Omeprazole once or twice daily with clarithromycin and metronidazole for *Helicobacter pylori* eradication in a Canadian community practice

Naoki Chiba MD FRCPC[1,2], Cheryl P Marshall RN[1]

N Chiba, CP Marshall. Omeprazole once or twice daily with clarithromycin and metronidazole for *Helicobacter pylori* eradication in a Canadian community practice. Can J Gastroenterol 2000;14(1):27-31.

BACKGROUND: Triple therapy for one week with omeprazole, clarithromycin and metronidazole (OCM) is accepted worldwide as a first line therapy for *Helicobacter pylori* eradication. It is unclear whether omeprazole needs to be given once or twice daily.
OBJECTIVES: To assess the efficacy and safety of these regimens in a single-centre, Canadian practice.
METHODS: Histologically proven *H pylori*-positive patients were treated for seven days with clarithromycin 250 mg bid and metronidazole 500 mg bid, and randomly allocated to omeprazole 20 mg either once or twice daily in this open, cohort study. Endoscopy with histology (two antrum and two body biopsies, Giemsa stain) was done four weeks or longer after the pills were completed to assess *H pylori* eradication.
RESULTS: Whether omeprazole was given once or twice daily, eradication was high and the same in both arms. All-patients-treated eradication was 85% (39 of 46 in the omeprazole once daily group and 41 of 48 in the omeprazole twice daily group) and intent-to-treat eradication was 80% (39 of 49 in the omeprazole once daily group and 41 of 51 in the omeprazole twice daily group). Side effects were frequently seen, suffered by 65% to 69% of patients treated. However, these were mild and compliance was high, with 94% of patients taking all of their pills. Mild side effects included loose stools, taste disturbance, nausea, headache and upper or lower gastrointestinal gas. Only one patient (1%) from the omeprazole once daily arm stopped taking metronidazole due to excessive perspiring.
CONCLUSIONS: In this community practice, OCM triple therapy was effective whether omeprazole was given once or twice daily. For those with financial constraint, omeprazole 20 mg once daily can be considered. The regimens were well tolerated without serious adverse events.

Key Words: Helicobacter pylori; *Clarithromycin; Controlled clinical trial; Eradication; Metronidazole; Omeprazole*

Pour le résumé, voir page suivante

This article was originally presented at the Canadian Assocation of Gastroenterology Annual Meeting, March 1 to 8, 1998, Banff, Alberta
[1]Surrey GI Clinic, Guelph and [2]McMaster University, Hamilton, Ontario
Correspondence: Dr Naoki Chiba, Surrey GI Clinic, 105-21 Surrey Street West, Guelph, Ontario N1H 3R3.
Telephone 519-836-8201, fax 519-836-1341, e-mail chiban@fhs.mcmaster.ca
Received for publication August 28, 1998. Accepted November 24, 1998

Oméprazole une ou deux fois par jour avec clarithromycine plus métronidazole pour l'éradication d'*Helicobacter pylori* dans une pratique communautaire canadienne

HISTORIQUE : La trithérapie pendant une semaine à l'oméprazole, clarithromycine et métronidazole (OCM) est acceptée partout dans le monde comme traitement de première intention pour l'éradication d'*Helicobacter pylori*. On ignore si l'oméprazole doit être administré une ou deux fois par jour.

OBJECTIF : Évaluer l'efficacité et l'innocuité de ces schémas thérapeutiques auprès d'un cabinet canadien.

MÉTHODES : Des patients avérés *H. pylori*-positifs à l'examen histologique ont été traités pendant sept jours au moyen de clarithromycine 250 mg b.i.d. et de métronidazole 500 mg b.i.d. et d'une dose de 20 mg d'oméprazole administrée selon une assignation aléatoire, une fois ou deux fois par jour dans le cadre de cette étude de cohorte ouverte. L'endoscopie avec histologie (deux biopsies, une de l'antre et l'autre du corps de l'estomac, colorées au Giemsa) a été effectué quatre semaines ou plus après le traitement oral afin d'évaluer l'éradication d'*H. pylori*.

