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A randomized openly comparative study between rifaximin suspension versus rifaximin pills for the eradication of Helicobacter pylori

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Abstract. – ***Background:*** **It has been recently shown that Rifaximin, although given as a suspension, plus omeprazole, may be a promising antibiotic against Helicobacter pylori (H pylori) and worthy of further study.**

Aim: **We have therefore evaluated Rifaximin suspension versus Rifaximin pills, in a randomly openly allocated fashion study, in H pylori positive patients.**

Methods: **Twenty patients with upper gastrointestinal symptoms (M/F: 13/7, age range 28-68; mean 49.6 yrs) were found to have H. pylori associated gastritis. They were allocated in an open randomized study to two different treatment groups for two weeks: (A) Rifaximin suspension 1800 mg three times a day plus Omeprazole 20 mg twice a day (n=10), (B): Rifaximin pills 1800 mg three times a day plus Omeprazole twice a day (n=10). Symptoms such as pirosis, bloating, epigastric pain and nausea were recorded by diary card and were evaluated before and four weeks after stopping treatment. Patients were assessed by endoscopy, histology and urease testing at entry and four weeks after stopping treatments. All the twenty patients were available four weeks after stopping treatment.**

Results: **A statistically significant improvement of the symptoms were found overall after Rifaximin treatments for pirosis, bloating, epigastric pain ($p<0.001$ respectively). A significant difference in the symptom's score at the end of the two treatments were recorded between the two groups for bloating alone ($p<0.070$).**

A different and major fall in the neutrophils, between the two treatments was observed with Rifaximin pills compared to Rifaximin suspension. The same observation was obtained according to the intensity of H. pylori reaching an eradication rate of 40% and 60% for Rifaximin suspension versus Rifaximin pills plus omeprazole respectively.

In conclusion, these data suggest that Rifaximin pills may be an effective antibiotic against H pylori and worthy of further study.

Key Words:
Rifaximin, Helicobacter pylori.

Introduction

Helicobacter pylori (H pylori) causes active chronic gastritis, is strongly associated with duodenal ulcer and is considered to be an important risk factor for gastric cancer[1-3]. We now recognize that H pylori and NSAIDs are the two primary causes of ulcer disease; and it has been shown that eradication of H pylori in patients with ulcers results in recurrence rates of 0 to 10%[4].

Triple therapy has been advocated as a treatment of choice of H pylori infected patients with eradication rate up to 96% of patients treated but does have considerable side effects[5]. Poor compliance with treatment because of side effects, frequent dosing, and the lenght of treatment is also a factor[5]. Simpler and better tolerated regimens are urgently needed. Omeprazole, a H^+/K^+ ATPase inhibitor, has been proposed as a suitable adjunct to H. pylori treatment regimens for several reasons. It seems to suppress H pylori directly[6-7] and to increase the antibacterial effectiveness of some antibiotics by increasing the gastric pH towards their negative logarithms of the acidic dissociation constant. Rifaximin is a new antibiotic belonging to the rifampicin family. It is not absorbed from the gastroenteric mucosa and for this reason it

persists longer and with higher levels in the lumen of the gastroenteric tract minimising the risk of systemic side effects. It has been already assessed its in-vitro activity against 40 strains of H pylori which have shown that Rifaximin has a MIC50 of 4 mcg/ml and a MIC90 of 8 incg/ml[8]. It has also been shown the promising efficacy of Rifaximin suspension plus omeprazole in the eradicating H pylori positive patients[9]. This encouraging results with Rifaximin suspension (the patients were supposed to have 1800 mg of suspension three times a day i.e.; 14 suspension bottles for all the treatment period) lead us to a convintion that Rifaximin pills could lead a higher eradication rate mainly because of the better compliance.

The aim of this study was to evaluate the efficacy and the tolerability of Rifaximin suspension versus Rifaximin pills plus Omeprazole in H. pylori positive patients.

