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BRIEF ARTICLE

Gastrointestinal tuberculosis is not associated with proton pump inhibitors: A retrospective cohort study

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Abstract

AIM: To evaluate the effect of proton pump inhibitors (PPIs) on the development of gastrointestinal tuberculosis.

METHODS: All patients who were more than 20 years old and who had received a prescription for PPIs among those who visited Seoul National University Hospital from January 1, 2005 to December 31, 2009 were identified. Due to the low sensitivity of the microbiologic test and the nonspecific pathologic findings, the diagnosis of gastrointestinal tuberculosis was confirmed through the presence of active ulcerations and the responses to anti-tuberculosis medications. The patients were divided into two groups according to treatment duration (group 1: $\leqslant$ 3 mo; group 2: > 3 mo) and were followed up from the time they took the first prescription of PPIs until their last visit. Logistic regression analysis was used to calculate the relative risks (RR) and 95%CI, adjusting for covariates.

RESULTS: Among the 61 834 patients exposed to PPIs (50 534 in group 1; 11 300 in group 2), 21 patients were diagnosed with PPI-associated gastrointestinal tuberculosis during 124 274 person-years of follow-up. Of 21 patients, the 12 who revealed only scar changes in the colonoscopy were excluded from the statistical analyses. Of those who remained, 2 were excluded because they underwent gastrointestinal endoscopy within 4 wk of the first prescription for PPIs. Longer exposure to PPI was associated with a higher mean age (55.0 ± 14.5 in group 1 *vs* 58.2 ± 13.3 in group 2, $P < 0.001$) and a higher Charlson co-morbidity index (0.50 ± 0.93 in group 1 *vs* 0.77 ± 1.14 in group 2, $P < 0.001$). The true incidence of active gastrointestinal tuberculosis was 0.65 per 1000 person-years in group 1 and 0.03 per 1 000 person-years in group 2. Like the less-than-three-month PPI treatment period in group 1, the over-three-month PPI therapy period in group 2 was not associated with increased risk of acquiring gastrointestinal tuberculosis, after adjusting for age and co-morbidities, whereas the Charlson co-morbidity index was associated with increased risk of acquiring gastrointestinal tuberculosis based on the score [RR: (reference 1) in group 1 *vs* 1.518 in group 2; 95% CI: 1.040-2.216, $P = 0.03$].

CONCLUSION: Long-term PPI therapy does not seem to be associated with increased risk of acquiring gas-

trointestinal tuberculosis, but a higher Charlson comorbidity index is associated with such.

Key words: Proton pump inhibitor; Acid suppression; Tuberculosis; Gastrointestinal tuberculosis; Tuberculous colitis

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INTRODUCTION

Gut flora is closely related to human health and disease[1]. The intestinal microflora is assumed to be affected by a series of factors that determine the intraluminal environment: the pH in the gastrointestinal tract, oxygen tension, nutrient availability, colonic physiology, bacterial interference, *etc.*[2]. One of the major factors controlling the bacterial distribution in the gastrointestinal tract is the gastric acid barrier, which may be affected by the use of inhibitors of gastric acid secretion, gastrectomy, and dietary indiscretion and stress[3]. The establishment of enteric infection has been considered directly related to gastric acidity reduction[4,5]. Several recent studies associated proton pump inhibitors (PPIs) with a two- to three-fold increase in the risk of *Clostridium difficile* infection[6-8].

PPIs are currently the most powerful gastric acid suppressants and the drug of choice for the treatment of gastroesophageal reflux disease and peptic ulcer. PPIs are very powerful acid suppressants whose effects mean the percentage time intragastric pH > 4 may increase from 20% at baseline to over 60% within a week[9]. Today's life expectancy is longer than ever before, and the number of patients who take antiplatelet agents to prevent the onset of vascular diseases is increasing. Along with this, more and more patients are obliged to take prophylactic gastric acid suppressants, including PPIs, to prevent severe complications, such as peptic ulcer bleeding.