RÉSULTATS : Que l'oméprazole ait été administré une ou deux fois par jour, l'éradication a été tout aussi élevée dans les deux groupes. L'éradication chez tous les patients traités a été de 85 % (39 sur 46 dans le groupe sous oméprazole 1 f.p.j. et 41 sur 48 dans le groupe sous oméprazole b.i.d.). L'éradication selon l'intention de traiter a été de 80 % (39 sur 49 dans le groupe sous oméprazole 1 f.p.j. et 41 sur 51 dans le groupe sous oméprazole b.i.d.). Les effets secondaires ont été fréquents, signalés par 65 à 69 % des patients traités. Par contre, il s'agissait de symptômes bénins et l'observance thérapeutique a été élevée, 94 des patients ayant pris tous leurs comprimés. Les effets secondaires, légers, ont entre autres été : diarrhée, dysgueusie, nausées, céphalées et ballonnements au niveau du grêle et du côlon. Un seul patient (1 %) du groupe sous oméprazole 1 f.p.j. a cessé de prendre son métronidazole en raison de transpiration abondante.

CONCLUSION : Auprès de cette pratique communautaire, la trithérapie par OCM s'est révélée aussi efficace, que l'oméprazole ait été administré une ou deux fois par jour. En présence de restrictions budgétaires, l'oméprazole 20 mg, 1 f.p.j., peut être envisagé. Les schémas ont été bien tolérés, sans réactions indésirables graves.

In 1993, Bazzoli (1) introduced the highly effective *Helicobacter pylori* eradication regimen of omeprazole 20 mg once daily, clarithromycin 250 mg bid and tinidazole 500 mg bid for one week. However, tinidazole is not available in Canada. Since that time, many other studies using a proton pump inhibitor (PPI) in combination with clarithromycin and another nitroimidazole, metronidazole, have been reported with consistent efficacy (2-6). The first of these was the landmark MACH 1 study (2), which used omeprazole 20 mg bid with clarithromycin 250 mg bid and metronidazole 400 mg bid for one week to achieve 94.3% eradication. Subgroup analysis of the Canadian patients in this study demonstrated that results were the same as for the European patients (7). In Canada, the 400 mg dose of metronidazole is not available; however, the 500 mg dose is as effective (8). Other PPIs such as lansoprazole (4,5) and pantoprazole (6) have similar efficacy.

Due to its efficacy, European (9) and Canadian *H pylori* consensus conferences (10) have recommended that triple therapy with a PPI, clarithromycin and metronidazole be one of the first line therapies for *H pylori* eradication. The Mäastricht Consensus Report (9) considered tinidazole and metronidazole to be interchangeable.

The omeprazole once daily dose has been used extensively in combination with clarithromycin and tinidazole, in contrast to studies using metronidazole where omeprazole was mostly given twice daily. It is unclear and unknown whether omeprazole needs to be given once or twice daily when used in combination with clarithromycin and metronidazole. Furthermore, in today's financial climate, a lower dose of omeprazole would help contain costs.

Thus, in this study, clarithromycin 250 mg bid was used with metronidazole 500 mg bid, combined with omeprazole 20 mg either once or twice daily for one week to assess their efficacies in eradicating *H pylori* in a single, Canadian, community-based gastroenterology practice.

PATIENTS AND METHODS

Patients were recruited from a single gastroenterology practice in Guelph, Ontario. Guelph has 94,000 inhabitants and is located near several large academic medical centres. In this community, it is not possible to culture *H pylori* and perform antibiotic susceptibility testing. The nearest centre performing ^{14}C urea breath tests is a large teaching centre in Hamilton, Ontario, 45 km from Guelph. The ^{13}C-urea breath test was not readily available when this study was performed. The study was approved by the ethics review committee of the Guelph General Hospital.

Patients referred to the practice and subjected to endoscopy for evaluation had two antral and two body biopsies to confirm *H pylori* infection. Patients were invited to participate in this open cohort study if they were positive for *H pylori* by histology using the Geimsa stain. All patients gave written informed consent.