Methods

Patients referred for endoscopy because of upper gastrointestinal symptoms were enrolled into the study if they satisfied the following inclusion criteria:

1. A positive biopsy urease test;
2. Bacteria seen by Giemsa staining of a histology section;
3. Aged over 18.

All partecipants gave their informed consent to the study. Patients were excluded for the following reasons:

1. A history of gastric surgery,
2. Gastric carcinoma;
3. Concurrent disease severe enough to complicate the evaluation of the study drug, eg significant liver or kidney disease, severe cardiac or pulmonary disease, suspected or confirmed malignancy;
4. A contra-indication to study drug eg known or suspected allergy, pregnancy, breast feeding, treatment with sucralfate, warfarin, H_2 receptor, or antimicrobial agents within 4 weeks prior to the study.

After baseline gastroscopy, by "blind" endoscopists, with gastric mucosal biopsies for histologic examination and urease test, patients were assigned to one of the different schedules listed under medications. Symptoms as pirosis, bloating, epigastric pain, nausea were recorded by daily card and were evaluated before and 4 weeks after stopping treatments, by a masked independent investigator. The seventy of the above symptoms was scored as 0 = absent, 1 = mild (symptoms present but not influencing the usual activities), 2 = moderate (symptoms diverting from but not urging modification from usual activities), 3 = severe (symptoms severe enough to require modification of usual activity and/or bed rest)[10]. A follow-up endoscopy, with biopsies were performed 4 weeks after stopping treatment. A negative urease test and absence of organism defined eradication of H pylori by histology 4 weeks post-therapy. The study was approved by the Ethical Committee each of the two partecipating centers, and each patient provided written informed consent.

Medications

The present study involved two Italian centres; 20 consecutive patients were therefore enrolled and were allocated, in an open randomized fashion study, to receive: Rifaximin 1800 mg suspension three times a day (before breakfast, lunch, and dinner) plus Omeprazole 20 mg twice a day versus Rifaximin 1800 mg pills three times a day plus Omeprazole 20 mg twice a day.

Study compliance was assessed by an examiner masked as to treatment group by returned suspension or pill count. According to previous report on anti H pylori regimens[11] an intake of >60% of medication was considered a reliable indicator of accettable compliance.

Endoscopic Biopsies

Three antral biopsy were taken at each endoscopy: from the greater and lesser curvature within 2-5 cm of the pylorus. The first specimen was used to test the urease activity (CP-Test)[12] and the remaining two specimens were placed in 10% buffered formalin for subsequent histologic examination. From each sample one slide was stained with Hematoxylin and Esosin and one with Giem-

sa stain.

Histological Examinations of Biopsies

All biopsy specimens were reviewed by one pathologist who was masked to the treatment protocol of the patients. In each biopsy specimen, the number of neutrophils was graded on a semi-quantitative scale as follows: 0 = complete absence; 1 = rare, scattered neutrophils in the lamina propria; 2 = few scattered neutrophils also within the epithelium; 3 = moderate/large number of neutrophils. The monuclear cells was graded on a similar scale, with the differences that 0 indicated the presence of normal population of lymphocytes and plasma cells in the lamina propria and a score of 3 indicated complete obliteration of the lamina propria by monuclear cells. The glandular atrophy, intestinal metaplasia (1 = complete, 2 = incomplete, 3 = colonic or incomplete closely linked to the carcinoma) and dysplasia has been recorded. The intensity of H pylori infection was made on Giemsa stained slides. This scale was graded as follows: 0 = no demonstrable organisms; 1 = less than 15 H pylori per slide; 2 = one to 20 H pylori per high power field; 3 = 21 -> 100 H pylori per high power field[13].

Results

Twenty patients with upper gastrointestinal symptoms (M/F: 13/7, age range 28-68; mean 49.6 yrs) were found to have H pylori associated gastritis and were allocated to the two different treatment groups. The endoscopic findings were: macroscopically antral gastritis 7 (35%); antral erosions 4 (20%), duodenal ulcer 8 (40%) and gastric ulcer 1[5].

