

A randomized trial comparing seven-day ranitidine bismuth citrate and clarithromycin dual therapy to seven-day omeprazole, clarithromycin and amoxicillin triple therapy for the eradication of *Helicobacter pylori*

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OBJECTIVE: To assess *Helicobacter pylori* eradication after one week dual ranitidine bismuth citrate-clarithromycin (RBC-C) or triple omeprazole, clarithromycin and amoxicillin (OCA) therapy.

METHODS: In this multicentre Canadian trial, *H pylori*-positive patients with functional dyspepsia or inactive peptic ulcer disease were randomized to open-label treatment with RBC-C (ranitidine bismuth citrate 400 mg plus clarithromycin 500 mg) or OCA (omeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1000 mg), given twice a day for seven days. Treatment allocation was randomly assigned. *H pylori* infection was confirmed by positive ¹³C-urea breath test (¹³C-UBT). *H pylori* status was reassessed by UBT at least four and 12 weeks after treatment (negative: $\delta^{13}\text{CO}_2$ below 3.5 per mil). Intention-to-treat (ITT) eradication rates were determined for all patients with confirmed *H pylori* infection. Per protocol (PP) rate was determined for all patients treated with at least two evaluable follow-up visits.

RESULTS: Three hundred five patients were included in the ITT and 222 in the PP analysis. The ITT eradication rates were 66% for RBC-C and 78% for OCA. The PP success rates were 84% for RBC-C and 96% for OCA. The difference for both ITT 12% (95% CI 2 to 22) and PP 12% (95% CI 4 to 19) were statistically significant, P=0.030 and P=0.007, respectively. Treatment was generally well tolerated.

CONCLUSION: The eradication rate for the seven-day dual RBC-C regimen was lower than that for OCA.

Key Words: Amoxicillin; Bismuth; *C difficile colitis*; Clarithromycin; Dyspepsia; Eradication; Functional dyspepsia; *Helicobacter pylori*; Omeprazole; Patient satisfaction; Peptic ulcer disease; Randomized clinical trial; Ranitidine bismuth citrate; Treatment; Treatment failure

Un essai randomisé comparant un traitement à double modalité de sept jours de citrate de bismuth de ranitidine à une trithérapie de sept jours d'oméprazole, de clarithromycine et d'amoxicilline pour éradiquer une infection *Helicobacter pylori*

OBJECTIF : Évaluer l'éradication d'une infection *Helicobacter pylori* après un traitement à double modalité d'une semaine de citrate de bismuth de ranitidine-clarithromycine (RBC-C) ou une trithérapie d'oméprazole, de clarithromycine et d'amoxicilline (OCA).

MÉTHODES : Au cours d'un essai multicentrique canadien, on a administré de façon aléatoire à des patients *H pylori*-positifs souffrant d'une dyspepsie fonctionnelle ou d'un ulcère peptique inactif un traitement avec étiquetage en clair de RBC-C (citrate de bismuth de ranitidine 400 mg plus clarithromycine 500 mg) ou d'OCA (oméprazole 20 mg, clarithromycine 500 mg et amoxicilline 1000 mg), deux fois par jour pendant sept jours. On a sélectionné les patients recevant le traitement au hasard. L'infection *H pylori* a été confirmée par une épreuve respiratoire à l'urée ¹³C (ERU-¹³C). On a réévalué l'état de l'infection *H pylori* à l'aide d'une ERU au moins quatre à 12 semaines après le traitement (négatif : $\delta^{13}\text{CO}_2$ sous 3,5 par mil). On a déterminé les taux d'éradication selon l'intention de traiter (ITT) chez tous les patients souffrant d'une infection *H pylori* confirmée. On a déterminé le taux par protocole (PP) chez tous les patients traités avec au moins deux visites de suivi évaluable.

RÉSULTATS : 305 patients faisaient partie de l'analyse ITT et 222 de l'analyse PP. Les taux d'éradication de l'analyse ITT s'établissaient à 66 % pour le traitement au RBC-C et à 78 % pour le traitement au OCA. Les taux de succès de l'analyse PP s'établissaient à 84 % pour le traitement au RBC-C et à 96% pour le traitement au OCA. L'écart tant pour l'analyse ITT 12 % (95 % CI 2 à 22) et l'analyse PP 12% (95 % CI 4 à 19) était statistiquement important, P=0,030 et P=0,007, respectivement. En général, les patients ont bien toléré le traitement.