Tuberculosis is still an important health problem in many developing countries, including South Korea[10]. Unlike in developing countries, the disease used to be uncommon in developed countries, but it has re-emerged in the Western countries as a result of the acquired immunodeficiency syndrome (AIDS) epidemic therein as well as the influx of immigrants from developing countries[11-13]. Gastrectomy has been known to be a potential risk factor for tuberculosis for decades[14-16]. To these authors' knowledge, however, there has been no report about a possible association between PPI use and gastrointestinal tuberculosis. This study was thus conducted to evaluate the effect of PPIs on the development of gastrointestinal tuberculosis.

MATERIALS AND METHODS

Setting and design

This study is part of a hospital-based longitudinal cohort study entitled "Seoul National University Hospital (SNUH) PPI Safety Study," in which these authors analyzed the data regarding patients who visited SNUH and who were treated with PPI between January 1, 2005, and December 31, 2009. SNUH is a large urban tertiary care center in Seoul, South Korea. The hospital's institutional review board approved the study with a waiver of informed consent.

Data sources

Data were obtained from a clinical data warehouse fully synchronized with the electronic medical recording (EMR) system created as part of the usual care. SNUH Clinical Data Warehouse (CDW) contains all the information from each visit, not only routine clinical data such as the demographics, diagnosis, medication profiles, laboratory results, and lengths of stay of inpatients since 2001 but also the electronic charts since 2004.

Patients and case definitions

All patients who were at least 20 years old at their first visit and who ingested PPI on prescription during the five-year screening period were included in the study. According to a large retrospective study including 225 Korean patients, histological examination of the colonoscopic biopsy specimens revealed caseous necrosis in only 11.1% of the patients, and acid-fast bacilli (AFB) in 17.3% of the patients. *Mycobacterium tuberculosis* was isolated from the culture of biopsy specimens in 29.3% of the patients[17]. Even though granulomas were observed in 72.4% of the patients, granuloma is not a specific finding in intestinal tuberculosis. Due to the low sensitivity of the microbiologic test and the nonspecific pathologic findings, the diagnosis of active gastrointestinal tuberculosis was confirmed through both an endoscopic finding of active transverse ulcerations and a good response to anti-tuberculosis treatment, which was confirmed through a follow-up colonoscopy within three months from the initiation of the treatment. The definition of good therapeutic response was complete or near-complete healing of all the ulcerations in the follow-up colonoscopy.

The patients in whom colonoscopy revealed only scar changes were excluded from the statistical analysis for two reasons: (1) the exact temporal relationship between PPI ingestion and the development of gastrointestinal tuberculosis could not be verified; and (2) the diagnosis of tuberculosis could not be confirmed as there was no need for anti-tuberculosis treatment and due to the low sensitivity of the histological evaluation of the biopsy specimens. As tuberculosis is a chronic inflammatory disease, the patients who were diagnosed with gastrointestinal tuberculosis within four weeks of their first prescription for PPIs were also excluded from the statistical analyses.

The primary exposure of interest was receipt of PPIs. PPI

Table 1 Clinical information of the patients who were endoscopically diagnosed with suspicious tuberculosis