Histologically active on chronic gastritis was present in 18 patients in the remaining 2 patients a chronic gastritis was present. Neutrophils, graded on a semi-quantitative scale, were as follows: 11 scale 1; 7 scale 2; 2 scale 3. The monuclear cells, graded on a similar scale were: 1 scale 1, 7 scale 2, 1 scale 3. Glandular atrophy was present in 4 patients only (2 mild, 1 moderate and 1 severe), intestinal metaplasia in 3 (type I: 1, type II: 1, and type III: 1) and mild dysplasia in none.

The intensity of H pylori infection, made on Giemsa stained slides was as follows: 11 intensity 1; 6 intensity 2 and 3 intensity 3. At the entry no significant differences were recorded between the two allocated treatment's group. Treatment was carried out for 14 consecutive days.

Follow-up was performed 30 days after stopping the treatment.

After Treatment

All the twenty patients were available at the follow-up appointment and all the patients were able to assume >60% of drugs. Table I shows the eradication rate of different regimens used.

Table II shows the overall symptoms score before and after treatment. Overall a significant difference in the symptom's score at the end of the treatments were recorded for pirosis, bloating and epigastric pain ($p<0.00$ 1 respectively).

Table III shows the symptoms score before and after treatment between the two different regimens used. A significant difference in the symptom's score at the end of the two treatments were recorded between the two groups for bloating alone ($p<0.070$).

Histologically active on chronic gastritis was still present in 4 out of 20 follow up available patients, in the remaining 16 patients a chronic gastritis was present. A fall in the neutrophils was observed: from 11 to 5 for

Table I. Demography of enrolled patients and eradication rate different regimens used.

Therapy	Patients n.	M/F	Age range	Mean	Eradication rate	p value
R susp + O	10	5/5	31/68	53.4	40	0.33 (NS)
R pills + O	10	8/2	28/62	45.8	60	

R susp + O = Rifaximin suspension plus Omeprazole.
R pills + O = Rifaximin pills plus Omeprazole.

Table II. Number of patients complaining of each symptoms and overall symptoms score before and after (20 pts evaluated at follow up) therapy.

	Before Tx				After Tx			p value
	Patients n°	Symptoms score I	II	III	Patients n°	Symptoms score I	II	III	
Pirosis	20/20	6	8	6	5/20	2	3		0.001
Bloating	18/20	7	9	2	5/20	2	3	-	0.001
Epigastric pain	18/20	6	1	10	4/20	3	1	-	0.001
Nausea	14/20	7	7	-	9/20	2	7	-	0.01

I = mild symptoms (symptoms present but not influencing the usual activities).
II = moderate symptoms (symptoms diverting from but not urging modification from usual activities).
III = severe symptoms (symptoms severe enough to require modification of usual acitivity and/or bed rest).

scale 1; from 7 to 2 for scale 2; from 2 to 0 for scale 3. No significant variation in the monuclear cells was observed. A fall in the intensity of H pylori was recorded: from 11 to 8 intensity 1, from 6 to 2 intensity 2; and from 3 to none for intensity 3 (Table IV). None of the patients enrolled was withdraw from the study due to adverse events.

Discussion

This new combination of the powerful acid inhibitor omeprazole and an antibiotic (dual therapy) has both theoretical and practical advantages over standard triple therapy for eradicating H pylori. It is a logical, rational first line "curative" treatment of H pylori positive patients with excellent compliance because it is well tolerated and uses less than half the tablets of two weeks triple therapy.

A meta-analysis of 27 studies has recently been reported and shown eradication rates (averaged) of 18.6% (monotherapy), 48.2% (dual therapy) and 82.3% (triple therapy). Triple therapy with bismuth, metronidazole and tetracycline gave the highest eradication rates (94.1%) compared to 73.1% for bismuth, metronidazole and amoxycillin[14].

In the present study we have assessed the H pylori eradication activity of a new ri-

Table III. Number of patients complaining of each symptoms and overall symptoms score before and after different regimens used.

