forms of gastric cancer. Cytotoxin-associated gene A (CagA) of *H. pylori* is found to be associated with more severe clinical manifestations, like peptic ulcer disease (PUD) and gastric cancer in studies in Western populations. Therefore, determining the CagA status in primary care patients may be a potential non invasive discriminative factor between patients with PUD and patients with non ulcer disease (NUD).

Many different efficacious treatments of *H. pylori* are available. Nowadays, the recommended *H. pylori* eradication therapies, which are most successful, consist of a proton pump inhibitor (PPI), clarithromycin (Cla) and amoxycillin or metronidazole (MTZ), twice daily for at least seven days. The eradication rates in some studies consisting of a mixed population of patients with NUD and PUD are lower as compared to studies with ulcer patients alone. It is assumed that CagA+ *H. pylori* may be responsible for this effect. However, whether this is of any clinical relevance in a chronic dyspeptic primary care population is unclear since thusfar studies concern mostly secondary care populations.

In this study the prevalence of CagA+ *H. pylori*, its relationship with disease and treatment outcome in *H. pylori* positive chronic dyspeptic patients from primary care were investigated.

Materials and Methods

Patient population

This study was conducted in the period of April 1997- October 1999. Included patients were participating in the study ‘Chronic dyspepsia in General Practice’ in which several diagnostic instruments and interventions concerning a more efficacious use of acid suppressant drugs were investigated. Eligible for the study were chronic dyspeptic patients on acid suppressant maintenance therapy in the age of 18-85 years. Chronic dyspepsia was defined as chronic upper abdominal pain/discomfort or reflux symptoms (with or without oesophagitis grade one) requiring maintenance acid suppressant drugs in at least the preceding 8 weeks before entry of the study. Patients were identified by means of computerised medication data of all pharmacists co-operating with the participating general practitioners. In the Netherlands all patients are listed and documents are kept in the patient history file stored in the office of the general practitioner. The original documents were checked by the principal investigator.

The following patients were excluded: patients with documented gastroesophageal reflux disease grade II, III, IV (Savary-Miller); patients with documented significant cardiovascular, pulmonary, renal, hepatobiliary or pancreatic disease or malignancy; patients with sinister
dyspeptic symptoms; patients with documented abdominal surgery with relevance to the study; pregnant or lactating women; patients requiring an interpreter; patients taking antibiotics or bismuth containing compounds during the previous month, patients taking NSAIDs, patients with any condition associated with poor compliance (e.g. drug or alcohol abuse, mental illness or dementia).

Data about the documented history results of upper GI-endoscopy or barium meal, medication and co-medication of the eligible patient, were obtained by the principal GP-investigator (G.H.) on behalf of the participating GP’s in their practice. Verification and completion of the obtained data took place between the principal GP-investigator and the GP.

All eligible patients were invited to participate by letter from their GP, in which the study was explained. The patients were asked to stop ingestion of their acid suppressant medication at least one week before upper GI-endoscopy.

Demographic and dyspepsia questionnaires were filled out in hospital. Demographic data included the ethnic background, defined as natives for patients born in the Netherlands and immigrants for patients born outside the Netherlands.

The study was approved by the Institutional Ethics Committee of the Academic Medical Center and a written informed consent was obtained from all patients at the time of endoscopy.

**Endoscopy and assessment of H. pylori infection**

Based on history and endoscopic examination at study entry, patients were classified as PUD and NUD. NUD was defined as patients with neither a history of ulcer disease nor endoscopic evidence of ulcer disease. During each endoscopic procedure, 3 antral and 3 corpus mucosal biopsy specimens were obtained for histological and bacteriological assessment. The biopsy specimens were processed and assessed for histopathology and culture as described before. Patients were defined as positive for *H. pylori* (the gold standard) if one of the biopsy specimens was positive in culture or in histopathology. *H. pylori* infection was absent if both bacterial culture and histopathology readings were negative. The histopathologist and microbiologist were blinded to each other’s results.

