Clinical Characteristics and Treatment Pathway of Patients Treated with *Helicobacter pylori* Infection-A Single Center Cohort Study Using Common Data Model

Seung In Seo1,2, Tae Jun Kim3, Yoon Jin Choi4, Chang Seok Bang1,2, Yong Kang Lee5, Moon Won Lee6, Su Youn Nam7, Woon Geon Shin1,2, Big Data Research Group, Korean College of Helicobacter and Upper Gastrointestinal Research

Department of Internal Medicine, Hallym University College of Medicine1, Chuncheon, Institute for Liver and Digestive Diseases, Hallym University2, Chuncheon, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine3, Seoul, Department of Internal Medicine, Yonsei University College of Medicine4, Seoul, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital5, Goyang, Department of Internal Medicine, Pusan National University School of Medicine6, Busan, Department of Internal Medicine, School of Medicine, Kyungpook National University7, Daegu, Korea

**Background/Aims:** Changing trends in the *Helicobacter pylori* (*H. pylori*) eradication protocol have not been investigated after the publication of the third-revised Korean guideline in 2013. We aimed to analyze the clinical characteristics of *H. pylori*-infected patients alongside their treatment protocols using a common data model (CDM).

**Materials and Methods:** A 16-year electronic health record (of 1,689,604 patients from 2004 to 2019) was converted into a CDM in Kangdong Sacred Heart Hospital. We extracted records of patients who underwent the rapid urease test or serum anti-*H. pylori* IgG assay. The treatment protocols were visualized using a sunburst plot. We investigated the clinical characteristics and medication history of patients who underwent a urea breath test after clarithromycin-based eradication therapy.

**Results:** Out of 29,438 patients tested for *H. pylori* infection, 7,647 received a treatment protocol. Among them, 72.5% received a 7~14 days protocol comprising a proton pump inhibitor (PPI), amoxicillin, and clarithromycin. The proportion of patients treated with the first-line protocol (PPI, bismuth, tetracycline, and metronidazole) slightly increased from 1.9% (before 2014) to 3.3% (after 2014) (*P*<0.001). The percentages of patients with of previous exposure to macrolides (14.7% vs. 5.5%, *P*<0.001) or amoxicillin (10.6% vs. 7.3%, *P*=0.006) were higher in patients with previous clarithromycin-based eradication failure.

**Conclusions:** The *H. pylori* treatment protocol was not significantly modified despite the updates in the clinical guideline. There was only 1.4 percentage point increase in bismuth-based quadruple therapy as first-line eradication therapy even after the announcement of revised Korean guideline in 2013. ([Korean] *Helicobacter* Up Gastrointest Res 2022 Aug 19. [Epub ahead of print])

**Key Words:** Common data model; *Helicobacter pylori*, Treatment

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**INTRODUCTION**

The fourth revision of the guideline for the diagnosis and treatment of *Helicobacter pylori* (*H. pylori*) infection in South Korea was published in 2020, but there is a lack of research on changes in treatment patterns in response to the publication of updated versions of the protocol.1 In South Korea, clarithromycin-based triple therapy, where a proton pump inhibitor (PPI), clarithromycin, and amoxicillin are administered twice a day for 7~14 days, has traditionally been used as the first-line *H. pylori* treatment. However, the eradication rate has continued to decline and recently fell under 80%. Therefore, the 2013 revision of the South Korean protocol recommended that bismuth-based quadruple therapy should be used as the first-line *H. pylori* treatment when resistance to clarithromycin is suspected.4 Since 2020, tailored treatment has been introduced; in this approach, the treatment is selected after determining resistance to clarithromycin using PCR or gene sequencing. However, it is not well understood whether this recommendation has led to any changes in treatment patterns. A recently published European registry study on *H. pylori* eradication found that the treatment patterns varied by country.5 Although the European guideline recommends shifting from triple therapy to quadruple therapy, the report showed that actual treatment patterns did not change.5,6

There have been technical difficulties in synthesizing data from hospitals to be used in research since medical data is characterized by heterogeneity in the data structure and format, large data size, and a tendency to be unrefined. There have also been difficulties sharing data...
among researchers due to differences in institutions’ data sharing policies and personal information privacy issues. Distributed research networks using a common data model (CDM) have recently been gaining attention to resolve these difficulties and allow easy application to research.\(^7\) The Observational Medical Outcomes Partnership (OMOP)-CDM has been developed and operated by the Observational Health Data Sciences and Informatics (OHDSI), and has been used in various multinational studies around the world.\(^8\) In South Korea, the Ministry of Trade, Industry and Energy started a CDM-based distributed bio-health big data platform project in 2018. Around 40 hospitals in South Korea converted their electronic medical records data to the OMOP-CDM, establishing a consolidated bio-health big data network.

The cohort characterization method makes it possible to analyze the prior medications and diseases easily in patients who received clarithromycin-based triple therapy. Studying the treatment pathway enables analysis and visualization of \(H.\ pylori\) treatment patterns. In this study, we aimed to analyze the characteristics and history of antibiotic exposure in patients who underwent clarithromycin-based eradication therapy using the data transformed to the CDM from a single institution. Furthermore, we aimed to determine whether there was a change in the treatment pattern after January 1, 2014 when the third revised guideline\(^4\) was applied.

