Pitfalls of Physician-Directed Treatment of *Helicobacter pylori* Infection: Results from Two Phase 3 Clinical Trials and Real-World Prescribing Data

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INTRODUCTION

- *Helicobacter pylori (H. pylori)* infects approximately 35% of Americans and can lead to serious sequalae if untreated. Clarithromycin (CLR)-based therapies have become increasingly ineffective at eradicating *H. pylori* due to increased antibiotic resistance.[1,2,3,4]
- Despite guidance from the American College of Gastroenterology (ACG) which recommends avoiding CLR in patients who have previously received macrolides, and where local resistance rates are ≥15% or unknown, CLR is still frequently prescribed.[5]
- Efficacy of CLR is strongly dependent on acid suppression by proton pump inhibitors (PPIs), which is reduced in individuals who are CYPC219 rapid/ultrarapid metabolizers (~30% prevalence).[6]

OBJECTIVE

- The current study aimed to assess the impact of CYP2C19 genotype on eradication rates with physician-directed therapy with CLR, and to understand contemporary utilization of CLR in the US.

METHODS

- Supplemental clinical data from two phase 3 clinical trials (ERADICATE Hp [NCT01980095]/ ERADICATE Hp2 [NCT03198507]) for RHB-105 (Talicia®) were reviewed to identify specific physician-directed regimens selected for subjects whose *H. pylori* infection was not eradicated during primary treatment.
- ERADICATE Hp was conducted between November 25, 2013 and August 24, 2015; ERADICATE Hp2 was conducted between July 2017 and November 2018. Both studies were conducted entirely in US medical centers.[7,8,9]
- CYP2C19 metabolizer status was analyzed using genotyping in subjects who then received a physician-directed CLR regimen.
- Additionally, an analysis of patient-level prescription claims from IQVIA PharMetrics® Plus medical and prescription claim database was performed to characterize real-world utilization of CLR.

DEMOGRAPHICS AND CYP2C19 GENOTYPING

ERADICATE Hp Study[7]

- The study enrolled 118 subjects. Key demographics included mean age (46 ± 10.18 years), female (62.7%), White (92.4%), and Black (7.6%); 80.5% was Hispanic/Latino.

ERADICATE Hp2 Study[8]

- The study enrolled 445 subjects. Key demographics included mean age (45.9 ± 12.77 years), female (62.2%), White (77.1%), Black (19.3%); 60% was Hispanic/Latino.

CYP2C19 Genotypes[7,8]

- In ERADICATE Hp, 65 subjects who received RHB-105 provided blood samples for CYP2C19 status testing.
- In ERADICATE Hp2, all enrolled subjects were assessed for CYP2C19 status based on blood sample testing.
- Based on the CYP2C19 genotype assessment, the CYP2C19 genotypes were similar in both studies. The majority of subjects were normal metabolizers in both studies: 58.5% in ERADICATE Hp and 48.6% in ERADICATE Hp2.
- Table 1 shows the results of CYP2C19 genotypes of both studies.

Table 1. CYP2C19 Genotypes (mITT Population)[7,8]

	ERADICATE Hp (N=118)	ERADICATE Hp2 (N=445)
Number of subjects assessed for CYP2C19 status	65*	445†
Type of Metabolizer, n (%)		
Ultrarapid	0	13 (2.9)
Rapid	11 (16.9)	100 (22.0)
Normal	38 (58.5)	221 (48.6)
Intermediate	16 (24.6)	100 (22.0)
Poor	0	9 (2.0)

*Subjects received RHB-105 had blood samples for CYP2C19 status tested. †Data in 9 subjects were not reported due to samples arrived in an expired container and were not processed; missing data in 3 subjects due to samples that were not taken, and 1 sample that arrived in the wrong condition. Note: mITT, modified intent-to-treat

RESULTS

Cure Rates in Subjects Who Failed Initial Treatment

- Following completion of "ERADICATE Hp", 38 subjects remained positive for *H. pylori*; 33 had been randomized to receive placebo and 5 had received RHB-105.[7]
  - Follow-up data on physician-directed therapy were available for 31 subjects; cure rate was 61.3%. A CLR-regimen was prescribed for 27 of these 31 subjects; cure rate with this regimen was 59.3%.
- Following completion of "ERADICATE Hp2", 94 subjects had persistent infection; 67 had been randomized to active comparator and 27 to RHB-105.[8]
  - For those with persistent infection following primary study treatment, the overall cure rate with physician-directed treatment was 56.2%.
  - For the 48 subjects who received CLR-based therapies, the cure rate was 60.4%; for the 22 who received a bismuth-based quadruple regimen, the cure rate was 45.4%.
- Table 2 shows cure rates based on therapy and initial treatment regimen.

