ORIGINAL RESEARCH

The effect of eradicating *Helicobacter pylori* on idiopathic central serous chorioretinopathy patients

Yalong Dang[1,2,*]
Yalin Mu[2,*]
Manli Zhao[2]
Lin Li[3]
Yaning Guo[4]
Yu Zhu[1,2]

[1]Department of Ophthalmology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, People's Republic of China; [2]Department of Ophthalmology and Visual Science, Yellow River Hospital of Henan University of Science and Technology, Sanmenxia City, Henan, People's Republic of China; [3]Department of Ophthalmology, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang City, Henan, People's Republic of China; [4]Gu-Cheng Eye Hospital, Xi'an City, Shanxi, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yu Zhu
The First Affiliated Hospital of Zhengzhou University, Jianshe East road, Zhengzhou, Henan, People's Republic of China
Tel +86 398 228 9268
Fax +86 398 282 3634
Email dr.dang@aol.com

Purpose: To evaluate the effect of *Helicobacter pylori* (*H. pylori*) eradication on the remission of acute idiopathic central serous chorioretinopathy (ICSCR).

Study design: A prospective, randomized, placebo-controlled study of 53 participants.

Main outcome measure: Twenty-seven acute ICSCR patients tested positive for *H. pylori* were given an eradication *H. pylori* therapy, and another 26 patients with the same diagnosis received matching placebo medication. All participants were tested for the following items: (1) disappearance rate of subretinal fluid (SRF); (2) best-corrected visual acuity (BCVA); and (3) central retinal sensitivity at baseline, 2 weeks, 4 weeks, 8 weeks, and 12 weeks after treatment. The difference between the two groups was analyzed by PASW statistics version 18.0.

Results: At each follow-up, the disappearance rate of SRF in the active treatment group seemed slightly better than in the control group, but no statistically significant differences were observed ($P > 0.05$ at each follow-up). The BCVA between the two groups also did not demonstrate statistically significant differences ($P > 0.05$ at each follow-up). Unlike the BCVA and the disappearance rate of SRF, we compared the change in central retinal sensitivity at 12 weeks after treatment; a statistical difference was observed ($P = 0.042$).

Conclusion: Our findings suggested that *H. pylori* eradication does not improve BCVA and the disappearance rate of SRF, but it could improve the central retinal sensitivity in acute ICSCR patients. We recommend that chronic ICSCR patients and more sensitive methods for *H. pylori* diagnosis should be involved in evaluating the effect of *H. pylori* eradication.

Keywords: *Helicobacter pylori*, acute idiopathic central serous chorioretinopathy, best-corrected visual acuity, subretinal fluid, central retinal sensitivity

Introduction

Idiopathic central serous chorioretinopathy (ICSCR) has been described as an accumulation of subretinal fluid (SRF) accompanied by serous macular detachment by von Graefe in 1866.[1] Most cases of acute ICSCR are unilateral, self-limited, and benign. ICSCR could have spontaneous resolution and a good visual prognosis; however, nearly half of cases tend to relapse, and this always in the same eyes. A small percentage of subjects could develop a chronic disease with widespread decompensation of the retinal pigment epithelium, and this could lead to permanent vision loss. Several risk factors may be associated with this disease such as cigarette smoking, systemic corticosteroid therapy,[2] pregnancy,[3] uncontrolled systemic hypertension,[4,5] endogenous mineralocorticoid dysfunction,[6] sympathomimetic agents,[7] and so-called type A personality.[8]

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium associated with several digestive and extra digestive pathologies. Recently, the correlation between

ICSCR and *H. pylori* infection has been demonstrated. In a prospective study, Asensio-Sánchez et al[9] noticed that the prevalence of *H. pylori* occurred in 68.75% of ICSCR patients, which was much higher than in the control group (30%). This result supported the observational study of Ahnoux-Zabsonre et al[10] and the interventional study of Mauget-Faÿsse et al.[11] Additionally, Giusti[12] reported an interesting case: recurrences of ICSCR in a 43-year-old Italian man were associated with the revival of an *H. pylori* infection. Moreover, Rahbani-Nobar et al[13] found that eradicating bacteria could provoke faster reabsorption of SRF.

Based on this evidence, in this study, we evaluated the effect of *H. pylori* eradication on the remission of ICSCR. The main outcome was measured by the disappearance rate of SRF, best-corrected visual acuity (BCVA), and central retinal sensitivity. To our knowledge, this is the first study to report that *H. pylori* eradication could benefit central retinal sensitivity in ICSCR patients.