CONCLUSION : Le taux d'éradication du traitement à double modalité de sept jours au RBC-C s'est avéré inférieur au OCA.

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There is increasing consensus that all patients known to be infected with *Helicobacter pylori* should be offered treatment (1,2). The target success rate for acceptable therapies to cure *Helicobacter* infection has been set at 80% or higher, based on intention-to-treat analysis of randomized controlled trials. Apart from high efficacy, treatments should be simple, well tolerated and safe. Ranitidine bismuth citrate (RBC), Pylorid, Glaxo Wellcome Inc, Canada) is the first approved drug specifically developed for the treatment of *H pylori* infection (3). Over the last five years the most successful treatments have been either triple therapy consisting of a proton pump inhibitor (PPI) and clarithromycin with either amoxicillin or metronidazole (PPI-CA or PPI-CM) or quadruple therapy consisting of a PPI with a bismuth compound, metronidazole and tetracycline (1,2). Dual therapy with RBC and clarithromycin (RBC-C) can achieve cure rates of *H pylori* infection in the range of 70% to 96% (4,5). However, this success is achieved with 14-day therapy while triple therapies are successful in seven days. The longer duration of RBC-C therapy makes it more expensive and less convenient. However, because the RBC-C regimen uses only two drugs, it is simpler and potentially better tolerated than triple therapies. One study showed that the duration of RBC-C therapy could be decreased to seven days without loss of efficacy (6).

The objective of the current study was to compare the efficacy and safety of seven-day dual therapy of RBC-C to seven-day triple therapy with omeprazole, clarithromycin and amoxicillin (OCA). Patient satisfaction with treatment was also assessed.

METHODS

This was a computer randomized open-label study carried out in 18 gastroenterology centres and one general practitioner/family practitioner centre across Canada. Patients suffering from chronic dyspepsia with or without proven previous peptic ulcer disease who underwent upper gastrointestinal endoscopy were eligible for the study if they were *H pylori* positive. Presence of *H pylori* was determined by a rapid urease test. Patients needed to have confirmation of infection with *H pylori* by a ¹³C-urea breath test (¹³C-UBT) to be enrolled in the study.

The following were the exclusion criteria: presence of an active duodenal or gastric ulcer observed on endoscopy, history of gastroesophageal reflux disease or endoscopic esophagitis that required ongoing treatment with acid suppressive therapy, renal insufficiency, serious comorbidity precluding participation in the study, or known allergy to any of the drugs used in the study. The use of antibiotics or bismuth-containing medications were not allowed in the four weeks before enrollment. The use of nonsteroidal anti-inflammatory drugs was not allowed in the study, but acetylsalicylic acid up to 325 mg a day could be taken. Patients who were taking acid suppressive therapy had to be off H₂-blockers or PPIs for at least four weeks before entry into the study. Patients were allowed to have up to one previous attempt at curing *H pylori* infection. The protocol was approved by the research ethics board of each participating centre. Informed written consent was obtained from each patient.

Treatments

Patients were randomized to receive either dual therapy with RBC-C (RBC 400 mg twice a day and clarithromycin 500 mg twice a day) or OCA triple therapy consisting of omeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1000 mg, given twice daily

for seven days. Assignment of treatments was randomized using tables of random numbers. Investigators and research personnel were blinded until treatment allocation was assigned. Once patients were assigned their treatment, the medications were provided in an unblinded fashion. Treatment started within 10 days of the endoscopy and ¹³C-UBT. Compliance was assessed by history and pill count of returned medication. A patient was considered compliant if the patient took 80% of all prescribed medications.

Assessment of *H pylori* status

At endoscopy, biopsies were taken from the antrum and the corpus, and tested by a rapid urease test for *H pylori* (CLOtest, Tri-Med Specialties Inc, USA). Positive results were confirmed by a positive ¹³C-UBT (PYLORITEST, Isodiagnostika Inc, Canada) before enrollment in the study. This test has previously been validated (7). The test was considered positive for *H pylori* if excess ¹³CO₂ per mil was 3.5 or higher. ¹³C-UBTs were performed at least four to six weeks and 12 to 14 weeks after the completion of the seven-day treatment.

Patients were considered negative for *H pylori* infection only if both follow-up ¹³C-UBTs were negative and evaluable.