Patient diagnosis of inactive duodenal or gastric ulcer disease (considered collectively as peptic ulcer disease), gastroesophageal reflux disease and nonulcer dyspepsia were recorded. Inclusion criteria were 18 to 80 years of age and histologically proven *H pylori* infection. Patients who had taken antibiotics in the previous month, females who were pregnant or lactating, sexually active females in reproductive years who did not have adequate contraception and any patient currently involved in another clinical trial were excluded. Eligible patients were randomly assigned in this unblinded, cohort study to one of two regimens – seven days of treatment with clarithromycin 250 mg and metronidazole 500 mg bid in combination with omeprazole 20 mg, either once or twice daily.

All patients were warned to avoid alcohol and to expect potential side effects such as taste disturbance, nausea or loose stools. Patients were encouraged to complete all their medications and were informed that successful completion of treatment would offer a greater chance of eradication suc-

TABLE 1
Demographics of patients treated for seven days with clarithromycin and metronidazole plus either omeprazole once daily (O1CM) or omeprazole twice daily (O2CM)

	O1CM	O2CM
Intent to treat	49	51
Diagnosis	17	25
Peptic ulcer disease	21	20
Nonulcer dyspepsia	11	6
Gastroesophageal reflux disease		
Mean age, years (range)	52 (24-78)	55 (31-78)
Sex (male/female)	23/26	28/23
Took 100% of pills	46 (93.9%)	48 (94.1%)
Compliance with pills, mean percentage of pills taken (95% CI)	98.6 (96.9-100.5)	99.3 (98.3-101.3)
Exclusions from all-patients-treated analysis (no final *H pylori* test)	3	3
All-patients-treated analysis	46	48
Exclusions from per protocol analysis	2	3
Per-protocol analysis	44	45

TABLE 2
Eradication efficacy of seven days' treatment with clarithromycin and metronidazole plus either omeprazole once daily (O1CM) or omeprazole twice daily (O2CM)

	O1CM n erad/n treated (%, 95% CI)	O2CM n erad/n treated (%, 95% CI)
ITT eradication	39/49 (80, 70-90)	41/51 (80, 71-90)
APT eradication	39/46 (85, 75-94)	41/48 (85, 76-95)
PP eradication	38/44 (86, 77-96)	39/45 (87, 77-96)

APT All-patients-treated; erad Eradicated; ITT Intent-to-treat; n Number of patients; PP Per-protocol

cess. Patients were reassessed at the end of drug treatment after one week to check compliance to medication by pill count and record spontaneously reported side effects to medications.

At least four weeks after the end of drug treatment, repeat endoscopy with four gastric biopsies (two antral and two body, Giemsa stain) was done to assess *H pylori* eradication. *H pylori* had to be negative in all four specimens to be considered negative, and the pathologist was not aware of the drug treatment given.

All patients who took at least one dose of medication were included in a conservative intent-to-treat (ITT) analysis, where all patients without final *H pylori* determination were considered treatment failures. A more realistic, all-patients-treated (APT) analysis was also performed. In this group, patients who may have been noncompliant with medications were included as long as a final *H pylori* evaluation was performed. In the per-protocol (PP) analysis, patients who took less than 80% of any of the medications or had taken confounding medications such as other antibiotics were excluded. It was recognized a priori that to show statistical equivalence between regimens, a sample size far larger than is practically feasible would be required. All statistical evaluations were done using Statistix for Windows 95 (Analytical software, Tallahassee, Florida).

RESULTS

A total of 103 patients were initially enrolled in the study. Of these, 51 were in the omeprazole once daily arm and 52 were allocated to the omeprazole twice daily arm. Three patients were lost to follow-up immediately after the first visit and were excluded because it was not known whether any medications had been taken. Two of these were from the omeprazole once daily arm and one was from the omeprazole twice daily arm. Thus, the total ITT population was 49 in the omeprazole once daily arm and 51 in the omeprazole twice daily arm. Demographic data were similar in both ITT groups (Table 1). Patient diagnoses were not significantly different by χ^2 (P=0.23), and sex distribution was the same (P=0.43).