	Gender/ age	Group[1]	PPI duration before diagnosis (d)	Reason for endoscopy	Endoscopy findings	Pathology findings	Decision for analysis	Note
1	F/65	2	639	Diarrhea	Scar, cecum	No biopsy	Excluded	
2	F/73	1	844	Abdominal pain	Scar, cecum	No biopsy	Excluded	
3	F/65	2	1177	Routine check	Scar, cecum	No biopsy	Excluded	
4	F/60	1	415	Routine check	Scar, terminal ileum	No biopsy	Excluded	Small bowel resection due to tuberculosis 20 years ago
5	F/64	1	616	Anemia	Scar, descending colon	No biopsy	Excluded	
6	F/67	2	56	Abdominal pain	Scar, cecum	No biopsy	Excluded	
7	F/55	2	87	Routine check	Scar, cecum	No biopsy	Excluded	
8	F/82	2	523	Constipation	Scar, cecum	No biopsy	Excluded	
9	F/58	1	65	Lower abdominal pain	Scar, cecum	No biopsy	Excluded	
10	F/55	1	612	Routine check	Scar, cecum	No biopsy	Excluded	
11	M/52	1	894	Blood-tinged stool	Scar, cecum	No biopsy	Excluded	
12	F/61	2	29	Bloating	Scar, cecum	No biopsy	Excluded	
13	F/72	1	125	Hematochezia	Ulcers, cecum	Chronic active colitis	Included	
14	M/44	1	28	Anemia	Ulcers, cecum/ transverse colon	Non-caseating granuloma, negative PCR[2]	Included	
15	F/63	2	55	Epigastric pain	Ulcer, gastric cardia	Non-caseating granuloma, positive PCR[2]	Included	Palpable right supraclavicular lymph node
16	M/49	1	7	Melena	Ulcers, terminal ileum	Chronic active ileitis	Excluded	
17	M/41	1	574	Loose stool	Ulcers, cecum	Non-caseating granuloma, positive PCR[2]	Included	
18	M/20	1	49	Lower abdominal pain	Ulcers, ileocecal valve	Chronic active colitis	Included	
19	F/66	1	1	Melena	Ulcers, terminal ileum	Chronic active ileitis	Excluded	
20	F/59	1	224	Lower abdominal pain	Ulcers, ileocecal valve	Chronic active colitis,	Included	
21	F/46	1	28	Epigastric pain	Ulcers, mid-esophagus	Non-caseating granuloma, positive PCR[2]	Included	

[1]Patients with PPI treatment for three months or less as group 1, and patients with more-than-three-month PPI treatment as group 2; [2]Polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*. PPI: Proton pump inhibitor; M: Male; F: Female.

exposure was classified by overall dosing period before the first endoscopy showing suspicious gastrointestinal tuberculosis or the last prescription date in patients without gastrointestinal tuberculosis. The patients with less than three months of PPI treatment were defined as group 1, and those with three or more months of PPI treatment were defined as group 2. To normalize the different acid-suppressive capacities among the PPI regimens, omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg, pantoprazole 40 mg, and esomeprazole 40 mg were defined as standard daily doses of PPI. To calculate the adjusted dosing period, the period of the half-dose regimen was multiplied by 0.5, and the period for the double-dose regimen was multiplied by 2.

Statistical analysis

The covariates that may influence the risk of acquiring gastrointestinal tuberculosis and those that may influence the exposure to PPIs were included in the analysis. These variables were age, sex, and co-morbidities. The co-morbidities were determined from the registered diagnosis by the attending physician using the International Classification of Diseases 10th Revision code. Quan's algorithm was used to define the 17 Charlson co-morbidities, and the Charlson index was calculated[18,19].

Unadjusted comparisons were performed using the *t*-test, ANOVA test, Mann-Whitney test, χ^2 test, or Fisher exact test, as appropriate. Logistic regression modeling was used to estimate the relative risk of acquiring gastrointestinal tuberculosis in multivariate analyses. Statistical analysis was performed using the SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Among the patients who visited SNUH during the five-year study period, 61 834 patients received PPIs and 7 gastrointestinal tuberculosis cases were identified. After excluding the patients who were diagnosed with suspicious gastrointestinal tuberculosis through endoscopy prior to the first prescription of PPIs, a total of 21 patients were screened. Of these, 12 patients who revealed only scar changes in colonoscopy were excluded from the statistical analyses. Of those who remained, 2 were excluded because they underwent gastrointestinal endoscopy within 4 wk of the first prescription of PPIs (Table

Table 2 Summary of descriptive statistical analysis *n* (%)

	Group 1	Group 2
Patients (*n*)	50 534	11 300
Cases	6 (0.012)	1 (0.009)
Esophageal tuberculosis	1	0
Gastric tuberculosis	0	1
Colonic tuberculosis	5	0
Total follow-up (person-mo)	1 102 947	388 345
Average follow-up (mo)	21.8	34.4
Incidence per 1000 person/yr	0.65	0.03

1). Anti-tuberculosis medications (isoniazid, rifampicin, ethambutol, and pyrazinamide) were prescribed to the finally selected 7 patients. Follow-up endoscopy was performed 2 or 3 mo after the start of the anti-tuberculosis treatment, and revealed complete healing or almost-healed ulcerations in all 7 patients.

