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MINIREVIEWS

Chinese *Helicobacter pylori* vaccine: Solution for an old challenge?

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Abstract

Helicobacter pylori (*H. pylori*) is an important cause for gastric cancer in high risk individuals. *H. pylori* colonizes more than 50% of the world's population and associated peptic ulcer disease and gastric malignancy have important public health implications. It has been classified as a class Ⅰ carcinogen in 1994 by the World Health Organization. Clinicians are often prompted to eliminate the infection the moment it is detected. This also, unfortunately, led to reckless use of antibiotics and reports of increasing resistance are now worldwide. Each year, many of people die from gastric cancer; thus application of effective vaccine can reduce this relatively high mortality worldwide. *H. pylori* can be eliminated by antibiotics but efficacy is sharply decreasing. Moreover, current therapy is also expensive and with side effects. Vaccine may be the best solution to the above problem but there are many challenges in producing such an effective therapeutic vaccine. Recently, the Chinese group published in Lancet, a single-center, randomized, phase Ⅲ study of an oral recombinant vaccine (Urease B subunit fused with heat-labile enterotoxin B derived from *Escherichia coli*) prescribed in the Chinese children (6-15 years) without a history of *H. pylori* infection. This review provides an insight into this new solution for an old challenge.

Key words: *Helicobacter pylori*; Resistance; Therapy; Vaccine; Antibiotics

Core tip: *Helicobacter pylori* (*H. pylori*) remains the most prevalent gastric infection. One of the main questionable aspects of *H. pylori* is its high resistance to most of prescribed antibiotics and lack of useful vaccines. Vaccine may be the best solution to the above problem but there are many challenges in producing such an effective

therapeutic vaccine. That will be ideal that Chinese vaccine removes the need for bicarbonate administration because of its adverse side effects. Taking together, it is the first time that such a protective *H. pylori* vaccine is introduced to the world for high risk individuals.

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INTRODUCTION

It is time to stop Helicobacter pylori

Helicobacter pylori (*H. pylori*) infects over half of the world's population and associated peptic ulcer disease and gastric malignancy have important public health implications. Despite after two decades of antibiotics success, the primary problem still exists, and the reasons can be multifactorial[1-3]. Some *in-vivo* conditions favor the persistence of *H. pylori* in the stomach but others oppose, and the clinical outcomes can be dependent on a delicate balance between a harmless inflammation and a more severe kind[4]. Furthermore, we do not know the most effective eradication regime of *H. pylori*, as the following questions remained unsolved including the best duration of recommended regimens, best dosages and also the right combination of antibiotics[5-8]. Although *H. pylori* infection can be efficiently eradicated using antibiotics, at least, in some patients, there are now reports of antibiotic resistance worldwide (Table 1). Finding an effective vaccine is the answer if resistance continues to increase[9-12]. More than five international guidelines have been published that covers all aspects of *H. pylori* infection including diagnostic, treatment and also vaccine[13,14]. Following years of continuous clinical experiments and trials, the promising goal for an effective vaccine now seems feasible. In September 2015, a report published in *Lancet* by the Chinese group brings high hope on a highly effective vaccine that we have been waiting for[15]. If proven in further studies, then this groundbreaking finding will change management paradigm of *H. pylori* in the near future.

A *H. PYLORI* VACCINE THAT WORKS, FINALLY?