**MATERIALS AND METHODS**

1. **Database**

This study was conducted using the Kangdong Sacred Heart Hospital CDM. This database includes 16 years of treatment data (2004~2019) from 1,689,604 patients. The data were analyzed as described in our previous study.\(^{12}\) It contains variables such as prescriptions, diagnoses, procedures including endoscopy, operations, blood tests, rapid urease test results (CL0test, Pronto Dry New; Medical Instruments Co., Herford, Germany), and urea breath test results (\(^{13}\)C-UBT; UBIT-IR 300, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan).

ATLAS, developed by the OHDSI community, is a web-based open platform that supports study design, cohort sampling, prevalence calculation, large-scale propensity score matching, cohort characteristics analysis, and artificial intelligence-based predictions.\(^{15}\) ATLAS version 2.7.6 was used for the study design, and the analyses were conducted using FEEDER-NET, a coordinating platform that enables data user and supplier connections and multi-institution analyses.\(^7\) This study was approved by the Kangdong Sacred Heart Hospital Medical Research Institutional Review Board (decision No.: IRB 2021-11-001).

2. **Cohort definition**

To assess the \(H.\ pylori\) treatment pathway, we analyzed the patterns of antibacterial treatment among the target cohort of 29,458 adult patients over the age of 18 who underwent rapid urease test or \(H.\ pylori\) antibody test (Genedia \(H.\ pylori\) ELISA; Green Cross Medical Science Co., Seoul, Korea). The event cohort was defined as those who were prescribed clarithromycin, amoxicillin, metronidazole, bismuth subcitrate, tetracycline, or levofloxacin for 7~14 days after being included in the target cohort. The antibacterial treatment patterns before and after the announcement of the guideline were compared by dividing the cohort on January 1, 2014. We also created a cohort of patients who were prescribed clarithromycin-based triple therapy (PPI, amoxicillin, and clarithromycin) for 7~14 days as the first-line treatment and underwent a \(^{13}\)C-UBT after a month. Differences according to patients’ history of antibiotic exposure were analyzed by comparing those who were prescribed PPI, bismuth subcitrate, tetracycline, and metronidazole for 7~14 days as second-line treatment after the clarithromycin-based triple therapy and those who were not.

3. **Treatment pathway analysis**

Treatment pathway analysis, which is a method to summarize the events that occurred after patients entered the target cohort, can provide important evidence about the treatment status, including medication use, within a population sample.\(^{14}\) In a previous international OHDSI study, the first-line medication, most frequently used medi-
cation, and subsequent treatment patterns were visualized as sunburst plots for type 2 diabetes, hypertension, and depression after analyzing the characteristics of treatment pathways using OMOP-CDM data. Using the cohort pathway tab in the ATLAS platform, the target cohort and event cohort were activated, and graphs to visualize treatment pathways were created using the R statistical program. The percentages of patients in specific treatment pathways and the patterns of subsequent treatment were identified by clicking on the generated graphs.

4. Analysis of clinical characteristics

The characteristics of a target cohort can be analyzed using the characterization tab on ATLAS. This function can be applied to a multi-institution database. Characteristic analysis requires at least one cohort and at least one characteristic to be analyzed. First, the characteristic to be analyzed is defined using the feature analysis tool for the target cohort. In this study, basic sociodemographic information, prescriptions, and diagnoses during the past year before entering the cohort were analyzed. In addition, exposure to macrolides, amoxicillin, and metronidazole before cohort entry was analyzed.

5. Statistical analysis

Based on the results from ATLAS, categorical variables were analyzed using the chi-square test. The statistical software MedCalc® version 20.106 (MedCalc Software, Ostend, Belgium) was used. Statistical significance was defined as a P-value below 0.05.

RESULTS

1. Changes in H. pylori treatment patterns

Among 29,458 patients who were tested for H. pylori, 15,444 received a rapid urease test, and 14,014 had the serum anti-H. pylori IgG test. From these patients, 7,647 (26% of all patients tested) entered the treatment pathway. The overall study flow and patient inclusion and exclusion are presented in Fig. 1. Among the 7,647 patients who entered the treatment pathway, 5,547 (72.5%) were prescribed clarithromycin and amoxicillin at the same time for 7~14 days. Meanwhile, 138 patients (1.8%) were prescribed bismuth subcitrate, metronidazole, and tetracycline for 7~14 days during the same period as the first-line treatment (Fig. 2A). Sequential therapy and concomitant therapy were not conducted in this hospital. Furthermore, 175 patients (2.3%) were treated with metronidazole and amoxicillin. The isolated use of clarithromycin was seen in 4.1%, metronidazole in 5.3%, and levofloxacin in 7.1%. It was assumed that these findings reflect antibacterial exposure unrelated to H. pylori treatment (Fig. 2A). When the treatment pathways before and after January 1, 2014 were analyzed, 75 out of 3,956 patients (1.9%) received first-line treatment of bismuth subcitrate, metronidazole, and tetracycline before January 1, 2014. After January 1, 2014, 63 out of 1,904 (3.3%) received this treatment, showing a statistically significant difference (P < 0.001) (Fig. 2B). The number of patients receiving amoxicillin and metronidazole treatment increased from 31 out of 3,956 (0.8%) before 2014 to 144 out of 1,904 (7.6%) after 2014 (P < 0.001).

