Effect of Treatment of Helicobacter pylori Infection on Rosacea

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Objective: To evaluate the clearing and intensity of symptoms of rosacea 60 days after the treatment of Helicobacter pylori infection.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Setting: The dermatology section of a large multispecialty clinic in the North Central United States.

Participants: Men and women older than 25 years with active signs of rosacea who tested positive for H pylori with both the rapid whole blood test and the urea breath test.

Intervention: Treatment of H pylori infection with 14-day therapy using clarithromycin, 500 mg orally 3 times a day, and omeprazole, 40 mg orally once a day.

Main Outcome Variables: The extent and intensity of rosacea as measured by the number of papules and pustules and the extent and intensity of erythema and telangiectasia.

Results: Three hundred twenty patients presented with rosacea. For 50 patients, the results of a urea breath test were positive for H pylori, and 44 patients were enrolled in the study. Rosacea abated in almost all patients, but none were cured. Notably, lessening of rosacea for patients treated for H pylori was not significantly better than for the control cohort.

Conclusions: Rosacea abated in most participants in this study, whether they were in the treatment or the control cohort. There was no statistical difference when the results of active treatment were compared with those of placebo. Treating H pylori infection has no short-term beneficial effect on the symptoms of rosacea to support the suggested causal association between H pylori infection and rosacea.

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OSACEA is a common dermatologic problem that occurs in midlife in papulopustular or erythrotelangiectatic (or both) forms. It sometimes progresses to include rhinophyma, a benign disfiguring condition of the nose. Prevalence estimates, based on research done in Sweden, suggest that about 10% of adults have rosacea.

In the 1980s, the role of Helicobacter pylori in causing gastric ulcers was proposed to a largely skeptical medical profession. By 1994, 2 consensus conferences affirmed the role of H pylori in the pathogenesis of gastroduodenal ulceration and gastric cancer. Within 2 years, its role in urticaria, the Sjogren syndrome, and Henoch-Schönlein purpura was also suggested.

Investigators in several countries, including the United States, Italy, Russia, and Germany, have considered a role of the gastrointestinal tract in the origin of rosacea. We find speculation on associated gastrointestinal tract disease by Barber and Ryle in 1920 and lack of involvement of the gastrointestinal tract by Marks et al in 1967. By 1994, Rebora and colleagues in Italy suggested a causative association, reporting that of 31 patients with rosacea, 28 (90%) had gastroscopic evidence of H pylori, compared with a 50% prevalence in the general Italian population. In Ukraine, Abramovych in 1996 reported that of 160 patients with rosacea, 158 (98.8%) had endoscopic evidence of gastric disease, and 134 of those patients also had histological and urease breath test confirmation of H pylori infection. From Russia in 1996, Kolibasova et al evaluated 1 patient in whom rosacea cleared only at the time of H pylori eradication. In Germany in 1995, Jansen and Plewig reported a relationship between rosacea and H pylori. In the United States, one of the first reports on H pylori serologic findings in patients with rosacea was made by Schneider et al in 1992. More recently, in 1998, Sharma et al reported that only 12 (27%) of 45 patients with rosacea were seropositive for H pylori com-
PATIENTS AND METHODS

STUDY DESIGN

This study was a double-blind, randomized, placebo-controlled trial. Half of the patients were assigned to receive active medication, and the other half were assigned to receive a placebo. Screening and enrollment of candidates occurred between February 9, 1996, and June 3, 1997. All participants signed an institutional review board–approved informed consent document before entering the clinical trial. Patients were randomly assigned to groups receiving active treatment or placebo, and the treatment status was not disclosed to the investigators, coordinators, or patients throughout the study. Study medications were dispensed according to a randomized registry list provided by the project programmer.

SAMPLE POPULATION

Volunteers who responded to television and radio advertisements or invitation during a clinic visit were fully informed about the study and signed their understanding by signing a consent form before any testing was performed. After they were interviewed and tested for *H pylori* infection, the following criteria for inclusion were used: diagnosis by principal investigator of active rosacea involving the face, including erythema, papulopustules, or both; positive results on the rapid whole blood test (RWBT) (Helisal; Cortecs Diagnostics Ltd, London, England); positive results on a urea breath test (UBT) using glucose labeled with radioactive carbon UBT[13C] (Merelek UBT; Merelek Diagnostics, Inc, Houston, Tex); age older than 25 years; subject agreed to adhere to the medication regimen and required visits; and subject agreed not to use topical treatment of rosacea during the study. The following exclusion criteria were used: allergy to clarithromycin, omeprazole, or UBT[13C]; negative RWBT results; negative UBT results; pregnant or breast-feeding; antibiotic therapy within the past 2 months; and topical treatment of rosacea in past 3 weeks.

