1. INTRODUCTION

Helicobacter pylori (H. pylori) is the most successful human pathogen infecting an estimated 50% of the global population. It is a common and potentiallycurable cause of dyspepsia and peptic ulcer disease and is also associated with mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer. In more than 20 years, researchers dealing with the eradication of this pathogen have been unable to find the ideal protocol, because the generally accepted minimum success rate of treatment regimens for H. pylori eradication is 80% (1, 2).

Standard first-line therapy consists of a proton pump inhibitor (PPI) plus clarithromycin and amoxicillin or metronidazole and achieves successful eradication in up to 80% of patients (3-6). During the past decade, an alarming decrease in eradication rates has been observed, especially in some Mediterranean regions (3, 4). However, the most recent data show that this combination has lost some efficacy and often allows the cure of only a maximum of 70% of the patients, which is less than the 80% rate aimed for at the beginning and far below what should be expected for an infectious disease (5). In fact the percentage of eradication of H. pylori with triple therapy in Kosovo ranges from 68 up to 71% (6).

There are several explanations for the decrease in efficacy of the standard triple therapy: compliance, high gastric acidity, high bacterial load, type of strains, but by far the most important is the increase in H pylori resistance to clarithromycin (2).

Fluoroquinolones have in vitro activity against H. pylori (7). A recent in vitro study also showed a synergistic effect of quinolone antimicrobial agents and PPIs on strains of H. pylori (8). Levofloxacin is quickly and almost completely absorbed after oral administration with bioavailability of 100% and a good distribution in tissues and fluids. It has a half-life of 9-16 h with a predominant renal excretion and may be administered in a single daily dose with limited drug interactions and low incidence of side effects (9, 10).

Recently, some studies have evaluated the efficacy of new fluoroquinolones, such as levofloxacin, that could prove to be a valid alternative to standard antibiotics as first-line therapies (11-19).

2. GOALS

The goal of this study was to compare the efficacy of 7 and 10-day triple therapy including omeprazole, levofloxacin and amoxicillin for H. pylori eradication as a first-line therapy.

3. METHODS

This prospective controlled randomized open-label clinical trial is designed to determine the eradication rate of 7 and 10-day omeprazole, levofloxacin and amoxicillin regimens for...
adults infected with H. pylori in Clinical University Centre of Kosovo in Prishtina during September 2010 and September 2012. One hundred and five patients with dyspeptic complaints or melena, and H. pylori positive were enrolled in this study.

Exclusion criteria included: ingestion of antibiotics, H2 receptor antagonists or PPI within the prior 4 weeks; patients with allergic history to the medications used; patients with previous gastric surgery; the coexistence of serious concomitant illness and pregnant women.

Patients demonstrating a positive histology, rapid urease test or positive H. pylori stool antigen were randomly separated into two groups to receive treatment as either 7 days (Group 1) or 10 days (Group 2). Treatment protocol was omeprazole (20 mg b.i.d.), levofloxacin (500 mg o.i.d.) and amoxicilline (1g b.i.d.). Compliance was questioned and the patients were actively inter-viewed about side effects. Peptic ulcer and non-ulcer dyspepsia were diagnosed patholo-gies on endoscopic examination. Patients with erosions and ulcers are rec-ognized as peptic ulcer while others accepted as non-ulcer dyspepsia. The earliest tests to confirm H. pylori eradication were performed at the 4th week. Eradication was confirmed by negative histological analyses, rapid urease tests and negative H. pylori stool antigen.

Data was evaluated by the Statistical Package for the Social Sciences (SPSS) 17.0 computer program. Statistical analyses were carried out by T tests and chi-square tests. P values less than 0.05 were significant.

4. RESULTS

One hundred and five patients were included in this study, 16, 2% with non-ulcer dyspepsia and 83, 8% with peptic ulcer disease. Mild adverse effects were reported by 5 patients (5, 25%). The most frequent complaint was nau-sea reported by 3 patients. Two patients were with diarrhea. No severe side ef-fects were reported. Fifty eight of them (55, 2%) were treated for one week, while 47(44, 8%) were treated for 10 days with omeprazole 20 mg b.i.d., levofloxacin 500 mg once a day and amoxicilline 1 g b.i.d. The two groups were similar with respect to sex and age distribution. There was no difference between two groups due to peptic ulcer disease and non-ulcer dyspepsia. All of 105 patients completed the study. Eradication rates were 86, 2% and 93, 6% in Group 1 and 2, respectively, and the difference was non-significant (86,2% vs. 93,6%, p=0,218) (Table 1).

5. DISCUSSION

Eradicating H. pylori is the most im-portant aspect of managing H. pylori-related gastrointestinal diseases. Le-vofloxacin could be used as an alternative agent for clarithromycin in either a standard triple, quadruple, or sequential regimens. The use of levofloxacin in first-line therapy has also been sur-veyed. The eradication rates of levofloxacin based triple therapy ranged from 72% to 96% (19).

However, the number of studies evaluating a combination of levofloxa-cin and amoxicilline (together with an antisecretory drug ) as first-line regi-men has been very small, and the number of patients included in each of the studies very limited (11-19).