		R susp+O		R pills+O		p value
		before	after	before	after	
Pirosis	I	5	3	1	-	
	II	4	2	4	-	0.070 (NS)
	III	1	-	5	-	
Bloating	I	3	2	4	-	
	II	5	3	4	-	0.015
	III	1	-	1	-	
Epigastric pain	I	6	3	-	-	
	II	1	1	-	-	0.051 (NS)
	III	1	-	10	-	
Nausea	I	3	2	4	-	
	II	4	-	3	-	0.23 (NS)
	III	-	-	-	-	

I = mild symptoms (symptoms present but not influencing the usual activities).
II = moderate symptoms (symptoms diverting from but not urging modification from usual activities).
III = severe symptoms (symptoms severe enough to require modification of usual activity and/or bed rest).

Table IV. Histological grading score before and after the different regimens used.

		R susp+O		R pills+O	
		before	after	before	after
Neutrophils	1	6	4	5	1
	2	3	2	4	-
	3	1	-	1	-
Mononuclear cells	1	-	1	1	4
	2	1	-	6	3
	3	-	-	1	-
Glandular atrophy		4	-	-	-
Intestinal metaplasia	1	-	1	1	-
	2	1	-	-	-
	3	1	-	-	-
H pylori	1	6	4	5	4
	2	3	2	3	-
	3	1	-	2	-

Neutrophils: 1 = rare, scattered neutrophils in the lamina propria; 2= few scattered neutrophils also within the epithelium; 3 = moderate/large number of neutrophils.

Mononuclear cells: was graded on a similar scale, with the differences that 0 indicated the presence of normal population of lymphocytes and plasma cells in the lamina prorpia and a score of 3 indicated complete obliteration of the lamina propria by mononuclear cells.

Intestinal metaplasia: 1 = complete; 2 = incomplete; 3 = colonic or incomplete closely linked to the carcinoma.

H pylori infection: 1 = less than 15 H pylori per slide; 2 = one to 20 H pylori per high power field; 3 = 21 -> 100 H pylori per high power field.

fampicin antibiotic, Rifaximin, given as a suspension compared to a better compliance administration (pills) in association with omeprazole which is the drug most commonly used in H pylori eradication regimen. Omeprazole does not eradicate H pylori if given as monotherapy but if combined with antibiotics can achieve good eradication rates. A regimen of omeprazole for four weeks with bismuth plus tetracycline plus metronidazole for one week achieved a 95% eradication rate but only 4% if given alon[15]. Although several H pylori eradicating regimens have been recently approved by FDA for use in the United States the optimal treatment for H pylori associated disease is still being sought and therapeutic trials with different agents are being evaluated. Recently, guidelines for conducting therapeutic trials of H pylori anti-infective regimens have been published[16]. Lack of compliance with a multi drug regimen can lead to failure of therapy particularly if the patients suffer side effects from the antibiotics. A non-absorbable antibiotic may have particular advantage in this respect. Rifaximin is a non-absorbable antibiotic that we have assessed for its in-vitro activity against 40 strains of H pylori. Our previos results have shown that Rifaximin has an MIC50 of 4 mcg/ml and a MIC90 of 8 mcg/ml, the rate of development of spontaneous resistance was found to be as low as less than 1 in 10^8 for most of H pylori isolates tested in previous study[8] although resistance could be induced. Because the MIC of Rifaximin is comparable to other antibiotics used for the eradication of H pylori and because the drug is non-absorbable and therefore likely to achieve high concentrations in the gastro-enteric tract and not to produce systemic side effects, we assessed its use in the eradication of H pylori. We have shown that monotherapy with Rifaximin achieved an eradication rate of 37%[9], a substantially higher eradication rate than previously reported for singly antimicrobial therapy except for clarithromycin[17].

In the present study Rifaximin pills showed to have a higher eradication rate compared to Rifaximin suspension and this result is supported by the histological improvement as well as by the symptomatic response at this

latter treatment. The therapeutic arm including Rifaximin pills plus omeprazole achieved an eradication rate comparable to those previously reported with double therapy and could represent a base for further attempts to develop more efficacious Rifaximin based schedules.

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