STATISTICAL POWER CONSIDERATIONS

The study was designed to detect a 2-fold or greater clearing rate for rosacea among patients cured of *H pylori* infection compared with those not treated. A total of 20 patients in the treatment group and 20 patients in the control group were needed to complete the study to detect this difference.

pared with 15 (35%) of 43 healthy controls. Another North American researcher found a higher prevalence of *H pylori* infection (12/52 [23%]) in patients with rosacea than in consecutive patients having endoscopy for gastrointestinal tract symptoms (30/133 [22.6%]).

There is no therapy that permanently cures rosacea. This study was designed to test the effect of *H pylori* on clinically active rosacea and to see if the cure of *H pylori* infection would bring a corresponding clearing of rosacea.

H *pylori* INFECTION EVALUATION

Patients were tested with the RWBT, which has a sensitivity of 91% and specificity of 94% for past or present *H pylori* infection. All tests were read by the same research nurse (J.L.B.).

The RWBT results were expected to remain positive for any patient having *H pylori* infection within the past 6 months, even if the infection was cured. For this reason, a positive UBT result was used to confirm an active *H pylori* infection. An increase of 2.4 parts per thousand in the ratio of [13C] oxygen to [12C] oxygen between the baseline specimen and a specimen obtained after dosing (125 mg of [13C] urea) was considered a positive UBT[13C] result. Sixty days after the treatment, at the final follow-up examination, the UBT[13C] was repeated to determine if the infection had been cleared, as suggested by Slomianski et al. The RWBT was not repeated because its results were not expected to revert within the trial period.

TREATMENT

Patients assigned to the active treatment group were given therapy consisting of clarithromycin, 500 mg orally 3 times a day, and omeprazole, 40 mg orally daily, for 14 days. At the time the study was planned, the reported cure rates for *H pylori* infection with this regimen ranged from 75% to 90% with good tolerance. The patients assigned to the placebo group similarly received 14 days of treatment with 2 formulations that resembled the active drugs.

DEMOGRAPHIC AND OUTCOME MEASURES

Demographic information was obtained at the time of enrollment. Outcome measurements were made at the beginning (day 0) and the end of the trial (day 60) by 1 experienced dermatologist (J.T.M.B) using the Duluth Rosacea Scoring Instrument.22

DATA MANAGEMENT AND ANALYSIS

Data were collected and edited by the clinical research coordinator (J.L.B.). The case report forms were reviewed and checked by several members of the research team. An electronic data entry system was written in a commercial database software package (Foxpro 2.6; Microsoft Corporation, Redmond, Wash), and the data from the forms were entered into an electronic format. A commercial statistical software package (SPSS Base System; SPSS, Inc, Chicago, Ill) was used for data analysis.

Values were calculated using the Fisher exact test, the Mann-Whitney or Wilcoxon rank sum test, or the χ2 test with the Pearson correlation coefficient; *P* ≤ 0.05 was considered significant.

RESULTS

COMPARABILITY OF TREATMENT GROUPS AT ENTRY

Of 320 patients with rosacea who were evaluated, 145 were seropositive for *H pylori*. Of these, 143 subjects were available to be tested using the UBT[13C]. Fifty patients...
had positive test results, 23 22 of whom were enrolled in each arm of the study, for a total of 44. Two patients from the active treatment cohort did not complete the study: one died of a myocardial infarction, and the other had incapacitating headaches when taking the active medication. The 42 subjects completing the study reported no significant difference between baseline and follow-up in both the active treatment and placebo groups (P = .00 and P = .02, respectively). The scores for erythema intensity demonstrated a significant difference between baseline and follow-up in both the active treatment and placebo groups (P = .00 and P = .00, respectively). For the number of pustules, a significant decrease was seen in both groups (P = .00 for both).