**CagA testing and antibiotic susceptibility**

CagA status was assessed by determining anti-CagA antibodies in patients’ sera by ID Blot *H. pylori* IgG according to the manufacturer’s protocol (DPC Biermann, Germany) (6). A pilot study with the sera of 61 patients with a previously resolved CagA status (26/61 CagA+) to assess the performance of the ID Blot test in determining patient’s CagA status showed a sensitivity and specificity of 91% and 92%, respectively. The susceptibility to Cla and MTZ of *H. pylori* was assessed by the E-test (AB Biodisk, Sweden) as described before. *H. pylori* isolates with a MIC > 8μg/ml MTZ were considered MTZ resistant and isolates
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with a MIC > 2µg/ml Cla were considered Cla resistant.

Randomisation and treatment regimens
Of 207 H. pylori positive patients 76 patients had PUD and 131 had NUD. Two weeks after endoscopy, 25/76 PUD patients were randomised for 7 day b.d. 20 mg omeprazole, 400 mg MTZ and 250 mg Cla (OMC7). NUD patients were allocated to one of two double-blind treatment regimens of OMC7 or Omeprazole Placebo antimicrobials (OP7).

Results of the gastroscopy, potential (rarely observed) side effects of eradication therapy and the expectations with regard to cure or potential complaints after completion of the therapy were discussed. A written hand-out about these aspects was also given to the patient. Compliance was assessed by tablet counting and patients were asked to report serious adverse events to the investigator.

Post H. pylori eradication therapy follow-up
Patients underwent control endoscopy 4-6 weeks after cessation of the regimen and biopsy specimens were again taken for culture and histology according to the aforementioned procedure. Patients, who refused endoscopy, were assessed for H. pylori infection by $^{13}$C Urea Breath Test using a Laser-Assisted-Ratio-Analyser (Alimenterics B.V., Hoofddorp, Netherlands) according to the instructions provided by the manufacturers. The LARA $^{13}$C Urea Breath Test is an accurate tool for the detection of H. pylori with a sensitivity of 93% and specificity of 96%.

Statistics
Analysis was performed using SPSS for Windows (version 7.5.3). The Chi-square test was used for comparison of proportions. CagA status in relation with disease is expressed as relative risk. Significance was set at $\alpha = 0.05$ (two-sided).

Results
Patients
In fifty four general practices 2230 patients were using long-term acid suppressant medication of whom 1083 chronic dyspeptic patients met the eligibility criteria; 434 (40%) of these agreed to participate for endoscopy. Of the patients undergoing endoscopy 227 (52%) was H. pylori positive: 78 with PUD and 149 with NUD (figure 1). Twenty patients (2 with PUD and 18 with NUD) were excluded before randomisation (language problem (n=1), refusal to participate further (n=10), oesophagitis grade 3 (n=2), Barrett’s oesophagitis(n=7)).
Demographic and clinical characteristics of the 207 remaining patients are summarised in table 1. The immigrants (80/207; 38.6%) were born in Surinam or the Caribbean (n=35), other South-America (n=3), Turkey (n=13), Morocco (n=9), Middle East (n=4), sub-Saharan Africa (n=8), Asia (n=8).

**Cag A status, relation to disease and microbial resistance**

Of all patients, 80% (161/202, 95%CI: 74.2-85.2) had serum anti-CagA antibodies, indicating infection with CagA+ *H. pylori* (table 1). From 5 patients (2 PUD, 3 NUD) the CagA status was not available.

The occurrence of patients with a positive CagA status among native PUD patients (92%; 95%CI: 80.4-97.7) was higher than among native NUD patients (63%; 95%CI: 51.1-73.5) (p<0.0003). In CagA+ *H. pylori* native patients the relative risk was 1.5 (95%CI: 1.2-1.8) and in CagA- *H. pylori* native patients the relative risk on PUD was 0.21 (95%CI: 0.1-0.6). In the subgroup of patients ≤ 55 years results were similar (data not shown).