Materials and methods
Study design and patient recruitment
This study was a prospective, randomized, placebo-controlled study conducted among *H. pylori*-positive patients with acute ICSCR between September 2010 and December 2012 at the Department of Ophthalmology and Visual Science, Yellow River Hospital, Henan University of Science and Technology (Zhengzhou, Henan, People's Republic of China). The study received approval from the Institutional Review Board of Yellow River Hospital (number 2010-12-036). Written informed consent was obtained from all patients who were clearly explained all potential risks and possible benefits. The procedures followed the tenets of the Declaration of Helsinki.

Inclusion and exclusion criteria
The inclusion criteria were: (1) single idiopathic leakage detected by fluorescein angiography excluding any other diseases; (2) SRF confirmed by optical coherence tomography (OCT; 3D OCT-2000; TOPCON Corporation, Tokyo, Japan); and (3) *H. pylori* infection diagnosed according to a specific protocol.

The exclusion criteria were: (1) chronic ICSCR (duration more than 12 weeks); (2) multiple leakage areas; (3) large pigment epithelial detachment (≥1 pupillary diameter); (4) diffused retinal pigment epitheliopathy; (5) patient less than 20 years old and more than 70 years old; and (6) pregnancy, steroid use, and any other systemic diseases.

Randomization
Participants were randomly assigned through a web-based data entry system maintained at the Data Coordinating Center (The MEDABC Corporation, Zhengzhou, Henan, People's Republic of China), with equal probability of receiving either *H. pylori* eradication (referred to as the active treatment group) or placebo drugs (referred to as the control group) using a permuted-block design with random block sizes.

H. pylori infection diagnosis and retest
We used the two-step protocol prescribed by Chey[14] to diagnose the *H. pylori* infection. Briefly, diagnosis began with a serology test. Negative results are considered accurate and do not need any additional testing, but positive results should be confirmed by urea breath test. All patients should be retested to evaluate the effectiveness of the "anti-*H. pylori* therapy" after 4 weeks of treatment.

Study treatment
The active treatment group received a standard *H. pylori* eradication therapy recommended by Malfertheiner et al.[15] Briefly, omeprazole (20 mg), clarithromycin (500 mg), and amoxicillin (1,000 mg) were orally administered twice a day after meals for 14 days. The control group received an identical placebo that was the same color, size, and had the same identification name as the treatment. The placebos were taken in the same manner as the study drugs. Both drugs were also in identical opaque bottles and prepared by one nonclinician research assistant.

Main outcome measure and follow-up
All participants were tested according to the following items: (1) disappearance rate of SRF; (2) BCVA; and (3) central retinal sensitivity at baseline, 2 weeks, 4 weeks, 8 weeks, and 12 weeks after treatment.

The disappearance of SRF was judged by a specialist according to the fundus photograph captured by OCT. A BCVA letter score was measured at 3 m by a masked, certified tester using the electronic Early Treatment for Diabetic Retinopathy Study method, as reported by Beck et al.[16] Central retinal sensitivity was measured as Uetani et al[17] prescribed. Briefly, Micro Perimeter (MP-1, Nidek Corporation, Japan) and a white Goldmann 3 spot size in a 4-2-1 staircase strategy was used in this examination. Thirty-three stimulus points covering the entire central area (about 151 diameters around the macula) were examined. The mean sensitivity of the 33 points was considered to be the central retinal sensitivity.

Statistical analyses

All data were analyzed by PASW statistics version 18.0 (SPSS Inc., IBM Corporation, Chicago, IL, USA). Fisher's exact test was used to compare differences in gender and the disappearance rate of SRF between the two groups. Independent *t*-tests were used to address the other clinical data. Results were considered significant at *P*-values of 0.05.

Results

Characteristics of patients

A total of 64 eyes in 64 patients were enrolled and randomized equally into two groups. Eleven eyes (17.18%) were lost to follow-up or did not yield enough data (five eyes in the active treatment group and six eyes in the control group). A total of 53 eyes (82.81%) were included in the study.