Effective vaccine should not just reduce the incidence but also global prevalence of *H. pylori*. Furthermore, to prove its efficacy we need a longer period of study observation and with a greater number of study participants to conclude its reliability before it can be recommended into any healthcare systems. There have been considerable interests to develop such an effective *H. pylori* vaccine for a long time but many obstacles had hampered the development[16]. Many of the *H. pylori* virulence factors and also secreted proteins such as urease were used as recombinant proteins to produce a protective vaccine, but because these factors only induced weak forms of immunity and also lack of safety, therefore many projects were abandoned[13,17]. Therapeutic vaccines should be able to administer to both *H. pylori* positive children but also adults; although there is a potential risk for developing gastritis in susceptible patients[18,19]. In these susceptible patients, however, we can still recommend therapeutic vaccine; since it can reduce: (1) risk of re-infection; and (2) decrease treatment duration. The disappointment in vaccine development may tip following the Chinese *H. pylori* vaccine published in Lancet[15]. This was a single-center, randomized trial and a phase Ⅲ study that examined an oral recombinant vaccine (based on Urease B subunit fused with heat-labile enterotoxin B derived from *Escherichia coli*) among the Chinese children (aged 6-15 years) without a prior history of *H. pylori* infection. In brief, after 12 mo of vaccination, 71% efficacy rate was observed, and this rate was around 55% after 3 years. Although seems effective in children, this study needs repeat among adults. Another limitation of this vaccine is that the authors found 20% of younger children were not protected from the infection. Notably, using better adjuvant in order to remove boosters for this vaccine may increase its popularity among clinicians for widespread prescription. Also it will be ideal that the Chinese vaccine removes the need for bicarbonate administration because of its adverse side effects. Taking together, it is the first time that such a protective *H. pylori* vaccine is introduced to the world for high risk individuals.

WHAT NOW AFTER THE CHINESE VACCINE?

While the published results for the Chinese vaccine seems promising, but there are still barriers before it gains wide acceptance. Besides the limitations mentioned in above section, the vaccine needs a proper Phase-Ⅲ clinical trials for other populations. Besides the Chinese vaccine, there are other novel developments in the pipeline. Currently, there is a lack in knowledge on exact molecular mechanisms that contributed to cellular immunity against *H. pylori*. The urease enzyme was the first recombinant protein used to provide an effective vaccine for *H. pylori* in animal models[20,21]. Recently, it has been established that regulatory T-cells are necessary to mount sufficient immune responses and this is important information for future development of a protective anti-*H. pylori* vaccine[22]. *H. pylori*-immunogenic antigens such as catalase, vacuolating cytotoxin (VacA), urease, cytotoxin-associated gene A (CagA), heat shock proteins and also neutrophil-activating protein (NAP) had been examined to see if they are potential candidate antigens for vaccine[23-27], but so far, the results have been inconclusive. Moreover, different mucosal routes such as

Table 1 Worldwide report of increasing *Helicobacter pylori* antibiotic resistance

Year	Eradication rate	Ref.	Antibiotics
2001	97%	Asaka *et al*[9]	Clarithromycin Amoxicillin
2014	61%	Chen *et al*[10]	Clarithromycin Amoxicillin
2014	55%	Kutluk *et al*[32]	Clarithromycin Amoxicillin
2013	76%	Sardarian *et al*[11]	Clarithromycin Amoxicillin tinidazole
2013	80%	Zullo *et al*[33]	Clarithromycin Amoxicillin tinidazole
2014	69%	Nishida *et al*[7]	Clarithromycin Amoxicillin
2011	87%	Greenberg *et al*[6]	Clarithromycin Amoxicillin
2014	98%	Sugimoto *et al*[12]	Metronidazole Clarithromycin
2013	38%	Nishizava *et al*[34]	Metronidazole Amoxicillin Clarithromycin

sublingual, rectal and intranasal were being evaluated but results were inconsistent[27-30]. Recently, Chen *et al*[31] examined *oipA* DNA construct carried by the bacterium, Salmonella typhimurium as a therapeutic vaccine. The authors concluded that *H. pylori* virulence factors including OipA and NAP may seem to be the better candidates to induce effective immunity, at least in the mouse models, and we shall await more results.

CONCLUSION

Due to the relatively high rate of antibiotic therapy failure in recent years, we have to investigate more about novel vaccines on *H. pylori*. At last, Chinese group proposed a useful formulation with less side effects which can inspire more hopes for clinicians to think actually about *H. pylori* mass eradication worldwide.