Table 3 shows that no significant difference was found at a P ≤ .05 level between the 2 groups at either baseline or follow-up. In Table 3, the patients who had clearing are separated from the treatment cohort. Even when those subjects cleared of H pylori (ie, the patients who became negative on the UBT[13C]) were compared with the control group, no significant difference was seen for any measure of rosacea at either the baseline or the end of the study. Except for the number of pustules, no statistically significant lessening of rosacea was observed that could be attributed to a cure of H pylori infection in this group of patients who had both H pylori infection and rosacea.

Because this was a randomized clinical trial, we expected comparable patients in both the treatment and control groups. This expectation was fulfilled, but several others were not. We expected that clearing H pylori infection would permanently clear or markedly decrease the rosacea 9,10,13 and this did not happen. We also expected that most of the patients who were seropositive for H pylori and who did not have antibiotic therapy would demonstrate an active infection on the UBT[13C].24 Instead, only 35% of the patients who were seropositive and who did not receive antibiotic therapy also had positive results on the UBT[13C].

For those with confirmed active H pylori infection who did not receive active treatment, we did not expect any spontaneous cures.25 At the end of the study, however, 10% (2/22) of our patients in the placebo-treated...
group no longer had positive results on the UBT[13C], which has 97% sensitivity.20 Because the natural history of rosacea includes swings in the extent of the signs and symptoms and remission is often seen, we expected to see some decreased severity of rosacea in the control group, but not to the same extent as in the treatment group.

The active treatment and placebo groups were similar before the intervention. Patients in both arms of the study had lessening of their rosacea after 60 days, as measured by the Duluth Rosacea Scoring Instrument (Figure). All the symptoms of rosacea showed some lessening during the trial. Both active treatment and placebo groups showed the largest degree of abatement of the symptoms of pustules and erythema, with only a small improvement for hue and no lessening at all of telangiectasia, which we expected to be slow in responding. Because the magnitude of improvement seen in both arms of the study is similar, the major improvement in rosacea appears to be due to the “placebo effect,” or “remembered wellness,” as described by Benson and Friedman.25 The placebo effect would be the portion of the improvement labeled A to B. The treatment effect is the difference between the treatment and control groups at follow-up (line C to D).

As described in the “Results” section (see the subsection “Response of Rosacea to Treatment”), the treatment cohort had some additional, but not significant, improvement on the total score compared with the control group. This treatment effect would be the difference between the treatment and control groups at follow-up (line C to D in the Figure). The treatment effect with this sample size is not significant ($P = .21$).

Whether evaluating all subjects in the treatment group or only those cleared of $H$ pylori by treatment (15 [75%] of 20 patients), we found no significant difference in the total score for rosacea compared with that in the placebo group at day 60.

During this trial, a significant measurable benefit was observed that was not caused by active treatment. In recent years, the placebo effect has not been the subject of many specific English-language articles about skin diseases.26 Our study seems to confirm that “remembered wellness” plays a beneficial role in the treatment of rosacea.

Of 20 patients who received active medication, 15 were cleared of $H$ pylori infection. Our cure rate was similar to that of others using this regimen.27 Also, 2 of our control patients apparently had spontaneous remission of $H$ pylori infection during the study. A possible explanation might include false-negative results on the final UBT, but the company performing the test (Meretek Diagnostics, Inc) systematically rechecked all records to make sure the results were correct.

The speculation of Rebora and Kolibasova and their colleagues10,13 on the relationship of $H$ pylori to rosacea is not supported by our research. Curing $H$ pylori infection does not clear rosacea within 60 days, and active