2. Characteristics of patients who underwent clarithromycin-based triple therapy

Among the 5,547 patients who received PPI, clarithromycin, and amoxicillin for 7~14 days as first-line therapy, 3,138 received a 13C-UBT (Fig. 1). The average age of these patients was 53.10±13.34 years, and the proportion of men was 60.6% (Table 1). The proportion of patients with peptic ulcers, an indication for eradication treatment, was 83.2% (n=2,612), while 178 patients (5.7%) had stomach cancer and 348 (11.1%) had other conditions. When patients’ prescription history of medication related to peptic ulcers before eradication treatment was analyzed, 16% had been prescribed non-steroidal anti-inflammatory drugs, 14.3% had been prescribed antithrombotics, and 7.5% had been prescribed steroids. Among the antithrombotics, 8.5% of the prescriptions were for aspirin, and 3.2% were for clopidogrel. Patients’ history of antibiotic prescriptions before eradication treatment was analyzed, including all ingredients...
of medications, and exposure to amoxicillin was most frequent, with 7.4% of patients having received macrolide antibiotics (clarithromycin: 3.3%; roxithromycin: 1.9%; azithromycin: 1.8%), 3.7% having received metronidazole, and 7.9% having received amoxicillin (Table 1). Among the 3,138 patients who had a \(^{13}\)C-UBT after clarithromycin-based triple therapy, 632 received bismuth-based quadruple therapy, while 2,506 did not re-
characteristics of H. pylori treatment.

Table 1. Baseline Characteristics of Patients Who Underwent a Urea Breath Test after the Clarithromycin-based Triple Therapy (n=3,138)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>512 (16.3)</td>
</tr>
<tr>
<td>Male</td>
<td>1,903 (60.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Past medical history</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>2,612 (83.2)</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>1,625 (51.7)</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>1,485 (47.3)</td>
</tr>
<tr>
<td>Hypertensive disorder</td>
<td>232 (7.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>106 (3.4)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>125 (4.0)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>110 (3.5)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>30 (1.0)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>51 (1.6)</td>
</tr>
<tr>
<td>Acute respiratory disease</td>
<td>70 (2.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>502 (16.0)</td>
</tr>
<tr>
<td>Steroid</td>
<td>237 (7.5)</td>
</tr>
<tr>
<td>Antithrombotic agents</td>
<td>450 (14.3)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>268 (8.5)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>101 (3.2)</td>
</tr>
<tr>
<td>Others</td>
<td>81 (2.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolide</td>
<td>232 (7.4)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>104 (3.3)</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>60 (1.9)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>56 (1.8)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>8 (0.3)</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>250 (7.9)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>118 (3.7)</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%).

Table 2. Variation in the Proportion of Patients with Previous Exposure to Antibiotics According to the Presence of Second Line Therapy in Patients Who Received the Clarithromycin-based Triple Therapy

<table>
<thead>
<tr>
<th>Antibiotic exposure</th>
<th>Patients with BQT (n=632)</th>
<th>Patients without BQT (n=2,506)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolide</td>
<td>94 (14.7)</td>
<td>138 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>27 (4.2)</td>
<td>91 (3.6)</td>
<td>0.449</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>67 (10.6)</td>
<td>185 (7.3)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

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3. Comparison of the history of antibiotic exposure by second-line treatment status among patients who received clarithromycin-based triple therapy

The history of antibiotic exposure was compared based on bismuth-based quadruple therapy status among patients who had a 13C-UBT after clarithromycin-based triple therapy as their first-line treatment. A history of macrolide antibiotic exposure was present in 14.7% of patients who received bismuth-based quadruple therapy. Therefore, the patients can be assumed to have had an unsuccessful first-line eradication therapy (n=632). In comparison, previous exposure to macrolide antibiotics was found in 5.5% among those who did not receive bismuth-based quadruple therapy and therefore had successful eradication treatment (n=2,506) (P<0.001). The corresponding percentages for amoxicillin exposure were 10.6% and 7.3%, respectively (P=0.006). Previous exposure to macrolide antibiotics and amoxicillin was significantly more common among patients who received bismuth-based quadruple therapy (P<0.001). However, the two groups did not demonstrate a statistically significant difference regarding their history of metronidazole exposure (Table 2).

DISCUSSION

In the South Korean H. pylori treatment guideline announced in July 2013, bismuth-based quadruple therapy was recommended as the first-line eradication therapy when resistance to clarithromycin is suspected. However, studies have not examined the changes in actual treat-
ment patterns. This study used data from a single institution converted to the CDM to analyze changes in treatment patterns after January 1, 2014 among patients who had received H. pylori tests and the clinical characteristics and history of antibiotic exposure among first-line eradication treatment patients. Before January 1, 2014, 1.9% (75/3,956) received bismuth-based quadruple therapy as the first-line eradication therapy. After January 1, 2014, 3.3% (63/1,904) received bismuth-based quadruple therapy as first-line eradication therapy, indicating that the proportion increased to a statistically significant degree after the revision in the treatment protocol. However, this proportion remained low. There is a possibility that doctors prefer triple therapy due to concerns about the side effects of bismuth-based quadruple therapy. Another possibility is that doctors had difficulty interpreting the vague language in the revised treatment protocol, which stated that bismuth-based quadruple therapy is recommended when clarithromycin resistance is suspected. Another effect of the revised protocol could have been the significant increase in treatment using PPI, amoxicillin, and metronidazole triple therapy when the clarithromycin resistance test demonstrated patients’ resistance to clarithromycin.