Three patients in the omeprazole once daily arm took all their medications but did not have a final assessment and were excluded from the APT analysis but included in the ITT analysis. Reasons for drop out were that one patient was too busy and refused any final assessment, one moved away and the last was unreachable despite many attempts. Two patients in the omeprazole once daily arm took only half of their metronidazole pills by error. Because they were noncompliant, they were excluded from PP analysis, but a final assessment was available in both. *H pylori* was eradicated in one and persisted in the other. The patient in whom *H pylori* persisted was the only patient in this arm who had also received previous treatment and had received omeprazole and clarithromycin dual therapy.

Three patients in the omeprazole twice daily group who took their medications were excluded from APT analysis because final assessment was not done. One woman developed obstructive jaundice shortly after she completed her pills and pancreatic cancer was subsequently diagnosed. Another patient developed diabetic foot ulcers and was admitted to a hospital in another city; he was treated with confounding antibiotics and developed *Clostridium difficile* diarrhea that required treatment with metronidazole. The last patient felt well and refused further assessment. Three patients were excluded from PP analysis – one for noncompliance because only half the prescribed metronidazole was taken by error, and the other two for protocol violations. One had a confounding, 10-day course of penicillin for a salivary gland infection prescribed by a family practitioner, and the other had persistent symptoms and was given another 10-day course of omeprazole, clarithromycin and metronidazole by the family practitioner.

Two patients in the omeprazole twice daily arm had been treated previously, both with omeprazole, clarithromycin and amoxicillin triple therapy. One had successful *H pylori* eradication, while *H pylori* persisted in the other patient who also took only half the metronidazole dose by error.

Eradication rates: Whether omeprazole was given once or twice daily in combination with clarithromycin and

TABLE 3
Side effects of seven days' treatment with clarithromycin and metronidazole plus either omeprazole once daily (O1CM) or omeprazole twice daily (O2CM) (intent-to-treat population)

	O1CM (n=49)	O2CM (n=51)
No side effects (%)	17 (35%) 95% CI 27-42	16 (31%) 95% CI 24-38
Stopped taking pills due to side effects	1 (metronidazole stopped due to excessive perspiring)	0
Loose stools	14	12
Taste disturbance	12	18
Nausea	9	8
Headache	9	9
Upper gastrointestinal gas	5	4
Lower gastrointestinal gas	4	4

Thirty-two patients in the O1CM group had 77 side effects, and 35 patients in the O2CM had 78 side effects

metronidazole for one week, the eradication efficacy was no different between treatments (Table 2).

Side effects and safety: Side effects were reported spontaneously and not elicited through a structured questionnaire. The frequency and type of side effects did not vary between treatments (Table 3). At least one side effect was reported by the majority (65% to 69%) of patients. The most commonly reported side effects were loose stools and taste disturbance, but these were minor and did not prevent completion of medications. Overall, compliance with medications was excellent, with 94% of patients able to complete 100% of their pills (Table 1). Only one of 100 patients (1%) stopped taking medications due to drug side effects. This patient had to stop taking the metronidazole due to excessive perspiring after completing 88% of the metronidazole. Laboratory parameters assessed did not change significantly with drug therapy (data not shown).

DISCUSSION

Whether omeprazole was given once or twice daily in combination with clarithromycin and metronidazole, this one-week treatment regimen achieved 80% ITT, 85% APT and 86% to 87% PP *H pylori* eradication. Due to small sample size, statistically significant differences may have been missed. However, because the results were exactly the same in both study arms, it is unlikely that clinically significant differences were missed. These one-week results are similar to those of our previously reported two-week omeprazole twice daily results (11).

While mild side effects were frequent and seen in approximately two-thirds of the patients, there was only one treatment discontinuation (1%) due to metronidazole-induced excessive perspiring. Overall, 94% of the patients took all their medications. Three patients took only half their dose of metronidazole by error. This problem arose because the patients were prescribed two 250 mg tablets twice daily; the 250 mg tablet is much less expensive than the 500 mg dose and is automatically dispensed according to formulary by the pharmacy. This error resulted in two of the three patients continuing to be *H pylori* positive; thus, patients should be instructed carefully to take all their medications.