The true incidence of gastrointestinal tuberculosis was 0.65 per 1000 person-years in group 1 and 0.03 per 1000 person-years in group 2 (Table 2). The characteristics of each group are shown in Table 3. The mean age (± SD) was 55.0 ± 14.5 years in group 1 and 58.2 ± 13.3 years in group 2. Longer exposure to PPI was associated with a higher Charlson co-morbidity index and a higher age (Table 3).

Table 4 presents the demographic and clinical characteristics of the active-gastrointestinal-tuberculosis and non-tuberculosis groups. Due to the small number of patients in the active-tuberculosis group, there was no significant difference between the two groups.

Table 5 shows the results of the multivariable analysis using logistic regression. A longer PPI treatment period (over three months) was not associated with increased risk of acquiring active gastrointestinal tuberculosis. The Charlson index was associated with significantly increased risk of acquiring active gastrointestinal tuberculosis by over 50% per score 1.

Table 3 Demographic and clinical characteristics of each group (mean ± SD)

	Group 1	Group 2	*P*-value
No. of patients	50 534	11 300	
Age, yr	54.96 ± 14.50	58.18 ± 13.31	< 0.001
Gender, male (%)	52.5	46.7	< 0.001
PPI duration, d	25.17 ± 21.51	285.78 ± 437.02	< 0.001
Co-morbidities, *n* (%)			
AIDS	75 (0.15)	6 (0.05)	0.011
Cerebrovascular disease	3655 (7.23)	1201 (10.63)	< 0.001
Congestive heart failure	196 (0.39)	71 (0.63)	< 0.001
Chronic pulmonary disease	184 (0.36)	64 (0.57)	0.002
Dementia	332 (0.66)	159 (1.41)	< 0.001
DM	4438 (8.78)	1600 (14.16)	< 0.001
DM without chronic complication	4280 (8.47)	1532 (13.56)	< 0.001
DM with chronic complication	158 (0.31)	68 (0.60)	< 0.001
Liver disease, mild	3182 (6.30)	1475 (13.05)	< 0.001
Hemiplegia or paraplegia	57 (0.11)	8 (0.07)	0.213
Liver disease, moderate or severe	488 (0.97)	205 (1.81)	< 0.001
Any malignancy	62 (0.12)	13 (0.12)	0.833
Metastatic solid tumor	310 (0.61)	69 (0.61)	0.972
Myocardial infarction	598 (1.18)	121 (1.07)	0.313
Peripheral vascular disease	368 (0.73)	114 (1.01)	0.002
Peptic ulcer	7011 (13.88)	1569 (13.88)	0.977
Rheumatologic disease	284 (0.56)	421 (3.73)	< 0.001
Renal disease	498 (0.99)	342 (3.03)	< 0.001
Charlson index	0.50 ± 0.93	0.77 ± 1.14	< 0.001
Score = 0 *n* (%)	33297 (65.89)	6167 (54.58)	< 0.001
Score = 1 *n* (%)	15536 (30.75)	4363 (38.61)	
Score ⩾ 3 *n* (%)	1699 (3.36)	770 (6.81)	
History of admission (%)	29138 (57.66)	6692 (59.22)	0.002
History of ICU admission (%)	1668 (3.30)	352 (3.12)	0.315

PPI: Proton pump inhibitor; AIDS: Acquired immune deficiency syndrome; ICU: Intensive care unit; DM: Diabetes mellitus.

DISCUSSION

This cohort study was conducted not only to evaluate the possible role of more-than-three-month PPI treatment but also to calculate the incidence rate of, and to find the risk factors for, acquiring active gastrointestinal tuberculosis in all the at-least-20-year-old patients who visited SNUH and who were treated with PPI between January 1, 2005 and December 31, 2009. As a result, more-than-three-month PPI treatment was found not to be associated with increased risk of acquiring active gastrointestinal tuberculosis. The annual incidence rate of tuberculosis was reported to be 97 per 100 000 in 2010 in the South Korean general population[10]. The calculated incidence rate of active gastrointestinal tuberculosis seems to be much lower in PPI-treated patients in the present study (Table 2), even considering the reportedly small proportion of gastrointestinal tuberculosis in the whole tuberculosis population[20].