The mean ages in the active treatment group and the control group were 35.66 ± 5.47 years and 34.85 ± 5.53 years (mean ± standard deviation), respectively. No statistically significant difference was found (*P* = 0.57). The male-to-female ratio between the two groups also did not demonstrate a significant difference (*P* = 0.83). The mean interval between the onset of symptoms and the time of treatment was 9.83 ± 7.42 days in the active treatment group and 10.32 ± 6.52 days in the control group (*P* = 0.68) (Table 1).

The effectiveness of *H. pylori* eradication

After 4 weeks of each treatment, three patients in the active treatment group were still positive for *H. pylori* infection; however, patients in the control group were all positive for *H. pylori* infection.

Disappearance rate of SRF

At successive visits, the proportion of patients (the active treatment group versus the control group) in whom SRF

had disappeared was 3.7% versus 0%, 25.9% versus 15.4%, 40.7% versus 34.6%, and 63.0% versus 50%, respectively. The disappearance of SRF among the active treatment group seems a little higher, but the *P*-value demonstrated no statistical difference (*P* = 0.51, 0.17, 0.20, 0.14 when compared with the control group at each follow-up) (Table 2).

Changes in BCVA

At baseline, the mean BCVA in the active treatment group and the control group was 74.0 ± 3.9 letters versus 74.2 ± 3.7 letters, respectively. No statistically significant difference was found (*P* = 0.946) (Table 3).

From Table 3, we can see a slight improvement in BCVA during follow-up. However, compared with the baseline, a statistically significant difference was observed only at 12 weeks in the active treatment group (80.8 ± 2.9 letters versus 74.0 ± 3.9 letters; *P* = 0.048).

Moreover, we compared the difference between the active treatment group and the control group; although the active treatment group seemed to be a little better in terms of BCVA than the control group, the differences were not statistically significant at 2 weeks, 4 weeks, 8 weeks, 12 weeks. (73.8 ± 4.1 letters versus 74.5 ± 3.2 letters, *P* = 0.530; 75.3 ± 3.5 letters versus 74.9 ± 4.2 letters, *P* = 0.244; 77.9 ± 3.2 letters versus 76.3 ± 3.8 letters, *P* = 0.112; 80.8 ± 2.9 letters versus 77.6 ± 2.6 letters, *P* = 0.108, respectively).

Changes in central retinal sensitivity

At baseline, the mean central retinal sensitivity in the active treatment group and the control group was 15.5 ± 0.6 dB and 15.4 ± 0.5 dB, respectively. No statistically significant difference was found (*P* = 0.830) (Table 4).

From Table 4, as was similar with the change observed in BCVA, we can see a slight improvement in central retinal sensitivity in both groups during follow-up. However, when compared with baseline, a statistically significant difference was observed only at 12 weeks in the active treatment group (18.3 ± 1.1dB versus 15.5 ± 0.6 dB, *P* = 0.049).

Table 1 Baseline demographic characteristics in the two study groups

	Active treatment group (n = 27)	**Control group (n = 26)**	***P*-value**
Age (years)			
Mean ± SD	35.66 ± 5.47	34.85 ± 5.53	0.57
Range	22–48	25–47	
Gender			
Male:female	27:5	26:5	0.83
Interval between the beginning of symptoms and treatment (days)			
Mean ± SD	9.83 ± 7.42	10.32 ± 6.52	0.68
Range	3–20	4–21	

Abbreviations: n, number; SD, standard deviation.

Table 2 The disappearance rate of SRF between the two study groups

	2 weeks	**4 weeks**	**8 weeks**	**12 weeks**
Active treatment group	3.7% (1/27)	25.9% (7/27)	40.7% (11/27)	63.0% (17/27)
Control group	0% (0/26)	15.4% (4/26)	34.6% (9/26)	50.0% (13/26)
P-value	0.51	0.17	0.20	0.14

Note: Comparisons between the two groups using Fisher's exact test.
Abbreviation: SRF, subretinal fluid.

Table 3 Changes in BCVA between the two study groups

	Active treatment group (n = 27)	Control group (n = 26)	*P*-value
BCVA letter score at baseline			
Mean ± SD	74.0 ± 3.9	74.2 ± 3.7	0.946
Range	68–80	67–79	
2-week follow-up visit			
Mean ± SD	73.8 ± 4.1	74.5 ± 3.2	0.530
Range	68–81	68–80	
4-week follow-up visit			
Mean ± SD	75.3 ± 3.5	74.9 ± 4.2	0.244
Range	69–83	70–81	
8-week follow-up visit			
Mean ± SD	77.9 ± 3.2	76.3 ± 3.8	0.112
Range	70–83	70–82	
12-week follow-up visit			
Mean ± SD	80.8 ± 2.9	77.6 ± 2.6	0.108
Range	71–85	71–82	

Notes: Within-group comparison using Student's independent *t*-test. *P*-values <0.05 were considered to be statistically significant.
Abbreviations: BCVA, best-corrected visual acuity; n, number; SD, standard deviation.