Other assessments

Specific patient symptoms were assessed using a checklist. Patients were seen at the end of the treatment phase to document side effects. A patient satisfaction questionnaire measuring five treatment attributes was developed for this study by GlaxoSmithKline. The instrument has not been previously validated. It was completed by the patient before and after the one-week treatment period.

Study populations

The safety population was defined as any patient who was randomized and had received at least one dose of study medication. The intent-to-treat (ITT) population was defined as any randomized subject with confirmed *H pylori* infection (results of both UBT and CLOtest positive). Patients with discordant UBT results at the week 4 and week 12 follow-up were considered treatment failures in the ITT analysis. The per-protocol (PP) population was defined as subsets of the ITT population. Subjects in the PP population were required to be compliant with study medication, return for follow-up evaluations within the allotted timeframe and not receive concurrent medication known to interfere with the assessment of *H pylori* status, such as antibiotics.

For the PP analysis, patients were excluded if the week 4 or week 12 evaluation was missing or unavailable, occurred less than 26 days (week 4) or less than 77 days (Week 12) after the end of treatment, or was discordant with either the four- or 12-week evaluation.

Statistical methods

The primary outcome measure was the *H pylori* infection eradication rate in the ITT population. The proportion of patients with *H pylori* eradication in each treatment group was estimated along with the 95% CI for each proportion. The difference in the proportion of eradication success between treatment groups was reported, including the exact 95% CI for the difference in proportions (8). Treatment groups were also compared using a Fisher's Exact Test, appropriate for a two-by-two contingency table. An identical analysis strategy was adopted for the analysis of the eradication rates in the PP population, considered a secondary outcome measure in this study.

Another secondary outcome, patient satisfaction, was assessed by the patient before and after the one-week treatment period. The pretreatment questionnaire measured how important the attributes were in general on a five-point scale from "not at all important" to "extremely important". The post-treatment questionnaire measured how important the attributes were in relation to the randomized treatment regimen that they had just completed on a five-point scale from "very dissatisfied" to "very satisfied". Post-treatment responses were analyzed by collapsing the five-point scale into a binary outcome consisting of either "satisfied" (very satisfied or somewhat satisfied) or "not satisfied" (neutral or somewhat dissatisfied or very dissatisfied) and then compared using a χ^2 test for binary outcomes (9,10). The analysis was done initially based on all patients and then repeated based on the subset of patients who attached some importance (pretreatment) to the given attribute.

Sample size

Based on the assumption that the ITT eradication rates would be at least 85% (1,11,12), a sample size of 150 patients per treatment group was required to ensure that the width of the 95% CI for the difference in eradication rates would not exceed 16 percentage points.

RESULTS

Patients were enrolled from October 1998 until November 1999. Three hundred thirteen patients were enrolled. A summary of the disposition of patients in this study is provided in Table 1. Patient numbers in both groups were very similar. Treatment groups were similar with respect to demographics and baseline characteristics (Table 2).

The ITT population consisted of 305 patients and the PP population, 222 patients. The largest group of patients (N=56, 18% of randomized patients) excluded from the PP analysis were those with missing or discordant UBT results at week 4 and week 12 or those who had follow-up evaluations outside the target time windows (less than 26 days at week 4 or less than 77 days at week 12). Of these 56 patients, at least one follow-up ¹³C-UBT result was missing in 28 patients (8.9%). Both ¹³C-UBT results were missing in 10 patients and only one UBT was available in 18 patients. There were 15 patients (5% of randomized patients) who had discordant UBT results between their week 4 and week 12 follow-up evaluations. Following repeat tests for those patients with unevaluable UBT results, the number of patients with discordant results was reduced to eight. Patients with discordant results were considered to be treatment failures in the ITT analysis.

The *H pylori* eradication proportions according to the ITT and PP populations show that the OCA triple regimen was significantly better than RBC-C dual therapy in the ITT and PP groups' analysis (Table 3). The ITT difference between OCA and RBC-C was 12% (95% CI 2% to 22%, P=0.030). For the PP analysis, the difference was 12% (95% CI 4% to 19%, P=0.007). Twenty patients (6%) had received a prior attempt at eradication. The ITT eradication rates for these patients were 63% (five of eight) for OCA compared with 25% (three of 12) for RBC-C.