According to the results of a recent European registry study that reported the treatment patterns of H. pylori for 5 years from 2013 to 2018 among 30,394 patients in 27 countries, 78% of patients received empirical therapy. Clarithromycin-based triple therapy was most common (39%), but the treatment patterns and durations differed significantly by region. Quadruple therapy (including concomitant therapy) was performed in southwestern and central Europe, accounting for 63~82% of cases, while in most other parts of Europe, clarithromycin-based triple therapy was used. The European guidelines recommend quadruple therapy in regions where clarithromycin resistance exceeds 15%. However, quadruple therapy is not commonly used in actual treatment, and eradication failure rate might increase when the protocol is not followed.

This study used CDM-based big data, which can be utilized to analyze the treatment patterns of all medications prescribed during a certain period. A strength of this study is that the CDM data could reflect better actual clinical practice. OMOP-CDM transferred data are anonymized and have a minimal risk of privacy violation. Sharing the same data structure across hospitals facilitates multicenter studies, and the reliability can be improved by sharing the code for analysis with other researchers and correcting errors. In addition, we tried to minimize selection bias by creating a cohort that received H. pylori diagnostic tests, including all patients who had undergone rapid urease tests and serum H. pylori antibody tests.

In our hospital, 13C-UBT status was converted to the CDM, but the text data about results were not converted. Therefore, the eradication rate was inferred by checking whether patients completed bismuth-based quadruple therapy after clarithromycin-based triple therapy and a 13C-UBT. The presumed eradication rate of clarithromycin-based triple therapy conducted in this hospital from 2004 to 2019 was 79.8%, which was lower than the results (84.9~87.5%) from a study of the national eradication rate from 2001 to 2010. Nonetheless, the results were similar to the per-protocol eradication rate of 79.6% presented in the South Korean treatment protocol revised in 2020 based on the analysis of randomized clinical trials reported after 2007. Notably, the eradication rate of clarithromycin-based triple therapy in this study includes the results of both empirical and tailored treatment based on clarithromycin resistance tests; therefore, the actual eradication rate of empirical treatment would be lower. Of particular note, according to a recent multicenter randomized controlled trial, the eradication rate of amoxicillin and metronidazole treatment was lower than that of bismuth-based triple therapy when there was clarithromycin resistance (bismuth quadruple therapy vs. metronidazole-intensified therapy: 95.1% vs. 76.4%, \( P=0.001 \)).

In this study, amoxicillin and metronidazole were administered as a tailored treatment to the patients with clarithromycin resistance; hence, the overall eradication rate of first-line therapy might have been relatively low. The decrease in the eradication rate of clarithromycin-based triple therapy is related to an increase in antibiotic resistance, which is closely connected to a history of antibiotic exposure before eradication treatment. As hypothesized, previous exposure to macrolide antibiotics was more common among patients who had unsuccessful...
first-line treatment than among those whose first-line treatment was successful in this study (14.7% vs. 5.5%, P<0.001). Therefore, tailored treatment based on clarithromycin resistance testing, instead of empirical treatment, is particularly necessary for patients with a history of macrolide antibiotic exposure. A history of amoxicillin exposure was also more common in the initial treatment failure group (10.6% vs. 7.3%, P=0.006). An association between amoxicillin resistance and eradication failure was found in a previous study.22 However, the resistance rate of amoxicillin in South Korea is around 9.5%,3 and it has not been identified as the main antibiotic that influences the success of eradication treatment. Therefore, the clinical significance of differences in amoxicillin exposure seems to be low in this study.

This study analyzed a CDM database at a single institution and has limitations as follow. First, it is difficult to confirm the diagnoses and prescriptions received from other institutions in the same patient. Future studies should verify the results using CDM data from the National Health Insurance Service or Health Insurance Review and Assessment Service. Second, data such as $^{13}$C-UBT results, Giemsa staining findings, and clarithromycin-resistant mutation test were not converted to the CDM, making it difficult to confirm the exact eradication rate or analyze information about tailored treatment. Third, some patients who failed in first-line eradication therapy could have refused second-line eradication therapy; however, some might have erroneously classified as eradicated patients. Fourth, there is also a possibility of false-negative results of the $^{13}$C-UBT since the analysis did not include data on PPI intake before the $^{13}$C-UBT. The eradication rate of first-line treatment could therefore have been exaggerated.

Despite these limitations, this is the first study using CDM data that analyzed the treatment patterns and clinical characteristics of patients with *H. pylori* infection. The analysis code developed for this study can be easily applied to multicenter or public health data. Furthermore, the code can facilitate comparisons of antibiotic exposure history by region.

In summary, there was a 1.4 percentage point increase in bismuth-based quadruple therapy as first-line eradication treatment after announcing the 2013 treatment protocol. According to the present analysis of *H. pylori* treatment patterns in the past 16 years using CDM data from a single institution in South Korea, eradication protocol was not significantly modified despite the updated clinical guideline. Our analytic code could be applied to nationwide CDM-converted hospital databases to analyze real world changing trends in *H. pylori* treatment.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**SUPPLEMENTARY MATERIAL**

Supplementary material 1. Korean translation of the article is available from https://doi.org/10.7704/kjhugr.2022.0010.