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REFERENCES

1 **Ferreira J**, Moss SF. Current Paradigm and Future Directions for Treatment of Helicobacter pylori Infection. *Curr Treat Options Gastroenterol* 2014; **12**: 373-384 [PMID: 25187235 DOI: 10.1007/s11938-014-0027-6]
2 **Ren L**, Lu H, Li HY, Zhu LY, Xu XQ, Gu LY, Ge ZZ, Li XB. New dual therapy for primary treatment of Helicobacter pylori infection: A prospective randomized study in Shanghai, China. *J Dig Dis* 2014; **15**: 622-627 [PMID: 25205201 DOI: 10.1111/1751-2980.12186]
3 **Talebi Bezmin Abadi A**. Vaccine against Helicobacter pylori: Inevitable approach. *World J Gastroenterol* 2016; **22**: 3150-3157 [PMID: 27003991 DOI: 10.3748/wjg.v22.i11.3150]
4 **Abadi ATB**, Ierardi E, Lee YY. Why do we still have Helicobacter Pylori in our Stomachs? *Malays J Med Sci* 2015; **22**: 70-75
5 **Başyiğit S**, Kefeli A, Yeniova AÖ, Uzman M, Nazlıgül Y, Aktaş B. Different treatment choice for first-line treatment of Helicobacter pylori in an area with a high antibiotic resistance. *Turk J Gastroenterol* 2014; **25** Suppl 1: 293-294 [PMID: 25910347 DOI: 10.5152/tjg.2014.6085]
6 **Greenberg ER**, Anderson GL, Morgan DR, Torres J, Chey WD, Bravo LE, Dominguez RL, Ferreccio C, Herrero R, Lazcano-Ponce EC, Meza-Montenegro MM, Peña R, Peña EM, Salazar-Martínez E, Correa P, Martínez ME, Valdivieso M, Goodman GE, Crowley JJ, Baker LH. 14-day triple, 5-day concomitant, and 10-day sequential therapies for Helicobacter pylori infection in seven Latin American sites: a randomised trial. *Lancet* 2011; **378**: 507-514 [PMID: 21777974 DOI: 10.1016/S0140-6736(11)60825-8]
7 **Nishida T**, Tsujii M, Tanimura H, Tsutsui S, Tsuji S, Takeda A, Inoue A, Fukui H, Yoshio T, Kishida O, Ogawa H, Oshita M, Kobayashi I, Zushi S, Ichiba M, Uenoyama N, Yasunaga Y, Ishihara R, Yura M, Komori M, Egawa S, Iijima H, Takehara T. Comparative study of esomeprazole and lansoprazole in triple therapy for eradication of Helicobacter pylori in Japan. *World J Gastroenterol* 2014; **20**: 4362-4369 [PMID: 24764674 DOI: 10.3748/wjg.v20.i15.4362]
8 **Mokhtare M**, Hosseini V, Tirgar Fakheri H, Maleki I, Taghvaei T, Valizadeh SM, Sardarian H, Agah S, Khalilian A. Comparison of quadruple and triple Furazolidone containing regimens on eradication of helicobacter pylori. *Med J Islam Repub Iran* 2015; **29**: 195 [PMID: 26157713]
9 **Asaka M**, Sugiyama T, Kato M, Satoh K, Kuwayama H, Fukuda Y, Fujioka T, Takemoto T, Kimura K, Shimoyama T, Shimizu K, Kobayashi S. A multicenter, double-blind study on triple therapy with lansoprazole, amoxicillin and clarithromycin for eradication of Helicobacter pylori in Japanese peptic ulcer patients. *Helicobacter* 2001; **6**: 254-261 [PMID: 11683930]
10 **Chen MC**, Lei WY, Lin JS, Yi CH, Wu DC, Hu CT. Levofloxacin-amoxicillin/clavulanate-rabeprazole versus a standard seven-day triple therapy for eradication of Helicobacter pylori infection. *Biomed Res Int* 2014; **2014**: 158520 [PMID: 24995271 DOI: 10.1155/2014/158520]
11 **Sardarian H**, Fakheri H, Hosseini V, Taghvaei T, Maleki I, Mokhtare M. Comparison of hybrid and sequential therapies for Helicobacter pylori eradication in Iran: a prospective randomized trial. *Helicobacter* 2013; **18**: 129-134 [PMID: 23121338 DOI: 10.1111/hel.12017]
12 **Sugimoto M**, Uotani T, Sahara S, Ichikawa H, Yamade M, Sugimoto K, Furuta T. Efficacy of tailored Helicobacter pylori eradication treatment based on clarithromycin susceptibility and maintenance of acid secretion. *Helicobacter* 2014; **19**: 312-318 [PMID: 24690010 DOI: 10.1111/hel.12128]
13 **Moise L**, Moss SF, De Groot AS. Moving Helicobacter pylori vaccine development forward with bioinformatics and immunomics. *Expert Rev Vaccines* 2012; **11**: 1031-1033 [PMID: 23151160 DOI: 10.1586/erv.12.80]
14 **Guo L**, Liu K, Zhao W, Li X, Li T, Tang F, Zhang R, Wu W, Xi T. Immunological features and efficacy of the reconstructed epitope vaccine CtUBE against Helicobacter pylori infection in BALB/c mice model. *Appl Microbiol Biotechnol* 2013; **97**: 2367-2378 [PMID: 23064457 DOI: 10.1007/s00253-012-4486-1]
15 **Zeng M**, Mao XH, Li JX, Tong WD, Wang B, Zhang YJ, Guo G, Zhao ZJ, Li L, Wu DL, Lu DS, Tan ZM, Liang HY, Wu C, Li DH, Luo P, Zeng H, Zhang WJ, Zhang JY, Guo BT, Zhu FC, Zou QM. Efficacy, safety, and immunogenicity of an oral recombinant Helicobacter pylori vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015; **386**: 1457-1464 [PMID: 26142048 DOI: 10.1016/S0140-6736(15)60310-5]
16 **Li WQ**, Ma JL, Zhang L, Brown LM, Li JY, Shen L, Pan KF, Liu