In this community setting, the effects of antibiotic resistance were not assessed because culture was not available. In an American study (12), metronidazole resistance did not predict treatment failure. Our centre participated in the large, multicentre randomized controlled MACH 1 trial (2), and all 12 of our patients treated with omeprazole, clarithromycin, metronidazole (OCM) triple therapy had *H pylori* eradicated. Although antibiotic resistance was not assessed, the 100% success rate suggests that *H pylori* metronidazole resistance may not necessarily predict treatment failure. Two recently published Canadian studies have shown that baseline *H pylori* metronidazole resistance is low at 11% (13) to 12% (14). These numbers are lower than the 18% to 38% reported as abstracts (15,16), and may reflect an evolution in the methods and definitions used to define metronidazole resistance rather than a change in actual resistance patterns.

In contrast, recent evidence from the MACH 2 study suggests that metronidazole resistance only slightly reduces the efficacy of the OCM triple therapy from 95% to 76% (3). Importantly, this study also showed that the addition of omeprazole, ie, potent acid suppression, partially helped to overcome metronidazole resistance (3). Thus, there may be some rationale for favouring the greater acid suppression of omeprazole twice daily versus the once daily dose in clinical practice. In the MACH 2 study, omeprazole was given twice daily and the dosage of metronidazole was 400 mg bid – slightly lower than the 500 mg bid used in this study. This may be relevant because there may be a dose response to greater efficacy against resistant *H pylori* strains with higher doses of metronidazole (17).

Clarithromycin resistance was not assessed in this study; however, Canadian studies report that baseline clarithromycin resistance is less than 3% (13,14,18) and as yet probably plays little role in affecting eradication efficacy.

In this community setting, biopsy-based methods are the only methods readily available to assess *H pylori* status. ^{13}C-urea breath tests are now commercially available, but patients appear to be unwilling to to pay for them. Also, the ^{14}C-urea breath test is available at a teaching centre 45 km away, but the patients are reluctant to travel out of town.

A potential limitation of this study is that histology was the only method used to define eradication. However, taking two biopsies from both the antrum and the body of the stomach, as was done in the present study, compared with biopsying the antrum alone, is known to improve diagnostic yield (19). In a study assessing diagnostic tests to define *H pylori* eradication after treatment, taking four histological biopsies as done in this study had high sensitivity (96.6%) and specificity (100%) compared with a gold standard of a true positive by a rigorous combination of immunohistochemistry, culture, polymerase chain reaction and ^{13}C urea

breath test (20). Furthermore, the Geimsa stain as used in this study "may be the preferred technique for confirming *H pylori* infection, due to its accuracy, low cost and technical ease of preparation" (21). While no single stain is a perfect gold standard, histology as performed in this study is thought to be a practical and adequate method to define *H pylori* eradication. In some centres, a rapid urease test of biopsy samples may also be done to confirm *H pylori* eradication.

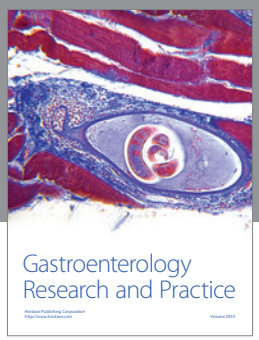
CONCLUSIONS

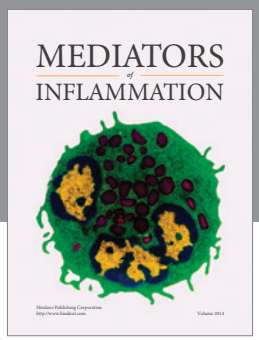
OCM triple therapy for one week is a convenient, twice daily regimen, well tolerated with high compliance and effective in community practice despite concerns about metronidazole resistance. How much *H pylori* antibiotic resistance actually affects the 'bottom line' of treatment success needs to be assessed in a future, prospective, community-based clinical trial.