The first study on a levofloxacin-containing triple therapy in H. pylori first-line therapy by Cammarota and colleagues showed more promising re-sults. The first prospective study with 100 patients compared two different levofloxacin-containing triple thera-pies together with rabeprazole and ei-ther amoxicilline or tinidazole. The dos-age of levofloxacin was 500 mg once a day. Both groups achieved high eradication rates with 92% and 90% in ITT analysis (12).

Two years later, the same group pub-lished a study comparing a triple ther-a-py consisting of levofloxacin, amoxicil-line, and rabeprazole for 7 days with a dual therapy consisting of levofloxacin and rabeprazole for 5, 7, or 10 days. Ac-cording to their preliminary findings, an eradication rate of 90% was reached for the triple therapy, while the dual therapies did not achieve acceptable eradication rates (50-70%), irrespective of the therapy extension (13).

This study was followed by a large randomized trial with 300 patients who were treated with either a standard therapy, consisting of a PPI, clarithro-mycin, metronidazole, or amoxicil-line, or a levofloxacin-containing triple therapy, this time combined with clarithromycin. Again, a high eradication rate of 87% in the levofloxacin-containing therapy was achieved, significantly higher than the standard regimens with eradication rates of 72% and 75 % (15).

Another Italian group could not achieve similar therapy containing le-vofloxacin, azithromycin, and a PPI with a standard triple therapy with amoxicilline, clarithromycin, and a PPI. Here, both regimens lead to eradication rates of 65% in ITT analysis, whereas the tolerability was significantly higher for the levofloxacin-containing ther-apy (21).

A study from Germany randomized 61 patients to either levofloxacin, amox-icilline, and esomeprazole or a standard triple therapy. Levofloxacin was prescribed in a higher dosage of 2x500 mg. The eradication rate was 87% after levofloxacin triple therapy and 84% following standard triple therapy (11).

An Italian study with 130 patients compared a triple therapy containing levofloxacin (2x250 mg) and amoxicilline with standard triple therapy containing clarithromycin and amoxicilline. By ITT analysis, eradication rates of 91% for the levofloxacin triple regimen and 77% for the standard therapy were achieved. Unfortunately, no spec-ifications about the local resistance sit-uation were applied (22).

In 2007 and 2009 Gisbert and colleagues from Spain published two pro-ective uncontrolled stu-dies with 64 and 75 patients, respectively, evaluating the combination of levofloxacin 2x500 mg and amoxicilline together with ran-nitidine bismuth citrate or a PPI for 10

<table>
<thead>
<tr>
<th>Patients (nr, %)</th>
<th>Group I (7 day )</th>
<th>Group II ( 10 day )</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ±SD</td>
<td>43,326±15,54</td>
<td>37,72±13,45</td>
<td>0,163</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>29/29</td>
<td>17/30</td>
<td>0,156</td>
</tr>
<tr>
<td>Side effects</td>
<td>3 (5, 17%)</td>
<td>2 (4, 54%)</td>
<td>0,64</td>
</tr>
<tr>
<td>Eradication rate</td>
<td>50 (86, 2%)</td>
<td>44 (93, 6%)</td>
<td>0,218</td>
</tr>
</tbody>
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Table 1. Demographic characteristics and eradication rate of our patients.
days. Eradication rates in both studies were similar at 84% and 83%. Both combinations were tolerated well. Based on a previous study in the same geographical area, the authors assumed for this patient population a low resistance rate to quinolones of about 6% (14, 23).

In a recently published study, the same group compared two triple therapies containing levofloxacin or clarithromycin with another two sequential regimens also containing levofloxacin or clarithromycin. The standard regimen with a low ITT eradication rate of 64% was inferior to the levofloxacin-containing triple therapy as well as to both sequential regimens, most likely due to a high resistance rate to clarithromycin and metronidazole in this population. Unfortunately, no pretreatment susceptibility testing was available. The eradication rate for the combination of levofloxacin, amoxicillin, and omeprazole for 10 days was reported to be 83%, just as in the sequential regimen omeprazole, amoxicillin for 5 days, followed by omeprazole, levofloxacin, and metronidazole for another 5 days (23).

A prospective study with 123 patients from The Netherlands, treating in first, second and third-line, achieved very high eradication rates of 96% and 93% for levofloxacin-containing (2x500 mg) triple therapies together with amoxicillin or clarithromycin in the first-line population (16).

In our study, we found that the eradication rate of patients receiving 7-day triple therapy including omeprazole, levofloxacin and amoxicillin was 86%, whereas this rate was 93%, 6% in patients receiving the same protocol for 10 days, and the difference between two groups was non-significant (86.2% vs. 93.6%, p = 0.218) (Table 1). Overall in our study adverse effects were reported by 5, 25% of the patients, but these were most often mild.

A major drawback of the present study is the lack of pre-treatment susceptibility testing to levofloxacin and the small number of patients in the study groups.

6. CONCLUSION

Triple therapy with omeprazole, levofloxacin and amoxicillin is very effective and safe for H. pylori eradication in Kosovo. This new combination represents an alternative to clarithromycin-based therapy, as it meets the criteria set for regimens used as primary H. pylori treatment: effectiveness, simplicity and safety.

REFERENCES