**ORCID**

Seung In Seo https://orcid.org/0000-0003-4417-0135
Tae Jun Kim https://orcid.org/0000-0001-8101-9034
Yoon Jin Choi https://orcid.org/0000-0002-1922-9388
Chang Seok Bang https://orcid.org/0000-0003-4908-5431
Yong Kang Lee https://orcid.org/0000-0003-2929-4447
Moon Won Lee https://orcid.org/0000-0002-8411-6398
Su Youn Nam https://orcid.org/0000-0002-5568-7714
Woon Geon Shin https://orcid.org/0000-0002-9851-5576

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서론

우리나라 헬리코박터 파일로리(Helicobacter pylori, H. pylori) 감염의 진단과 치료에 대한 진료 지침이 4번째 개정되어 2020년에 발표되었으나, 진료 지침에 따라 치료 패턴에 변화가 있었는지에 대한 연구는 부족한 실정이다. 우리나라에서는 양성자펌프억제제(proton pump inhibitor, PPI), clarithromycin, amoxicillin을 하루 2회 7~14일간 투여하는 clarithromycin 기반 삼제요법을 1차 제균 치료로 오랫동안 사용해 왔으나, 제균율은 지속적으로 감소하여 최근에는 80% 미만의 제균율을 보고하고 있다. 따라서, 2013년에 개정된 국내 진료 지침에서는 clarithromycin에 대한 내성이 의심되는 경우에 1차 제균 치료로 bismuth 기반 사제요법을 사용하도록 권고하였다. 이 후 2020년부터는 중합효소 연쇄반응(PCR) 검사 또는 유전자 염기서열분석 검사 후 clarithromycin 내성 돌연변이의 유무에 따라 치료제를 선택하는 맞춤형 치료가 도입되었으나, 실제로 치료 패턴의 변화가 있는지에 대해 잘 알려지지 않은 상태이다. 국내에서는 산업통상자원부에서 2018년부터 CDM 기반 분산형 바이오헬스 빅데이터 플랫폼 구축 사업을 추진하여 전국의 약 40개 병원들의 전자 의료정보 자료를 OMOP-CDM으로 변환하여 바이오헬스 융합 빅데이터망이 구축된 상태이다. 이는 CDM으로 변환된 원료를 이용하여 clarithromycin 기반 삼제요법을 받은 환자군에서 이전에 복용한 약제나 질병 등에 대한 분석이 용이하여 항생제 노출분석을 용이하고, 치료 경로(treatment pathway) 분석을 통해 헬리코박터 파일로리 치료 패턴에 대한 분석과 시각화가 가능하다. 따라서 이 연구에서는 CDM으로 변환된 원료를 이용하여 clarithromycin 기반 삼제요법으로 제균 치료를 받은 환자의 특성과 항생제 노출분석을 수행하였다. 이 연구는 3차 개정안이 발표된 이후, 2014년 1월 1일을 전후로 해구 치료의 패턴 변화에 있는지를 알아보고자 하였다.

대상 및 방법

1. 데이터베이스

CDM으로 변환된 강동성심병원 전자의료기록 데이터베이스(Kangdong Sacred Heart Hospital Common Data Model, KDH-CDM)를 사용하여 연구를 진행하였다. 이 데이터베이스는 1,689,604명 환자의 2004년부터 2019년까지 16년 동안의 진료 자료를 포함하고 있으며 이전에 발표한 연구에 사용된 바 있다. 이 데이터베이스는 환자가 내원하여 치료받은 약제, 진단명, 내원증을 포함한 시술, 수술, 혈액 검사, 금속 요소 분석을 위한 프레임워크(rapid urease test, CLOtest, Pronto Dry New, Medical Instruments Co., Herford, Germany), 요소호기검사(urate breath test, 13C-UBT; UBT-IR 300, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) 시행 여부가 포함되어 있다. OHDSI 커뮤니티가 개발한 ATLAS는 연구설계, 코호트 추출, 유형화 검사, 대규모 성향점수예측, CDM의 특성 분석, 인공지능 기반 예측 등의 분석을 할 수 있는 웹 기반 오픈 플랫폼이다. ATLAS 버전 2.7.6을 사용하여 연구를 설계하였고, 데이터 수집자와 연구 및 다기관 분석이 가능한 FEEDER-NET이라는 중개 플랫폼을 이용하여 분석을 시행하였다. 이 연구는 강동성심병원 의료연구 윌리심의위원회의 결정에 따라 심사가 면제되었다(IRB, 2021-11-001).
2. 코호트 생성

헬리코박터 패혈균 치료의 경로 분석을 위해 급속 요소 분해효소 검사 또는 혈청신 생량체 검사 (Genedia H. pylori ELISA; Green Cross Medical Science Co., Seoul, Korea)를 사용으로 시행받은 18세 이상의 성인 환자 29,458명을 대상 코호트 (target cohort)로 항생제 치료 패턴을 분석하였다. 사건 코호트 (event cohort)는 대상 코호트에 포함된 시점 이후에 clarithromycin, amoxicillin, metronidazole, bismuth subcitrate, tetracycline 혹은 levofloxacin을 7-14일간 치료 받은 경우로 정의하였다. 대상 코호트를 2014년 1월 1일 이전과 이후로 나누어 진료 지침 발표 전후 치료 패턴을 비교하였다. 또한, 최초로 clarithromycin 기반 삼제요법으로 PPI, amoxicillin, clarithromycin을 7-14일간 동시에 사용하고 clarithromycin, amoxicillin, metronidazole를 동시에 7-14일간 치료 받은 환자와 치료 받지 않은 환자군으로 나누어서 항생제 노출력의 차이를 분석하였다.