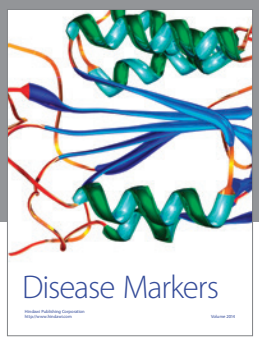
For patients with financial constraint, omeprazole once daily appears to be as effective as twice daily dosing, although there may be a theoretical rationale for favouring the twice daily dose. Patients should be cautioned to look carefully at the metronidazole prescribed to make sure that both 250 mg doses are taken twice daily.

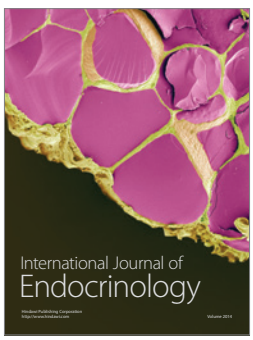
REFERENCES

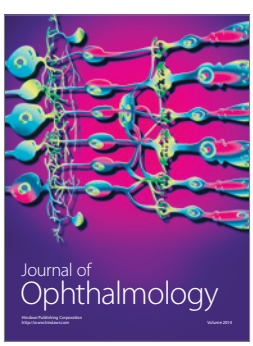
1. Bazzoli F, Zagari RM, Fossi S, Pozzato P, Roda A, Roda E. Efficacy and tolerability of a short term, low dose triple therapy for eradication of *Helicobacter pylori*. Gastroenterology 1993;104:A40. (Abst)
2. Lind T, Veldhuyzen van Zanten SJO, Unge P, et al. Eradication of *Helicobacter pylori* using one week triple therapies combining omeprazole with two antimicrobials – the MACH 1 study. Helicobacter 1996;1:138-44.
3. Lind T, Mégraud F, Unge P, et al. The MACH2 study: role of omeprazole in eradication of *Helicobacter pylori* with 1-week triple therapies. Gastroenterology 1999;116:248-53.
4. Jaup BH, Norrby A. Comparison of two low-dose one-week triple therapy regimens with and without metronidazole for cure of *H pylori* infection. Aliment Pharmacol Ther 1996;10:275-7.
5. Misiewicz JJ, Harris AW, Bardhan KD, et al. One week triple therapy for *H pylori*: a multicentre comparative study. Lansoprazole *Helicobacter* Study Group. Gut 1997;41:735-9.
6. Adamek RJ, Szymanski C, Pfaffenbach B. Pantoprazole vs omeprazole in one-week low-dose triple therapy for cure of *H pylori* infection. Gastroenterology 1997;112:A53. (Abst)
7. Chiba N, Veldhuyzen van Zanten SJO, Bradette M, Sinclair P. Canadian omeprazole triple therapy results from the MACH 1 study. Can J Gastroenterol 1998;12:90A-1A. (Abst).
8. Chiba N, Sinclair P. Metronidazole 500mg is as effective as metronidazole 400mg in the MACH 1 regimen for *H pylori* eradication: a meta-analysis. Can J Gastroenterol 1998;12 (Suppl A):91A. (Abst S50)
9. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. European *Helicobacter Pylori* Study Group. Gut 1997;41:8-13.
10. Hunt R, Thomson ABR, Consensus Conference participants. Canadian *Helicobacter pylori* Consensus Conference. Can J Gastroenterol 1998;12:31-41.
11. Chiba N. Omeprazole and clarithromycin with and without metronidazole for the eradication of *Helicobacter pylori*. Am J Gastroenterol 1996;91:2139-43.
12. Yousfi MM, El-Zimaity HMT, Al-Assi MT, Cole RA, Genta RM, Graham DY. Metronidazole, omeprazole and clarithromycin: an effective combination therapy for *Helicobacter pylori* infection. Aliment Pharmacol Ther 1995;9:209-12.
13. Weiss K, Laverdière M, Restieri C. Comparison of activity of 10 antibiotics against clinical strains of *Helicobacter pylori* by three different techniques. Can J Gastroenterol 1998;12:181-5.
14. Taylor DE, Jiang Q, Fedorak RN. Antibiotic susceptibilities of *Helicobacter pylori* strains isolated in the Province of Alberta. Can J Gastroenterol 1998;12:295-8.
15. Fallone CA, Loo V, Barkun AN, De Souza E, Lavallee J, Wickham C. Rate of *Helicobacter pylori* resistance to metronidazole, clarithromycin and six other agents. Can J Gastroenterol 1996;10:30A. (Abst S33)
16. Best LM, Haldane DJM, Veldhuyzen van Zanten SJO. Susceptibility of *H pylori* in Canada to clarithromycin and metronidazole. Gut 1996;39:A13. (Abst 1A:39).
17. Bardhan KD, Bayerdorffer E, Delchier JP, et al. *H pylori* (Hp) eradication with omeprazole (O), metronidazole (M) and amoxicillin (A): the impact of drug dosing & resistance on efficacy – the HOMER story. Gastroenterology 1998;114:A65. (Abst G0264)
18. Best LM, Haldane DJ, Bezanson GS, Veldhuyzen van Zanten SJO. *Helicobacter pylori*: primary susceptibility to clarithromycin in vitro in Nova Scotia. Can J Gastroenterol 1997;11:298-300.
19. Misiewicz JJ, Tytgat GNJ, Goodwin CS, et al. The Sydney System: A new classification of gastritis. Working party reports. World Congress of Gastroenterology, Sydney, August 26-31, 1990:1-10.
20. Navratil E, Soule JC, Rousseau M, et al. Comparison of immunohistochemistry and histology for the diagnosis of *Helicobacter pylori* infection after treatment. Gut 1995;37(Suppl 1):A35. (Abst 140)
21. Cohen H, Laine L. Endoscopic methods for the diagnosis of *Helicobacter pylori*. Aliment Pharmacol Ther 1997;11(Suppl 1):3-9.