Table 2. Cure Rates Among Subjects in ERADICATE Hp and ERADICATE Hp2 Who Failed Initial Treatment and Then Completed Physician-Directed Therapy and Post-Treatment UBT (mITT Population)

	ERADICATE Hp Initial Treatment Group Failures			ERADICATE Hp2 Initial Treatment Group Failures		
mITT Population	RHB-105 (n=5) Eradication Rate	Placebo (n=33) Eradication Rate	Combined (n=38) Eradication Rate	RHB-105 (n=27) Eradication Rate	Comparator (n=67) Eradication Rate	Combined (n=94) Eradication Rate
Any Physician-Directed Therapy	(n=4) 50.0%	(n=27) 63.0%	(n=31) 61.3%	(n=26) 46.2%	(n=63) 56.7%	(n=89) 56.2%
CLA-Based Triple	(n=4) 50.0%	(n=23) 60.9%	(n=27) 59.3%	(n=16) 50.0%	(n=32) 65.6%	(n=48) 60.4%
Bismuth-Based Quadruple	(n=0) 0.0%	(n=2) 100.0%	(n=2) 100.0%	(n=6) 33.3%	(n=16) 50.0%	(n=22) 45.4%
Other Regimens*	(n=0) 0.0%	(n=2) 50.0%	(n=2) 50.0%	(n=4) 50.0%	(n=15) 53.3%	(n=19) 52.6%
Missing Data†	(n=1) N/A	(n=6) N/A	(n=7) N/A	(n=1) N/A	(n=4) N/A	(n=5) N/A

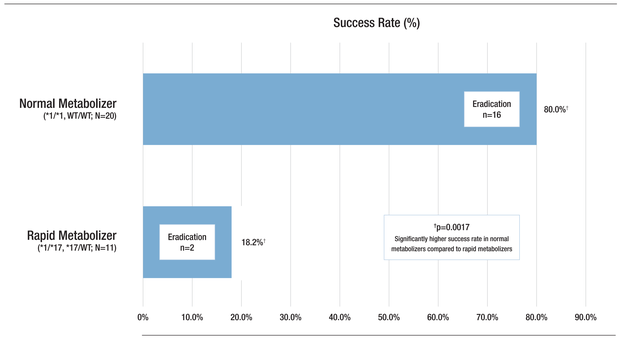
*Some other regimens included clarithromycin (CLA) but were not standard CLA-based triple therapy. †Subjects who did not complete treatment or did not have a test-of-cure UBT. RHB-105: low-dose rifabutin, amoxicillin, and omeprazole (12.5 mg/250 mg/10 mg). Comparator: amoxicillin 250 mg and omeprazole 10 mg. Note: UBT, urea breath test; mITT, modified intent-to-treat; N/A, not available.

RESULTS (CONTINUED)

Cure Rates and CYP2C19 genotypes

- Figure 1 shows statistically significant results (p=0.0017) of the CYP2C19 genotypes of those subjects who received physician-directed CLR-based therapy and its relationship to eradication success.

Figure 1. Subject CYP2C19 Metabolic Status vs. Success of Clarithromycin Triple Therapy (mITT Population)