WD, Hu Y, Han ZX, Crystal-Mansour S, Pee D, Blot WJ, Fraumeni JF, You WC, Gail MH. Effects of Helicobacter pylori treatment on gastric cancer incidence and mortality in subgroups. *J Natl Cancer Inst* 2014; **106**: dju116 [PMID: 24925350 DOI: 10.1093/jnci/dju116]

17 **Baldari CT**, Lanzavecchia A, Telford JL. Immune subversion by Helicobacter pylori. *Trends Immunol* 2005; **26**: 199-207 [PMID: 15797510]

18 **Lv X**, Yang J, Song H, Li T, Guo L, Xing Y, Xi T. Therapeutic efficacy of the multi-epitope vaccine CTB-UE against Helicobacter pylori infection in a Mongolian gerbil model and its microRNA-155-associated immuno-protective mechanism. *Vaccine* 2014; **32**: 5343-5352 [PMID: 25093281 DOI: 10.1016/j.vaccine.2014.07.041]

19 **Rossi G**, Ruggiero P, Peppoloni S, Pancotto L, Fortuna D, Lauretti L, Volpini G, Mancianti S, Corazza M, Taccini E, Di Pisa F, Rappuoli R, Del Giudice G. Therapeutic vaccination against Helicobacter pylori in the beagle dog experimental model: safety, immunogenicity, and efficacy. *Infect Immun* 2004; **72**: 3252-3259 [PMID: 15155627 DOI: 10.1128/IAI.72.6.3252-3259.2004]

20 **Lee CK**, Weltzin R, Thomas WD, Kleanthous H, Ermak TH, Soman G, Hill JE, Ackerman SK, Monath TP. Oral immunization with recombinant Helicobacter pylori urease induces secretory IgA antibodies and protects mice from challenge with Helicobacter felis. *J Infect Dis* 1995; **172**: 161-172 [PMID: 7797906]

21 **Hatzifoti C**, Roussel Y, Harris AG, Wren BW, Morrow JW, Bajaj-Elliott M. Mucosal immunization with a urease B DNA vaccine induces innate and cellular immune responses against Helicobacter pylori. *Helicobacter* 2006; **11**: 113-122 [PMID: 16579841]

22 **Larussa T**, Leone I, Suraci E, Imeneo M, Luzza F. Helicobacter pylori and T Helper Cells: Mechanisms of Immune Escape and Tolerance. *J Immunol Res* 2015; **2015**: 981328 [PMID: 26525279 DOI: 10.1155/2015/981328]