3. 치료 경로 분석

치료 경로 분석은 대상 코호트 진입 시점 이후 발생한 사건을 요약하는 방법으로, 인구조사 내의 주요 사항을 포함한 치료 현황에 관한 중요한 근거를 제공할 수 있다. 실제 이전 GHDSI 국제 연구에서 OMOP-CDM 자료로 2행당노병, 고혈압, 우울증에 대한 치료 경로의 특징을 분석하여 각 질병에서 처음 사용하는 약물, 가장 흔하게 사용하는 약물과 이후의 치료 패턴을 sunburst plot으로 시각화하여 보고하였다. ATLAS 플랫폼에 있는 코호트 경로 (cohort pathway) 탭을 이용하여 대상 코호트와 사건 코호트를 분석하기를 하고 R 통계 프로그램을 통해 치료 경로에 대한 시각화 도표를 생성하였다. 생성된 도표를 클릭하여 전체 대상 코호트 중 치료 경로에 속하는 환자의 분율과 이후 치료에 대한 패턴을 확인하였다.

4. 임상적 특성 분석

ATLAS의 characterization 탭에서는 대상 코호트의 특성 분석이 가능하며, 이를 이용하여 다양한 데이터베이스에 적용할 수 있다. 특정 분석을 위해서는 하나 이상의 코호트와 분석하고자 하는 하나 이상의 속성이 필요하다. 우선, 설정한 대상 코호트에 대해서 특정 분석 도구 (feature analysis)를 통해 우리가 알아보고자 하는 속성에 대하여 정의하게 되는데, 본 연구에서는 기존의 인구통계학적 정보와 코호트 진입 이전 1년 내의 약물과 진단명 이외에 코호트 진입 이전 macrolide, amoxicillin, metronidazole 항생제 노출에 대한 코호트를 만들어 이 속성에 대하여 추가로 분석하였다.

5. 통계적 분석

ATLAS를 통해 얻은 결과를 토대로, 범주형 변수는 카이제곱 검정 (chi-square test)을 사용하여 비교 분석하였고 MedCalc® 통계프로그램 version 20.106 (MedCalc Software, Ostend, Belgium)를 통해 시행하였다. P값이 0.05 미만일 때 유의하다고 판정하였다.

결과

1. 헬리코박터 파일로리 치료 패턴의 변화

헬리코박터 파일로리 검사를 시행한 환자 총 29,458명 중에서 급속 요소 분해효소 검사를 받은 환자는 15,444명. 할행형 염료박테리아 항체를 포함한 환자는 14,014명으로 이 중에서 치료 경로에 들어간 환자는 총 7,647명으로 전체 감사 환자 26.7%였다. 전체적인 요소로 화재 또는 포함된 환자는 Fig. 1에 도식화되어 있다. 치료 경로에 들어간 7,647명 중 5,547명 (72.5%)에서 clarithromycin, amoxicillin을 7-14일간 동시에 사용하였고, 1차로 bismuth subcitrate, metronidazole, tetracycline을 7-14일간 치료 받은 환자는 138명 (1.8%)이었다 (Fig. 2A). 본문에서는 순차 치료나 동시 치료를 시행하지 않았고, metronidazole, amoxicillin 치료군이 175명 (2.3%)이었으며, 그 외의 단일 항생제 치료는 clarithromycin 4.1%, metronidazole 5.3%, levofloxacin 7.1%로, 이는 헬리코박터 파일로리 치료와 관련이 없는 항생제 노출일 것으로 생각한다 (Fig. 2A). 이를 2014년 1월 1일 전후로 나누어 치료 경로를 분석하였을 때 2014년 1월 1일 이전에는 3,956명 중 75명 (1.9%)에서 1차로 bismuth subcitrate, metronidazole, tetracycline 치료를 받은 반대, 2014년 1월 1일 이후에는 1,904명 중에서 63명 (3.3%)으로 차이가 있었다 (P<0.001) (Fig. 2B). 또한 amoxicillin, metronidazole 치료의 경우 2014년 이전에 3,956명 중 1,319명 (8.0%)에서 2014년 이후 1,904명 중 144명 (7.6%)으로 증가하였다 (P<0.001).