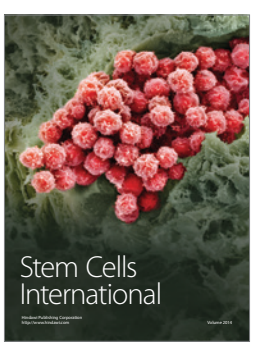


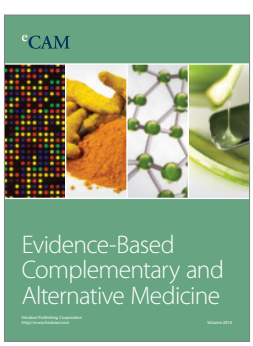


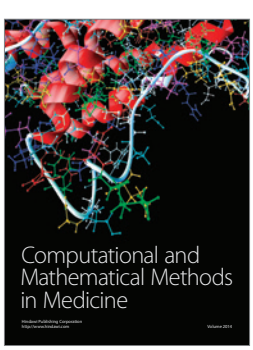


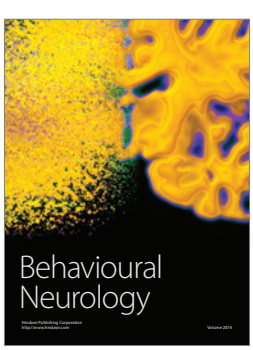


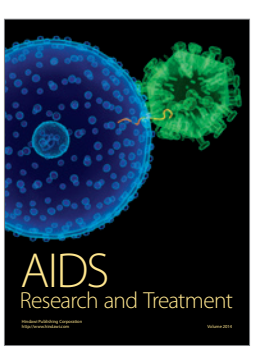


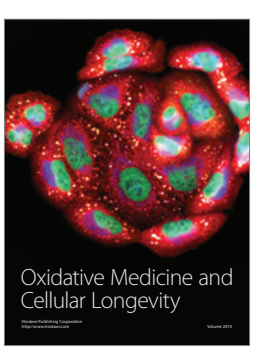












Hindawi

Submit your manuscripts at
http://www.hindawi.com