The proportion of immigrants and native patients with anti-CagA antibodies in their sera was 89% (95%CI: 82.3-96.3) and 74% (95%CI: 66.4-81.6), respectively (p<0.009). The proportion of patients with a positive CagA status among immigrant patients with PUD and among immigrant patients with NUD was similar (table 1).
Table 1. Demographic and clinical characteristics of patients with chronic dyspepsia stratified for peptic ulcer disease (PUD) and non-ulcer dyspepsia (NUD)

<table>
<thead>
<tr>
<th>Patients</th>
<th>All Patients</th>
<th>PUD n=76</th>
<th>NUD n=131</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age, years (range)</td>
<td>52 (18-81)</td>
<td>53 (21-81)</td>
<td>52 (18-79)</td>
</tr>
<tr>
<td>sex (M/F)</td>
<td>107/100</td>
<td>53/23</td>
<td>54/77</td>
</tr>
<tr>
<td>natives / immigrants</td>
<td>127/80</td>
<td>49/27</td>
<td>78/53</td>
</tr>
<tr>
<td>CagA positive status</td>
<td>161/202 (80%)</td>
<td>68/74 (92%)*</td>
<td>93/128 (73%)*</td>
</tr>
<tr>
<td>natives</td>
<td>94/127 (74%)†</td>
<td>45/49 (92%)*; ‡</td>
<td>49/78 (63%)*; †; ‡</td>
</tr>
<tr>
<td>immigrants</td>
<td>67/75 (89%)†</td>
<td>23/25 (92%)</td>
<td>44/50 (88%)†</td>
</tr>
<tr>
<td>metronidazole resistance</td>
<td>57/199 (29%)</td>
<td>16/74 (22%)</td>
<td>41/125 (33%)</td>
</tr>
<tr>
<td>natives</td>
<td>34/124 (27%)</td>
<td>8/47 (17%)</td>
<td>26/77 (34%)</td>
</tr>
<tr>
<td>immigrants</td>
<td>23/75 (31%)</td>
<td>8/27 (30%)</td>
<td>15/48 (31%)</td>
</tr>
<tr>
<td>clarithromycin resistance</td>
<td>1/199 (1%)</td>
<td>1/74 (1%)</td>
<td>0/125 (0%)</td>
</tr>
</tbody>
</table>

* p<0.05 , † p<0.05 , ‡ p<0.05 , † p<0.05 , † p<0.05

Of *H. pylori* isolates of 199 patients, 57 (29%, 95%CI:22.4-34.9) and 1 (1%) were resistant to MTZ and Cla, respectively (table 1). The isolates of 8 patients could not be assessed for susceptibility to MTZ and Cla. The prevalence of MTZ resistant *H. pylori* infection was not significantly different between natives and immigrants.

**H. pylori eradication rates**

OMC7 was given to 90 patients (25 PUD and 65 NUD). Seventy-eight patients underwent follow-up endoscopy and 5 patients received a $^{13}$C Urea Breath Test. Seven patients refused follow-up, either by endoscopy or by $^{13}$C Urea Breath Test. All seven took complete eradication treatment, without having serious side effects.

Of 25 PUD patients randomised to OMC7 therapy, 92% (23/25, 95%CI: 85.7-98.1) were infected with CagA+ *H. pylori*, whereas of the 65 NUD patients 67% (42/63, 95%CI:53.7-78.0) were colonised with CagA+ *H. pylori* (p<0.002).

Overall, intention to treat-eradication rate (ITT) was 88 % (79/90) and per protocol-
eradication rate (PP) was 95% (79/83) (table 2). Eradication rates between patients with PUD and patients with NUD were not different (ns).