There was no significant difference in eradication rates between the two treatment groups in patients with a prior ulcer history (OCA 80% or 47 of 59, RBC-C 65% or 34 of 52), based on the ITT population (95% CI 2% to 31%, P=0.133, Fisher's Exact Test). Similar results were noted in the comple-

TABLE 1
Disposition of patients and definition of patient populations

	OCA (n)	RBC-C (n)	Total (n)
Enrolled sample size	157	156	313
Received no study medication	1	0	1
Safety population	156	156	312
Negative breath test at baseline	4	3	7
Intent-to-treat population	152	153	305
Withdrawn due to adverse drug reaction	1	3	4
Consent withdrawn	2	0	2
Lost to follow-up	6	3	9
Withdrawn due to protocol violation	1	1	2
Withdrawn for other reasons	5	5	10
UBT not done or unavailable	27	29	56
PP population	110	112	222

OCA Omeprazole, clarithromycin and amoxicillin; RBC-C Ranitidine bismuth citrate-clarithromycin; PP Per protocol; UBT Urea breath test

TABLE 2
Demographic data

Intent-to-treat population	OCA (n=152)	RBC-C (n=153)
Age (years):		
Mean (SD)	52 (13.1)	52 (14.1)
Range	20-81	22-85
Sex (n, %):		
Males	80 (53%)	79 (52%)
Females	72 (47%)	74 (48%)
Ethnic origin (n, %)		
White	123 (81%)	135 (88%)
Black	8 (5%)	5 (3%)
Asian	17 (11%)	7 (5%)
American Hispanic	3 (2%)	5 (3%)
Other	1 (<1%)	1 (<1%)
Previous eradication therapy		
Yes	8 (5%)	12 (8%)
No	144 (95%)	141 (92%)
Ulcer history		
Yes	59 (39%)	52 (34%)
No	93 (61%)	101 (66%)

OCA Omeprazole, clarithromycin, amoxicillin; RBC-C Ranitidine bismuth citrate-clarithromycin

ment of ITT patients without prior ulcer history. The eradication rate in all patients with a prior ulcer history was 73% (81 of 111) versus 71% (138 of 194 patients) without a prior ulcer history, irrespective of treatment group. Other variables such as age and sex were not predictors of treatment success.

As shown in Table 4, patients in the RBC-C treatment group were significantly more satisfied than patients in the OCA treatment group, with respect to the number of drugs that were prescribed (82% versus 69%, P=0.008) and the number of pills that they took each day (81% versus 62%, P=0.001). Conversely, patients in the OCA treatment group were more satisfied with the relief that they received from their study medication than patients in the RBC-C treatment group (71% versus 62%, P=0.039). There were no statistically significant treatment differences with the number of side effects experienced while on treatment (P>0.35).

Overall, compliance with study medication was high. Approximately 89% of patients took 14 doses of all study

TABLE 3

Helicobacter pylori eradication rates and 95% confidence intervals for both treatment arms – for intent-to-treat (ITT) and per-protocol (PP) populations

Population	n	RBC-C	OCA	Treatment difference P value difference
ITT	305	66% (101/153); (59%, 74%)	78% (118/152); (71%, 84%)	12% (2-22); P=0.030
PP	222	84% (94/112); (77%, 91%)	96% (105/110); (92%, 99%)	12% (4-19); P=0.007

OCA Omeprazole, clarithromycin, amoxicillin; RBC-C Ranitidine bismuth citrate-clarithromycin

TABLE 4

Patient satisfaction questionnaire – post-treatment satisfaction with respect to prescribed treatment regimen – intent-to-treat population (n=305)

What was the patient's ranking of their satisfaction with the following treatment attributes are:	OCA (n=151)*	RBC-C (n=153)	P [§]
Number of drugs or medications that were prescribed for you			
Satisfied [†]	104 (69%)	126 (82%)	P=0.008
Not satisfied [‡]	42 (28%)	24 (16%)	
No data	5 (3%)	3 (2%)	
The number of pills that you took each day			
Satisfied	94 (62%)	124 (81%)	P=0.001
Not satisfied	52 (34%)	26 (17%)	
No data	5 (3%)	3 (2%)	
The number of days that the medication was prescribed			
Satisfied	122 (81%)	131 (86%)	P=0.358
Not satisfied	24 (16%)	19 (12%)	
No data	5 (3%)	3 (2%)	
The number of side effects you experienced while on treatment			
Satisfied	83 (55%)	88 (58%)	P=0.752
Not satisfied	63 (42%)	62 (41%)	
No data	5 (3%)	3 (2%)	
The relief that you received from the medication			
Satisfied	108 (71%)	95 (62%)	P=0.039
Not satisfied	37 (25%)	55 (25%)	
No data	6 (4%)	3 (2%)	