Unlike the change in BCVA, we compared the difference between the active treatment group and the control group. At 12 weeks after treatment, a statistical difference was observed (18.3 ± 1.1 dB versus 16.1 ± 0.7 dB; *P* = 0.042) (Table 4).

Safety

During the follow-up visit, no systemic or ocular adverse events occurred.

Table 4 Changes in central retinal sensitivity between the two study groups

	Active treatment group (n = 27)	Control group (n = 26)	*P*-value
Retinal sensitivity at the baseline (dB)			
Mean ± SD	15.5 ± 0.6	15.4 ± 0.5	0.830
Range	14.3–15.9	14.5–15.8	
2-week follow-up visit			
Mean ± SD	15.7 ± 0.7	15.5 ± 0.8	0.645
Range	14.3–16.9	14.2–16.9	
4-week follow-up visit			
Mean ± SD	15.9 ± 0.5	15.7 ± 0.6	0.328
Range	14.9–17.0	14.5–16.9	
8-week follow-up visit			
Mean ± SD	16.3 ± 0.6	15.8 ± 0.8	0.336
Range	15.0–17.4	14.5–17.3	
12-week follow-up visit			
Mean ± SD	18.3 ± 1.1	16.1 ± 0.7	0.042
Range	16.3–19.0	15.1–17.8	

Notes: Within-group comparison using Student's *t*-test. *P*-values <0.05 were considered to be statistically significant.
Abbreviations: n, number; SD, standard deviation.

Discussion

ICSCR is a serous macular detachment disease that often attacks young patients. Gray spots and blurred vision in the central visual field are common symptoms; reduced BCVA and central retinal sensitivity may persist after the fluid disappears. Treatments such as regular laser photocoagulation and photodynamic therapy seem to be good choices, but both therapies have limitations. In this study, we evaluated the effect of *H. pylori* eradication on ICSCR patients. To our knowledge, we were the first to demonstrate that *H. pylori* eradication could elevate the central retinal sensitivity in ICSCR patients, but this does not improve BCVA and the disappearance rate of SRF.

BCVA always decreases in ICSCR, but it seems to not respond to *H. pylori* eradication. Rahbani-Nobar et al[13] demonstrated that among *H. pylori*-positive ICSCR patients, BCVA improved to 0.003 ± 0.01 logarithm of minimal angle resolution (logMAR) in the active treatment group and 0.004 ± 0.02 (logMAR) in the control group after 16 weeks of follow-up; however, a statistically significant difference was not observed (*P* = 0.97). This supports the finding of Mauget-Faÿsse[11] in 2002. In our study, a mild elevation in BCVA was noted in both groups, but there were no significant differences between them. Although a significant difference appeared at the 12-week follow-up in the active treatment group when compared with baseline, this phenomenon could be explained by the spontaneous resolution feature of acute ICSCR. According to the evidence, we suggested that *H. pylori* eradication might not improve the BCVA in ICSCR patients.

Central retinal sensitivity is a sensitive indicator in evaluating the macular function of ICSCR patients. Previous studies[18,19] have shown a lower central retinal sensitivity with spontaneous resolution in ICSCR patients; in addition, even a better BCVA has been obtained. According to Fujita et al,[20] treatments (such as photodynamic therapy) may improve central retinal sensitivity for 12 months. In our study, central retinal sensitivity in the active treatment group was better than in the control group at the 12-week point (*P* = 0.042). This indicated better retinal function recovery obtained from the *H. pylori* eradication.

In addition, a previous study considered that *H. pylori* eradication may accelerate the SRF reabsorption time. Rahbani-Nobar et al[13] found that the SRF reabsorption time was 9.28 ± 3.20 weeks in the *H. pylori* eradication group compared with 11.63 ± 3.18 weeks in the control group; there was a statistically significant difference (*P* = 0.015). Contrary to the results reported by Rahbani-Nobar et al,[13] we observed that the disappearance rate of SRF did not lead to a significant

difference between the two groups, although the SRF rate in the active treatment group seemed a little higher. This difference may be attributed to the various inclusion criteria and baseline characteristics employed in our study.