### Table 3. Between-Group Comparison of Effect of Treatment on Grade and Scale of Acne Rosacea*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 22)</th>
<th>Treatment (n = 22)</th>
<th>Cleared (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score, No., mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11.1</td>
<td>10.8</td>
<td>10.6</td>
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<tr>
<td>Follow-up</td>
<td>7.9</td>
<td>6.3</td>
<td>6.2</td>
<td>0.20</td>
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<tr>
<td>No. of pustules on face, mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>22.0</td>
<td>21.5</td>
<td>20.0</td>
<td>0.92</td>
</tr>
<tr>
<td>Follow-up</td>
<td>12.6</td>
<td>6.2</td>
<td>5.9</td>
<td>0.18</td>
</tr>
<tr>
<td>Hue, mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.4</td>
<td>6.1</td>
<td>6.1</td>
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<td>4.1</td>
<td>4.2</td>
<td>0.49</td>
</tr>
<tr>
<td>Erythema location‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forehead</td>
<td>11 (50)</td>
<td>11 (50)</td>
<td>8 (53)</td>
<td>0.59</td>
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<tr>
<td>Nose</td>
<td>19 (86)</td>
<td>18 (82)</td>
<td>13 (87)</td>
<td>0.97</td>
</tr>
<tr>
<td>Cheeks</td>
<td>21 (96)</td>
<td>18 (82)</td>
<td>11 (73)</td>
<td>0.21</td>
</tr>
<tr>
<td>Jaw</td>
<td>16 (73)</td>
<td>16 (73)</td>
<td>10 (67)</td>
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<tr>
<td>Erythema location‡</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Telangiectasia location‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forehead</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.91</td>
</tr>
<tr>
<td>Nose</td>
<td>7 (32)</td>
<td>6 (27)</td>
<td>5 (33)</td>
<td>0.23</td>
</tr>
<tr>
<td>Cheeks</td>
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<td>6 (27)</td>
<td>2 (13)</td>
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<td>Chin</td>
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<td>7 (47)</td>
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<tr>
<td>Chin</td>
<td>5 (23)</td>
<td>7 (32)</td>
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</tr>
<tr>
<td>Pustules on face, mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2 (9)</td>
<td>2 (9)</td>
<td>1 (7)</td>
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</tr>
<tr>
<td>Follow-up</td>
<td>1 (4)</td>
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<td>3 (20)</td>
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<tr>
<td>Baseline</td>
<td>7 (33)</td>
<td>7 (35)</td>
<td>7 (50)</td>
<td>0.18</td>
</tr>
<tr>
<td>Follow-up</td>
<td>5 (28)</td>
<td>7 (39)</td>
<td>6 (46)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

* Data are given as number (percentage) unless otherwise indicated. For the treatment group, 2 patients were not available at follow-up, so the data are for 20 patients. P values are of comparisons between control group and cleared group.

‡Covering more than 10% of skin.

§Pearson χ² test.
treatment does not appear to have a more significant effect on the severity of rosacea than that of the use of placebo. The early studies that reported “curing” rosacea by treating H pylori did not use a case-control design. This feature seems to be important, given the large placebo effect seen in our study.

Further clinical trials of the treatment of rosacea should take this large placebo effect into consideration and consider having a smaller additive treatment effect in their statistical power considerations. Future studies might consider using triple-drug therapy for rosacea for patients seropositive for H pylori who have active gastrointestinal tract disease and using longer follow-up periods of 4 to 6 months.

CONCLUSIONS

Less than half of the patients with rosacea (145 [45.3%] of 320) had serologic evidence of current or past H pylori infection using the RWBT. UBT [13C] evidence of a currently active infection was present in 16%. Although 15 (75%) of the 20 patients treated for H pylori infection were cured, the active treatment regimen used in this study did not add any statistically significant lessening of rosacea.

A significant improvement, attributed to a placebo effect, was noted during this trial. A larger sample might also have shown a small treatment effect, but it would probably be substantially less than the placebo effect.

Active H pylori infection is not a major determinant in the presence, severity, or extent of rosacea. Cur ing patients of H pylori infection did not clear their rosacea, and it apparently did not decrease the severity of rosacea.

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Astra Merck, Wayne, Pa, provided the major funding for the study as well as omeprazole (Prilosec) and matching placebos. Abbott Laboratories, North Chicago, Ill, supplied the clarithromycin (Biaxin). Cortecs Diagnostics Ltd, London, England, donated the Helisal Rapid Whole Blood Test. Meretek Diagnostics, Inc, Houston, Tex, donated the [13C] urea breath tests, which allowed us to avoid gastroscopy.

We thank Colleen Renier for developing the randomization list and her reviews of the results. Richard Krivava, RPh, managed the randomization, binding, and dispensing of study medications and placebos. Heidi Meyer typed drafts and Barbara Jablonski, the final paper. Sally Leoni kept appointments and records in order as the research assistant.

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REFERENCES