*One patient did not have any questionnaire data; [†]SATISFIED Patients who were either VERY or SOMEWHAT SATISFIED; [‡]NOT SATISFIED Patients who were either NEUTRAL or SOMEWHAT/VERY DISSATISFIED; [§]Cochran-Mantel-Haenszel Statistic (Modified Ridit Scores) – Van-Elteren Test. OCA Omeprazole, clarithromycin, amoxicillin; RBC-C Ranitidine bismuth citrate-clarithromycin

medication over seven consecutive days during the treatment phase. The compliance rate in the RBC-C treatment group was 95% versus 84% in the OCA treatment group, a difference of 11% in favor of RBC-C (95% CI 4% to 18%, P<0.05).

Side effects

Both treatments were generally well tolerated. The incidence of adverse events occurring in at least 5% of patients overall is summarized in Table 5. Most of these side effects were minor and did not lead to discontinuation in the study. Patients randomized to OCA reported a higher frequency of diarrhea (41%), compared with 29% for RBC-C. Patients randomized to RBC-C reported a high frequency of abnormal stool color (38%) versus 4% for OCA. Taste disturbance was present in 8% of RBC-C and 12% of OCA-treated patients.

Four serious side effects occurred during the study. One patient treated with OCA had an acetaminophen overdose in the follow-up phase. Three RBC-C treated patients respectively had angina pectoris, pulmonary edema and pseudomembranous colitis. The report of pseudomembranous colitis was classified by the investigator as having a reasonable possibility that it was caused by the study medication. This patient recovered

without serious consequences, as did the other patients. In total, only four patients withdrew from the study because of adverse effects – one randomized to OCA (allergic reaction) and three to RBC-C (angina pectoris, headache, dizzy spells).

DISCUSSION

Currently, PPI-based triple therapies with clarithromycin and either amoxicillin or metronidazole are the most commonly recommended regimens worldwide (1,2). The recommended duration is seven days in most countries and 10 days in the USA. In the meta-analyses by Unge et al (11,12) the pooled one-week eradication rate for PPI-CA is 85% and 83% for PPI-CM. The eradication rate for the dual therapy of RBC-C given for 14 days has been reported in the range of 73% to 84% (5,13,14). One study, only reported in abstract form, has shown that decreasing the duration of RBC-C treatment from 14 to seven days does not lead to a loss in efficacy (6). A shorter course of treatment is helpful in improving compliance and reducing treatment costs. Indeed, in this study, patient satisfaction was greater in the RBC-C treatment group than in the OCA treatment group with respect to the number of medications that were prescribed and the number of pills taken each

day. Both treatments were well tolerated with mostly mild side effects, that seldomly led to discontinuation of therapy.

Despite these potential advantages, RBC-C dual therapy given for seven days was not as effective as OCA triple therapy in this study (ITT 66% versus 78%, PP 84% versus 95%, respectively). The difference between RBC-C and OCA was statistically significant. We consider the 12% difference to be clinically meaningful, especially since subsequent studies using RBC-based triple therapy with clarithromycin and either amoxicillin or metronidazole achieve higher cure rates that are equal to PPI-based triple therapy.

Both treatment regimens were not as effective as reported in prior studies. Although more effective than RBC-C, the 78% eradication rate with OCA was slightly below the ITT target eradication rate of 80%, recommended in several consensus guidelines (1,2). These results cannot be explained by a higher failure rate in patients with previous attempts of eradication, as only 20 patients had such prior attempts and exclusion of these patients did not alter the results. However, the PP results are well above 80% for both treatments. There was no significant difference in cure rates in patients with or without a history of ulcers in the past, suggesting that this does not influence treatment results. However, this is based on a subgroup analysis. The study was not powered to specifically answer the question of whether a prior ulcer history is a predictor of treatment results.