A diagnosis of gastrointestinal tuberculosis can be confirmed if a characteristic caseous granuloma, positive smear of AFB, or positive culture of mycobacterium is observed in the biopsy specimen[12]. Compared to pulmonary tuberculosis, however, there is a relatively small absolute number of AFB in gastrointestinal tuberculosis[21], and caseous granuloma is infrequently observed in patients with an early-stage disease or who have been treated with anti-tuberculosis medications[22]. Many studies have been performed to assess the diagnostic accuracy of such histological markers, and there have been a number of reports showing granuloma in 41%-48%[23-25], caseous granuloma in 8%-18%[24-26], positive smear of AFB in 0%-100%[24,25,27,28], and positive culture of AFB in 0%-69%[24-26,28] of gastrointestinal-tuberculosis patients. As there have been many reports showing variable results, it seems impossible to set universal standards for diagnosing gastrointestinal tuberculosis. There are adjunct diagnostic modalities, such as polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*, and endoscopic findings. Although PCR is a method that shows over 50% diagnostic sensitivity, its substantial false positivity limits its role to that of an adjunctive test for the diagnosis of gastrointestinal tuberculosis[29]. In the present study, both non-caseating granuloma and positive PCR were observed in two patients with gastroesophageal

Table 4 Demographic and clinical characteristics of the active-tuberculosis and non-tuberculosis groups (mean ± SD)

	Active tuberculosis	Non-tuberculosis[1]
No. of patients	7	61 790
Age, yr	50.6 ± 17.7	55.6 ± 14.3
Gender, male (%)	3 (43)	31 803 (51)
PPI duration	47.7 ± 97.9	72.8 ± 213.1
Charlson index	1.29 ± 2.36	0.55 ± 0.97
Score = 0 *n* (%)	5 (71)	39 459 (64)
Score = 1, 2 *n* (%)	0 (0)	19 899 (32)
Score ⩾ 3 *n* (%)	2 (29)	2467 (4)
History of admission	6 (86)	35 824 (58)

[1]Patients without gastrointestinal tuberculosis irrespective of the temporal relationship with proton pump inhibitor treatment or disease activity. PPI: Proton pump inhibitor.

Table 5 Results of the multivariable analysis using logistic regression

Factor	Relative risk (95%CI)	*P*-value
PPI exposure		
Group 1	Reference 1	
Group 2	0.697 (0.083-5.891)	0.74
Age, increase by year	0.972 (0.923-1.023)	0.27
Charlson index, increase by score 1	1.518 (1.040-2.216)	0.03
Sex	1.697 (0.374-7.690)	0.49
History of admission	4.317 (0.501-37.220)	0.18

PPI: Proton pump inhibitor.

tuberculosis, but non-caseating granuloma was observed in only 2 of the 7 patients with intestinal tuberculosis, and PCR was positive in 1 of the 2 patients who showed granuloma.

The endoscopic findings of gastrointestinal tuberculosis are often nonspecific[12,30]. Intestinal tuberculosis and Crohn's disease are chronic inflammatory bowel disorders that are difficult to differentiate from each other[31,32]. A study on colonoscopic findings reported that four parameters (involvement of fewer than 4 segments, a patulous ileocecal valve, transverse ulcers, and scars or pseudopolyps) were more frequently observed in intestinal tuberculosis patients than in Crohn's disease patients. Four parameters (anorectal lesions, longitudinal ulcers, aphthous ulcers, and cobblestone appearance) were significantly more common in Crohn's disease patients than in intestinal tuberculosis patients. A systematic analysis of the 8 parameters of colonoscopy was very useful in the differential diagnosis as it could differentiate between intestinal tuberculosis and Crohn's disease with 87.5% accuracy[33]. In the endemic areas of tuberculosis, it seems reasonable to prescribe anti-tuberculosis medications for patients with endoscopic findings favoring intestinal tuberculosis even if there is no specific histological finding from the biopsy specimens[12]. In the present study, anti-tuberculosis medications were also prescribed for 5 patients with only nonspecific chronic inflammations found through biopsy. Intestinal tuberculosis was confirmed in all 5 patients through follow-up colonoscopy, which revealed good therapeutic responses as well as symptom relief.