Table 2. Eradication efficacy of 7-days course of twice daily omeprazole 20 mg, metronidazole 400 mg, clarithromycin 250 mg

<table>
<thead>
<tr>
<th>Patients</th>
<th>ALL n=90</th>
<th>PUD n=25</th>
<th>NUD n=65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to treat analysis</td>
<td>79/90 (88%)</td>
<td>23/25 (92%)</td>
<td>56/65 (86%)</td>
</tr>
<tr>
<td>95% confidence interval(%)</td>
<td>81.0-94.5</td>
<td>74.0-99.0</td>
<td>77.8-94.6</td>
</tr>
<tr>
<td>Per protocol analysis</td>
<td>79/83 (95%)</td>
<td>23/23 (100%)</td>
<td>56/60 (93%)</td>
</tr>
<tr>
<td>95% confidence interval(%)</td>
<td>88.1-98.7</td>
<td>85.2-100.0</td>
<td>83.8-98.2</td>
</tr>
</tbody>
</table>

PUD Peptic ulcer disease
NUD Non ulcer dyspepsia

No difference was observed in eradication rates in patients with anti-CagA antibodies and patients without anti-CagA antibodies in their sera (table 3)(ns). Patients with eradication failure (n=4) were born in the Netherlands (n=2), Surinam (n=1) and Turkey (n=1).

Table 3. Correlation between CagA status and eradication efficacy

<table>
<thead>
<tr>
<th>Patients</th>
<th>ALL</th>
<th>PUD</th>
<th>NUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>analysis</td>
<td>CagA+</td>
<td>CagA-</td>
<td>CagA+</td>
</tr>
<tr>
<td>ITT</td>
<td>63/73 (86%)</td>
<td>14/15 (93%)</td>
<td>21/23 (91%)</td>
</tr>
<tr>
<td>PP</td>
<td>63/67 (94%)</td>
<td>14/14 (100%)</td>
<td>21/21 (100%)</td>
</tr>
</tbody>
</table>

PUD Peptic ulcer disease
NUD Non ulcer dyspepsia
ITT Intention to treat
PP Per protocol

74
Eradication rates were not different between patients colonised with MTZ resistant *H. pylori* and MTZ susceptible *H. pylori* (table 4).

Table 4. Correlation between metronidazole susceptibility and eradication efficacy

<table>
<thead>
<tr>
<th>Patients</th>
<th>ALL</th>
<th>PUD</th>
<th>NUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>analysis</td>
<td>MTZ-S</td>
<td>MTZ-R</td>
<td>MTZ-S</td>
</tr>
<tr>
<td>ITT</td>
<td>62/69 (90%)</td>
<td>16/19 (84%)</td>
<td>22/24 (97%)</td>
</tr>
<tr>
<td>PP</td>
<td>62/65 (95%)</td>
<td>16/16 (100%)</td>
<td>22/22 (100%)</td>
</tr>
</tbody>
</table>

MTZ-S metronidazole susceptible; MTZ-R metronidazole resistant
PUD peptic ulcer disease; NUD non ulcer disease
ITT intention to treat; PP per protocol

All four patients with eradication failure were CagA+ and three out of four were MTZ-S (one not known) before eradication therapy. At follow-up endoscopy in the three patients with CagA+/MTZ-S *H. pylori* MTZ and Cla susceptibility were assessed: MTZ-R/Cla-S (n=1), MTZ-R/Cla-R (n=1) and MTZ-S/Cla-S (n=1).

Out of 90 patients, 88 complied with their dose regimen. Two patients with NUD complained of rash and itching and discontinued the therapy at day four. One other patient with PUD complained of stomatitis and glossitis but was able to continue the therapy. All three patients were *H. pylori* negative at follow-up endoscopy.