2. Clarithromycin 기반 삼제요법 치료 환자들의 기본 특성
최초로 PPI, clarithromycin, amoxicillin을 동시에 7~14일 간 복용한 환자 5,547명 중에서 한달 이후 소요기간 검사를 시행한 환자는 3,138명이었다(Fig. 1). 이에 대한 임상적 특성 분석 결과 평균 나이는 53.10±13.34세, 남성의 비율은 60.6%었다(Table 1). 제균 치료의 적용증이 되는 소화성 궐양의 비율은 2,612명(83.2%)이었으며 위암은 178명(5.7%), 그 외의 경우는 348명(11.1%)이었다. 제균 치료 전에 소화성 궐양과 연관된 약제의 치료력은 분석한 결과 비스테로이드소염제 16%, 항혈전체 14.3%, 스테로이드는 7.5%였다. 항혈전체 중에서 aspirin 8.5%, clopidogrel 3.2%였다. 제균 치료 이전의 항혈전체 치료력은 약물의 성분을 모두 포함하여 분석하였고, macrolide계 항혈전체 7.4% (clarithromycin 3.3%, roxithromycin 1.9%, azithromycin 1.8%), metronidazole 3.7%, amoxicillin 7.9%으로 amoxicillin 노출력이 가장 많았다(Table 1).

3. Clarithromycin 기반 삼제요법 치료 환자에서 2차 치료 시행 여부에 따른 항생제 노출력 비교

1차 제균 치료로 clarithromycin 기반 삼제요법을 처방받은 이후에 소요기간 검사를 시행한 환자에서는 bismuth 기반 삼제요법 유무에 따라 항생제 노출력비를 비교하였다. 1차 제균 치료 실패로 유추할 수 있는 bismuth 기반 삼제요법 시행군(=632)과 제균 치료 성공으로 유추할 수 있는 bismuth 기반 삼제요법을 시행하지 않은 군(=2,506)을 비교한 결과, 3,138명 중에서 clarithromycin 기반 삼제요법이 시행된 경우는 652명, metronidazole 3.7%, amoxicillin 7.9%으로 amoxicillin 노출력이 가장 많았다(Table 1).

 Clarithromycin 기반 삼제요법을 받고 소요기간 검사를 시행한 환자는 1차 제균 치료 실패로 유추할 수 있는 경우가 3,138명 중에 bismuth 기반 삼제요법을 시행한 환자는 652명, metronidazole 3.7%, amoxicillin 7.9%으로 amoxicillin 노출력이 가장 많았다(Table 1).

고찰

2013년 7월에 발표된 우리나라 헬리코박터 포실로리 진료 지침에서 clarithromycin 항생제에 대한 내용이 없었던 경우 1차 제균요법으로 bismuth 기반 삼제요법을 권고하였으나 실제 치료 패턴 변화에 대한 국내 연구는 아직까지 없었다. 이번 연구에서는 FDR로 변환된 단일기관 보고를 이용하여 헬리코박터 포실로리 진료 검사를 시행한 환자에서 2014년 1월 1일 전 후로 치료 패턴의 변화와 1차 제균 치료 환자의 임상적 특성과 항생제 노출력에 대해 분석하였다. 2014년 1월 1일 이전에 치료를 받은 환자 5,956명 중에서 1차 제균 치료로 bismuth 기반 치료를 받은 1,956명(75/3,956)에서 1차 제균 치료로 bismuth 기반 치료를 받은 반면, 2014년 1월 1일 이후에는 3,390명(65/1,904)에서 bismuth 기반 치료범위를 1차 제균 치료를 받은 것으로 나타나 전산 지침 개정 후 그 비율이 통계적으로 의미 있게 증가하였고 그 비율이 여전히 높지 않음을 확인할 수 있다. 이러한 결과는 bismuth 기반 삼제요법의 부작용에 대한 걱정으로 인한 의료인의 삼제요법 선호로 인한 결과일 가능성이 높다. 또한 clarithromycin 내성 검사 후 내성이 있을 경우 PPI, amoxicillin, metronidazole 삼제요법으로 치료할 수 있는 반도가 현재까지 증가한 정도로 상향이 주었음을 것으로 생각한다.