Triple therapy using a PPI with clarithromycin and amoxicillin has been tested in several clinical trials in Canada. In the DU-MACH Study, seven-day treatment with OCA achieved a cure of *H pylori* infection ITT 78%, PP 87% (15). In a separate Canadian study comparing omeprazole to esomeprazole with clarithromycin and amoxicillin, ITT results were 90% and 88%, and PP results were both 91% (16).

One possible explanation for a decrease in cure rates of *H pylori* infection is clarithromycin resistance. However, the little available data on resistance to clarithromycin in Canada show that the rates are low, from 2% to 4% (17-19). This is in contrast to data from the USA where higher rates of clarithromycin resistance of 6% to 15% have been reported (20-22). Clarithromycin resistance was not assessed in this study. However, it is possible that *H pylori* resistance to clarithromycin has increased in Canada as a result of more widespread use, and this deserves further study.

Studies have shown that triple therapy of RBC-C with either metronidazole or amoxicillin achieve similar high eradication rates ranging from 80% to 90% as the PPI triple therapies (23). Consequently, RBC-C triple therapy appears to have largely replaced the RBC-C dual therapy. Interestingly, in a recent meta-analysis by Gisbert et al (24) it was shown that, when RBC is given together with clarithromycin and metronidazole, the success rate was slightly higher when compared with PPI triple therapy with clarithromycin and metronidazole. Although most included studies did not provide data on the effect of metronidazole resistance on eradication rates, the study did suggest that in the presence of metronidazole resistance, RBC-C triple therapy is better able to overcome metronidazole resistance than a triple PPI-CM regimen (23). Another systematic review confirmed this finding (25).

In our study, two UBTs were administered four to six and 12 to 14 weeks after the seven-day treatment. UBT has the advantage that it does not require endoscopy, and if ¹³C-urea is used rather than ¹⁴C-urea, the test can be done outside hospi-

TABLE 5
Summary of adverse events occurring in at least 5% of total patients

Safety patient population (n=312)	OCA (n=156)	RBC-C (n=156)
Adverse events experienced*	129 (83)	128 (82)
Diarrhea	64 (41)	45 (29)
Abnormal stool colour	6 (4)	59 (38)
Headaches	26 (17)	17 (11)
Nausea and vomiting	23 (15)	16 (10)
Taste disturbance	18 (12)	12 (8)
Abdominal discomfort and pain	14 (9)	14 (9)
Dyspeptic symptoms	11 (7)	13 (8)
Malaise and fatigue	11 (7)	8 (5)
Dizziness	12 (8)	5 (3)

*All data expressed as n (%). OCA Omeprazole, clarithromycin and amoxicillin; RBC-C Ranitidine bismuth citrate-clarithromycin

tals (26). The study protocol required two UBT's done six to eight weeks apart. In this study 15 of 313 patients (4.8%) had discordant results between follow-up evaluations. This suggests that in future clinical trials, a single UBT, performed at least four weeks after treatment is completed, is sufficient to document cure of the infection.

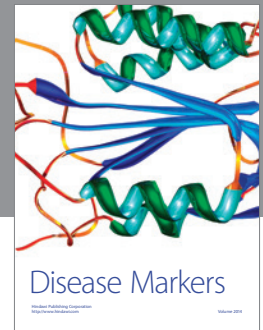
In this study, patient satisfaction data was collected pre-study and following one week of treatment. As little work had been done in this area, an importance-performance questionnaire was designed with the intent of determining first which factors were important to patients, and second, how the treatments compared with respect to the attributes that were deemed important. The results of the analysis, however, demonstrated that despite the perceived importance of baseline attributes, such as fewer medications and lower number of pills, this did not have any impact on the patient's level of satisfaction after seven days of treatment. Thus, the design and validation of future questionnaires may only need to be performed assessing post-treatment satisfaction. Patients were more satisfied in the RBC-C group with the number of drugs and the number of pills that they were required to take each day, indicating that patients are concerned about taking large amounts of medications. Patients in the OCA group were more satisfied than RBC-C treated patients with the relief that they received from the treatment, indicating a link between symptoms and treatment success.

In conclusion, a seven-day dual therapy regimen of RBC-C was not as effective as a seven-day OCA triple therapy. This suggests that when prescribing RBC, a seven-day RBC-C triple therapy with either amoxicillin or metronidazole would be preferred over RBC-C dual therapy. Unfortunately, due to lack of physician demand, RBC is no longer available in Canada and several other countries.

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