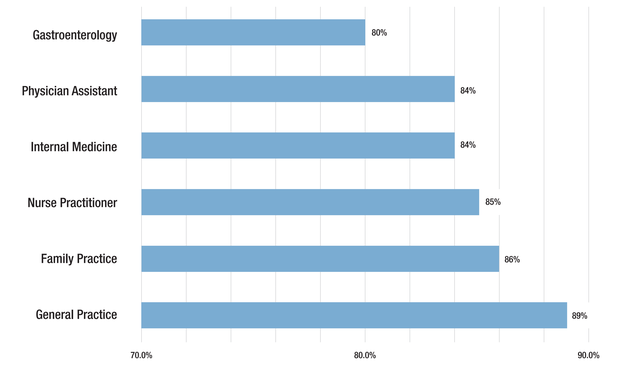


Note: mITT, modified intent-to-treat

Prescription Data of Clarithromycin-Based Regimen by Subspecialty

- Figure 2 shows the analysis of 12 months of domestic retail prescribing data for the treatment of *H. pylori* infection comprising over 1 million prescriptions and reveal that over 80% of the total combined prescriptions from each subspecialty contained clarithromycin.
- The majority of clinicians prescribed a high proportion of clarithromycin-based regimens despite ACG guideline recommendations.

Figure 2. Percent of Total Prescribed *H. pylori* Regimens Containing Clarithromycin by Subspecialty



SAFETY[9]

- The most common treatment emergent adverse events (TEAEs) occurring in ≥ 5% of receiving RHB-105 in ERADICATE Hp and ERADICATE Hp2 were diarrhea, headache, and nausea; the incidences were similar between RHB-105 treatment and comparators.
- Discontinuation due to TEAEs occurred in 1% (4/305) of patients receiving RHB-105, <1% (1/227) of patients receiving amoxicillin and omeprazole, and 2% (1/41) of patients receiving placebo. Adverse reactions leading to discontinuation of RHB-105 were nausea and vomiting, nausea, nasal congestion, and nasopharyngitis, in one patient each.

CONCLUSION

Despite sub-optimal eradication rates and ACG recommendations, inappropriate use of clarithromycin persists.

- Physician-directed therapy data confirmed high utilization of clarithromycin and low rates of eradication.
- Rapid CYP2C19 metabolizers who received physician-directed clarithromycin-based regimens had markedly low eradication rates, highlighting an additional concern complicating empirically prescribed CLR-based regimens.
- US prescription data confirm that clarithromycin-based regimens predominate, despite change to ACG guideline recommendations.
- Since RHB-105 does not contain clarithromycin, and since resistance to amoxicillin and rifabutin is very rare, RHB-105 can be used first-line with minimal concern for individual patient antibiotic resistance or CYP2C19 genotype.

REFERENCES

1. Adamu MA, Weck MN, Rothenbacher D, Brenner H. Incidence and risk factors for the development of chronic atrophic gastritis: five year follow-up of a population-based cohort study. *Int J Cancer.* 2011;128(7):1652-1658.
2. El-Serag HB, Kao JY, Kanwal F, et al. Houston Consensus Conference on Testing for Helicobacter pylori Infection in the United States [published correction appears in Clin Gastroenterol Hepatol. 2019 Mar;17(4):801. Crowe, Sheila [corrected to Crowe, Sheila E]]. *Clin Gastroenterol Hepatol.* 2018;16(7):992-1002.e6.
3. Eslick GD, Lim LL, Byles JE, Xia HH, Talley NJ. Association of Helicobacter pylori infection with gastric carcinoma: a meta-analysis. *Am J Gastroenterol.* 1999;94(9):2373-2379.
4. Kato S, Matsukura N, Tsukada K, et al. Helicobacter pylori infection-negative gastric cancer in Japanese hospital patients: incidence and pathological characteristics. *Cancer Sci.* 2007;98(6):790-794.
5. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection [published correction appears in *Am J Gastroenterol.* 2018 Jul;113(7):1102]. *Am J Gastroenterol.* 2017;112(2):212-239.
6. Furuta T, Shirai N, Takashima M, et al. Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. *Clin Pharmacol Ther.* 2001;69(3):158-168.
7. Kalfus IN, Graham DY, Riff DS, Panas RM. Rifabutin-Containing Triple Therapy (RHB-105) for Eradication of Helicobacter pylori: Randomized ERADICATE Hp Trial. *Antibiotics (Basel).* 2020;9(10):685.
8. Graham DY, Canaan Y, Maher J, Wiener G, Hulten KG, Kalfus IN. Rifabutin-Based Triple Therapy (RHB-105) for Helicobacter pylori Eradication: A Double-Blind, Randomized, Controlled Trial. *Ann Intern Med.* 2020;172(12):795-802.
9. Talicia. Prescribing Information. Raleigh, NC: RedHill Biopharma; Version 11/2019.

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