Adrenocortical hormone plays an important role in ICSCR. Elevation of serum glucocorticosteroid is associated with an increased risk of ICSCR.[21] In this study, we used omeprazole (20 mg), clarithromycin (500 mg), and amoxicillin (1,000 mg) to eradicate *H. pylori*. However, Ushiama et al[22] suggested that the oral administration of clarithromycin could reduce the circulating glucocorticosteroid. Therefore, clarithromycin may be playing multiple roles in improving the central retinal sensitivity of ICSCR patients. Moreover, the mineralocorticoid receptor (MR) appears to be involved in ICSCR. Zhao et al[23] reported that MR is involved in rat and human ocular chorioretinopathy; blockade of MR could be used therapeutically to reverse choroid vasculopathy. This result was confirmed by Bousquet et al.[24]

Failure to eradicate *H. pylori* is always accompanied by deterioration; Parkinson's disease (PD) as an extragastric disorder associated with *H. pylori* infection which has been demonstrated. Dobbs et al[25] reported that marked deterioration in PD accompanied failure to eradicate *H. pylori*. The effect on hypokinesia is an indication that is specific in PD. A longitudinal follow-up study[26] confirmed that improved hypokinesia following antimicrobials appeared to be unique to *Helicobacter* eradication. In our study, after 4 weeks of treatment, three patients in the active treatment group were still *H. pylori*-positive. At the 12-week follow-up, the mean BCVA in these three patients was lower than the BCVA of the other patients in the active treatment group, but was similar to the control group. Similar results could be seen in central retinal sensitivity. These outcomes support the idea that *H. pylori* eradication could benefit ICSCR patients, rather than clarithromycin's effect alone.

The precise pathophysiological relationship between ICSCR and *H. pylori* infection is poorly understood. *H. pylori* infection could lead to low-grade inflammatory stimulation. Proinflammatory, vasoactive substances, as well as autoantibodies could be found in *H. pylori*-positive patients' serum. It has been documented that anti-CagA antibodies may cross-react with vascular wall antigens, triggering an immunological cascade that damaged vascular endothelial cells.[27] Also, the immunoglobulin-G antibody response to the *H. pylori* infection has been regarded as a risk factor leading to endothelial dysfunction.[28] In addition, *H. pylori* infection causes an increase in antiheat shock protein antibodies and upregulates endothelial adhesion molecules, which

are finally induced to ischemia.[29] Georges et al[30] suggested that the interaction between *H. pylori* infection and diseases with vascular endothelial disorder (such as ICSCR and coronary artery disease) is mediated by variations in serum interleukin-6 levels. All of these mechanisms might take part in the pathophysiological processes involved in ICSCR.

Like the eye, the brain has been considered as "immune privilege." In PD, serum interleukin-6[30] and cortisol[31] levels are elevated. In a randomized, placebo-controlled trial,[32] gastric biopsy indicated that *H. pylori* eradication had an overall beneficial effect. Hypokinesia improved in the year after eradication and remained level over the next year. In addition, one relevant autoimmune mechanism that may be evident is that antinuclear antibody-seropositivity exhibited a poor response to proven eradication.

This study has its limitations. Chronic ICSCR has less spontaneous resolution and always got a poor visual prognosis. This subset of ICSCR might be the best model to evaluate the effect of *H. pylori* eradication in ICSCR patients. Recently, Casella et al[33] reported that *H. pylori* eradication could benefit BCVA outcomes in chronic ICSCR patients. More research is needed to illuminate the changes in retinal sensitivity after *H. pylori* eradication in chronic ICSCR patients. In our study, serology tests and urea breath tests were used to diagnose the *H. pylori* infection. However, in gastric biopsy, polymerase chain reaction is a more sensitive method. A large sample size, as well as an in-depth clinical study that includes pretreatment endoscopic biopsy to confirm antimicrobial sensitivities, and posttreatment biopsy to confirm eradication, is needed to elucidate these questions.

Conclusion
Our findings suggest that *H. pylori* eradication does not improve BCVA and the disappearance rate of SRF, but it could increase central retinal sensitivity. We recommend that chronic ICSCR patients and more sensitive methods for *H. pylori* diagnosis should be involved in evaluating the effects of *H. pylori* eradication.

Disclosure
The authors report no conflicts of interest in this work.

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