This study has a number of strengths. First, to these authors' knowledge, this study is the first study that evaluated PPI's role in the development of gastrointestinal tuberculosis. Second, all the data in this study were extracted from the SNUH CDW system that is fully synchronized with the EMR system and is optimized for research. Using the SNUH CDW system, 61 834 patients among the over one million patients who visited SNUH during the 5-year study period were rapidly screened, and the patients with gastrointestinal tuberculosis were sensitively sought out *via* browsing endoscopy and pathology reports. Most of all, compared to cohort studies using a public database, through which only the cumulative incidence rate could be estimated, it is notable that the true incidence rate of gastrointestinal tuberculosis in PPI-treated patients was calculated. The calculated incidence rate was as low as 0.65 per 1000 person-years in group 1 and 0.03 per 1000 person-years in group 2, and anti-tuberculosis medications were shown to be effective in all the patients with active gastrointestinal tuberculosis. Therefore, the risk of acquiring gastrointestinal tuberculosis does not seem to be clinically significant in PPI-treated patients.

This study, however, has several key limitations. First, the study was performed with patients from a single urbanized tertiary care hospital. In general, a hospital cohort is vulnerable to selection bias, and the results have poor generalizability. In South Korea, a single compulsory medical insurance takes effect. Due to the open medical delivery system, all the patients are practically free to visit tertiary care hospitals. In this study, 64% of the patients fall under Charlson index 0. Therefore, their possible difference from primary care patients in the aspect of clinical severity does not seem substantial. Another limitation of a hospital cohort is its dynamic nature, which enables the members to easily join or drop out. Fortunately, even if this study was performed in PPI-treated patients during a 5-year period, the patients could be followed up for 21.8 mo in group 1 and for 34.4 mo in group 2. Therefore, the adherence of the patients in this study seems to have been good.

The second limitation is the potentially different diagnostic sensitivity. This study is an observational study. Therefore, the patients did not necessarily undergo gastrointestinal endoscopy. The implementation of endoscopy was determined according to the patient's symptoms/signs, patient's will, and doctor's decision. There might have been differences in these factors between group 1 and group 2. In this study, most of the 12 patients with only ileo-colonic scars were females and underwent colonoscopy due to mild symptoms or as a routine check. Half of them belonged to group 2, showing a relatively higher incidence in group 2 compared to 1 in the patients with active gastrointestinal tuberculosis (Table 1). Presumably, this may be due to the more frequent requests for routine check-up from or the

stricter adherence to the hospital of female patients than male patients. In the 9 patients diagnosed with active gastrointestinal tuberculosis, however, there were nearly equal numbers of male and female patients. Endoscopy was performed to assess bloody diarrhea, anemia, and severe pain, which seemed to be symptoms suggesting active gastrointestinal tuberculosis (Table 1). In this study, statistical analysis was performed in the patients with active gastrointestinal tuberculosis, which could suggest that the results of this study were not highly biased by the patients' will or adherence.

In conclusion, long-term PPI therapy does not seem to be associated with increased risk of acquiring gastrointestinal tuberculosis whereas a higher Charlson comorbidity index is associated with such. These results, however, may not exempt further monitoring due to the small case number.

COMMENTS

Background

Proton pump inhibitors (PPIs) are currently the most powerful gastric acid suppressants. Several studies have associated acid suppression with increased risk of acquiring gastrointestinal infectious diseases, such as *Clostridium difficile* infection.

Research frontiers

Gastrectomy has been known to be a potential risk factor for tuberculosis, and gastric-acid suppression may play a role in its pathogenesis. There has been no report about a possible association between PPI use and gastrointestinal tuberculosis.

Innovations and breakthroughs

Seoul National University Hospital Clinical Data Warehouse is a database that is fully synchronized with an electronic medical recording system. Using the high-quality dataset, gastrointestinal-tuberculosis patients were efficiently screened, and the true incidence and relative risk of longer PPI treatment were calculated.

Applications

Long-term PPI therapy does not seem to be associated with increased risk of acquiring gastrointestinal tuberculosis.

Peer review

The response to therapy must be evaluated very strictly as this was adopted as a diagnostic criterion.

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