27개 국가의 30,394명을 대상으로 2013년부터 2018년까지 5년 동안의 헬리코박터 포실로리 치료 패턴을 보고한 유럽의 최근 메리스터 연구 결과를 살펴보면, 78%의 환자가 경합적 치료를 받았으며 clarithromycin 기반 삼제요법이 39%로 가장 많았으나, 지역마다 치료 패턴이나 기간이 현저히 달랐다. 유럽의 남서부와 중부에서는 63~82%에서 동시 치료를 포함한 삼제요법을 선호하고 있는 반면에, 유럽 대부분의 지역에서 clarithromycin 기반 삼제요법을 사용하고 있었다. 유럽 진료 지침은 clarithromycin 내성률이 15% 이상인 지역에서는 사제요법을 권고하고 있으나, 실제 치료에서는 사제요법을 많이 쓰지 않고 있으며, 이처럼 진료 지침을 따르지 않기 때문에 치료 실패율이 높다고 분석하였다. 이번 연구는 일정한 기간 동안에 처방받은 모든 약물의 치료 패턴을 분석할 수 있는 CDM 기반 박테리아 자료를 사용하였기 때문에 실제 임상 현황을 더 잘 반영할 수 있다는 장점이 있다. 특히, OMOP-CDM 변환 자료는 의료화되어 있어 개인 정보의 유출 위험이 없으며, 각 병원마다 특정한 데이터 구조로 변환되어 있어 다기관 연구를 수행하게 할 수 있고, 실제한 분석 코드를 다른 연구자와 공유하여 오류를 수정하여 신뢰성을 높일 수 있다는 장점이 있다. 또한, 감수 요소 분해요소 또는 혈청 헬리코박터 포실로리 형식 검사를 시행한 환자는 모두 포함하여 헬리코박터 포실로리 진료 검사를 받은 환자를 모두 포함하여 헬리코박터 포실로리 진료 검사를 받은 환자를 모든 경우를 고려하여 선정 비율률을 최소화하고자 하였다. 본 연구에서는 소요기간 검사 시행 여부가 CDM으로 변환되었으나 결과에 대한 탐색 자료 변환을 이루어지지 않았기 때문에 clarithromycin 기반 삼제요법 치료 후 소요기간 검사를 시행한 환자에서 bismuth 기반 삼제요법의 추가 치료 여부를 확신하기 어려웠다.
한하여 제균율을 추정하였다. 본 기관에서 2004년부터 2019년까지 시행한 clarithromycin 기반 삼계요법의 추정 제균율은 79.8%로, 2001년부터 2010년까지 조사한 전국 제균율을 연구에서 발표한 결과(84.9~87.5%)보다 낮았으며, 2007년 이후 발표된 무작위 배정 임상시험 결과를 분석하여 2020년에 개정된 국내 진료 지침에서 제시한 per protocol 제균율 79.6%와 유사한 결과를 보였다. 그러나 이 연구에서 제시한 clarithromycin 기반 삼계요법의 제균율은 경험적 치료와 clarithromycin 내성이 있는 환자 기반의 맞춤형 치료를 포함한 제균율이므로 경험적 치료의 실제 제균율은 더 낮을 것이다. 특히, 최근에 발표된 다기관 무작위 대조 연구에 의하면 clarithromycin 내성이 있는 경우 amoxicillin, metronidazole 치료의 제균율이 bismuth 기반 사제요법의 제균율보다 낮았음을 고려해 보면(bismuth quadruple therapy vs. metronidazole-intensified therapy: 95.1% vs. 76.4%, $P=0.001$), clarithromycin 내성이 있는 환자에서 맞춤형 치료로 사용한 amoxicillin, metronidazole 치료가 이 연구에 포함되어 있어서 전체적인 1차 제균을 또한 낮지 않았음을 것으로 예상한다.

Clarithromycin 기반 삼계요법 제균율의 감소는 항생제 내성율 증가와 관련이 있으며, 이는 제균 치료 이전의 항생제 노출과 밀접한 관계가 있다.3,10-11 5,12-21 예상대로, 이번 연구에서도 1차 치료 실패 환자군에서 macrolide계 항생제(14.7% vs. 5.5%, $P<0.001$)의 노출이 치료 성공 환자군에 비해 더 많았다. 따라서, macrolide계 항생제에 노출이 있는 환자는 경험적 치료보다 clarithromycin 내성이 있는 감사 기반의 맞춤형 치료가 더욱 필요할 것으로 생각한다. Amoxicillin 노출률(10.6% vs. 7.3%, $P=0.006$)도 치료 실패군에서는 많았는데, amoxicillin의 내성이 제균 실패와 연관이 있다는 연구 결과가 있으며,22 amoxicillin의 국내 내성률은 9.5% 정도이며, 제균 치료 실패에 영향을 미치는 주요 항생제는 아니 것으로 알려져 있어 본 연구에서의 통계적 차이의 임상적 의미는 작다고 생각한다.

이번 연구는 단일기관의 CDM 데이터베이스로 분석한 연구로서 다음과 같은 제한점이 있다. 첫째, 같은 환자가 다른 병원에서 진단된 질병 또는 약물에 대해서는 확인이 어려운 단점이 있다. 이에 대해서는 후속 연구로 국민건강보험공단이나 산사평가원 CDM 자료 등을 적용해 증명해 볼 필요가 있다. 둘째, 요소호기 검사 결과나 Giemsa stain 결과와 같은 텍스트 자료 및 clarithromycin 내성이 있는 환자가 CDM으로 변환되지 못하여 정확한 제균율이나 맞춤형 치료에 대한 정보 등을 확인하기 어려웠다. 셋째, 1차 제균 치료에 실패하였으나 2차 제균 치료를 자료에 포함한 환자가 제균된 환자로 잘못 분류되는 경우가 있고, 요소호기 검사 및 PPI 복용 여부를 통해 하지 않아 요소호기 검사의 위응성 결과가 포함되어 있음을 가능성이 있어, 이 연구에서 추정한 1차 제균 치료의 제균율은 과정 평가되었을 가능성이 있다.

그럼에도 불구하고, 이 연구는 처음으로 CDM 자료를 이용한 치료 패턴과 임상적 특성 분석을 시행하였으며, 이번에 개발한 분석 코드를 통해 비교적 쉽게 다른거거나, 공공의료 자료에 적용하여 지역별 항생제 노출률의 차이 등을 분석해 볼 수 있는 접에서의 의미가 있다고 생각한다.

결론적으로, 국내 단일기관의 CDM 자료로 지난 16년간의 헬리코박터 파이로리 치료 패턴을 분석한 데 2013년 진료 지침 발표 이후 1차 제균 치료로서 bismuth 기반 사제요법의 사용은 14.8% 증가에 그쳤다.