**Discussion**

In primary care a subset of patients with persisting dyspepsia may benefit of an eradication therapy for *H. pylori* infection. CagA+ *H. pylori* may be a potential non-invasive discriminative factor for predicting PUD. In our study population the overall prevalence of CagA+ *H. pylori* was 80%. We observed a higher prevalence of CagA+ *H. pylori* among PUD patients (92%) as compared to NUD patients (63%), which has been observed also by others. Furthermore, we showed in post-hoc subgroup analysis that it is of importance to consider the patients’ origin when using CagA status. Our study results indicate that the CagA status is not predictive for PUD in patients born in developing countries and therefore should not be seen as a universal virulence marker of PUD. These results are in accordance with studies showing equally high prevalence of infection with CagA+ *H. pylori* in PUD and NUD patients in Asian countries. However, our results are contradictory to those of Cover
and colleagues. They found that the prevalence of CagA+ *H. pylori* was lower among 16 Moroccan patients (31%) than among 57 Belgian patients (74%). The method used in our study detects specifically anti-CagA antibodies in a blot assay. Due to the high prevalence of CagA+ *H. pylori*, overall and in subgroups, the relevance of CagA status as a potential non invasive discriminative factor for PUD and NUD is limited in primary care.

Only a few studies have attempted to measure the influence of the CagA status on the efficacy of a commonly used therapy, consisting of omeprazole, MTZ and Cla. In intention to treat (ITT) analysis the OMC7 regimen revealed a high *H. pylori* eradication rate of 88%. In per protocol (PP) analysis a 95% eradication rate was achieved. This result is in concordance with intention to treat eradication results of other studies with low dosage 1-week treatments (twice daily omeprazole 20 mg, MTZ 400/500 mg, Cla 250 mg). Eradication rates in mixed population of patients with PUD and NUD are lower compared to studies with PUD patients alone. It has been assumed that CagA+ *H. pylori* being associated with PUD, may be more susceptible to antimicrobials. It may be that CagA+ *H. pylori* grow faster thereby being more susceptible to bactericidal antimicrobials in vivo. However, in vitro experiments do not support this assumption. In our study, in which CagA+ *H. pylori* is more common in PUD than in NUD, we did not observe any relation between the presence of PUD or the CagA status on the efficacy of the OMC therapy. It is even remarkable that the eradication failures were observed in patients with the combination of CagA+/MTZ-S strains and not in patients with the CagA-/MTZ-R strains as expected. This contradicts the observation that CagA+ strains seem to be more easily eradicated than CagA- strains.

Resistance of *H. pylori* to MTZ or to Cla, and poor compliance are often mentioned as important bias factors for impaired success rates of *H. pylori* eradication therapies. The overall prevalence of MTZ resistant *H. pylori* was 29%, which is in line with the 35% previously reported for the same region of the Netherlands. The prevalence of primary Cla resistant *H. pylori* (<1%) was negligible. The eradication rates were identical in patients with MTZ resistant *H. pylori* as compared to those patients infected with MTZ susceptible *H. pylori*. This is in concordance with those earlier reports, but contrasts with others. Reasons for the inconsistent reports on treatment response are unclear, but may be explained by the variation of susceptibility testing, MIC cut-off values, dosage or duration of therapy, compliance, or difference in patient cohorts.

One of the drawbacks of OMC treatments is the development of secondary resistance, which may occur both for MTZ and Cla. However, in about 70 patients infected with *H. pylori* isolates susceptible to MTZ and Cla prior to treatment, MTZ resistant *H. pylori* were isolated from the biopsy specimen of only two patients after treatment. In addition, Cla resistant *H. pylori* was cultured from the biopsy specimen of only one patient after treatment.
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In conclusion, in our population of chronic dyspeptic patients from primary care CagA+ H. pylori is so common that it has no value in predicting PUD. The anti-Helicobacter therapy in this study was not affected by clinical manifestations, CagA status or MTZ-R. We hypothesise that the high eradication rates in this study are due to the high compliance. This might be the result of the attention paid to health education, instruction of the patients and the low number of serious adverse events caused by the treatments as reported by the patients.

Acknowledgements
The serum CagA test was provided by DPC Biermann (Germany).

References
Chapter 5