23 **Kang QZ**, Duan GC, Fan QT, Xi YL. Fusion expression of Helicobacter pylori neutrophil-activating protein in E.coli. *World J Gastroenterol* 2005; **11**: 454-456 [PMID: 15637768]

24 **D'Elios MM**, Czinn SJ. Immunity, inflammation, and vaccines for Helicobacter pylori. *Helicobacter* 2014; **19** Suppl 1: 19-26 [PMID: 25167941 DOI: 10.1111/hel.12156]

25 **de Bernard M**, D'Elios MM. The immune modulating activity of the Helicobacter pylori HP-NAP: Friend or foe? *Toxicon* 2010; **56**: 1186-1192 [PMID: 19818802 DOI: 10.1016/j.toxicon.2009.09.020]

26 **Goh KL**, Chan WK, Shiota S, Yamaoka Y. Epidemiology of Helicobacter pylori infection and public health implications. *Helicobacter* 2011; **16** Suppl 1: 1-9 [PMID: 21896079 DOI: 10.1111/j.1523-5378.2011.00874.x]

27 **Malfertheiner P**, Schultze V, Rosenkranz B, Kaufmann SH, Ulrichs T, Novicki D, Norelli F, Contorni M, Peppoloni S, Berti D, Tornese D, Ganju J, Palla E, Rappuoli R, Scharschmidt BF, Del Giudice G. Safety and immunogenicity of an intramuscular Helicobacter pylori vaccine in noninfected volunteers: a phase I study. *Gastroenterology* 2008; **135**: 787-795 [PMID: 18619971 DOI: 10.1053/j.gastro.2008.05.054]

28 **Müller A**, Solnick JV. Inflammation, immunity, and vaccine development for Helicobacter pylori. *Helicobacter* 2011; **16** Suppl 1: 26-32 [PMID: 21896082 DOI: 10.1111/j.1523-5378.2011.00877.x]

29 **Ruggiero P**, Censini S. Helicobacter pylori: A Brief History of a Still Lacking Vaccine. *Diseases* 2014; **2**: 187-208

30 **Rupnow MF**, Chang AH, Shachter RD, Owens DK, Parsonnet J. Cost-effectiveness of a potential prophylactic Helicobacter pylori vaccine in the United States. *J Infect Dis* 2009; **200**: 1311-1317 [PMID: 19751153 DOI: 10.1086/605845]

31 **Chen J**, Lin M, Li N, Lin L, She F. Therapeutic vaccination with Salmonella-delivered codon-optimized outer inflammatory protein DNA vaccine enhances protection in Helicobacter pylori infected mice. *Vaccine* 2012; **30**: 5310-5315 [PMID: 22749593 DOI: 10.1016/j.vaccine.2012.06.052]

32 **Kutluk G**, Tutar E, Bayrak A, Volkan B, Akyon Y, Celikel C, Ertem D. Sequential therapy versus standard triple therapy for Helicobacter pylori eradication in children: any advantage in clarithromycin-resistant strains? *Eur J Gastroenterol Hepatol* 2014; **26**: 1202-1208 [PMID: 25171023 DOI: 10.1097/MEG.0000000000000190]

33 **Zullo A**, Hassan C, Ridola L, De Francesco V, Vaira D. Standard triple and sequential therapies for Helicobacter pylori eradication: an update. *Eur J Intern Med* 2013; **24**: 16-19 [PMID: 22877993 DOI: 10.1016/j.ejim.2012.07.006]

34 **Nishizawa T**, Maekawa T, Watanabe N, Harada N, Hosoda Y, Yoshinaga M, Yoshio T, Ohta H, Inoue S, Toyokawa T, Yamashita H, Saito H, Kuwai T, Katayama S, Masuda E, Miyabayashi H, Kimura T, Nishizawa Y, Takahashi M, Suzuki H. Clarithromycin Versus Metronidazole as First-line Helicobacter pylori Eradication: A Multicenter, Prospective, Randomized Controlled Study in Japan. *J Clin Gastroenterol* 2015; **49**: 468-471 [PMID: 24921211 DOI: 10.1097/MCG.0000000000000165]

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