

Beneficial Effect of Early Intervention with Garenoxacin for Bacterial Infection-Induced Acute Exacerbation of Bronchial Asthma and Chronic Obstructive Pulmonary Disease

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Keywords

Asthma · Chronic obstructive pulmonary disease · Chronic respiratory disease · Exacerbation · Antibiotics · Garenoxacin · Early intervention

Abstract

Background: Chronic obstructive pulmonary disease (COPD) and asthma have similar clinical features and are both exacerbated by airway infection. **Objective:** To determine whether garenoxacin mesylate hydrate (GRNX) added to the standard care for bacterial infection-induced acute exacerbation of asthma or COPD in adults has clinical benefits. **Method:** This single-arm clinical trial was conducted from January 2015 to March 2016. Adults with a history of asthma or COPD for more than 12 months were recruited within 48 h of presentation with fever and acute deterioration of asthma or COPD requiring additional intervention. Participants were administered 400 mg GRNX daily for 7 days without additional systemic corticosteroids or other antibiotics. The pri-

mary outcome was efficacy of GRNX based on clinical symptoms and blood test results after 7 days of treatment. Secondary outcomes were: (1) comparison of the blood test results, radiograph findings, and bacterial culture surveillance before and after treatment; (2) effectiveness of GRNX after 3 days of administration; (3) analyzation of patient symptoms based on patient diary; and (4) continued effectiveness of GRNX on 14th day after the treatment (visit 3). **Results:** The study included 44 febrile patients (34 asthma and 10 COPD). Frequently isolated bacteria included *Moraxella catarrhalis* ($n = 6$) and *Klebsiella pneumoniae* ($n = 4$). On visit 2, 40 patients responded, and no severe adverse events were observed. All secondary outcomes showed favorable results. **Conclusion:** GRNX effectively treated asthma and COPD patients with acute bacterial infection without severe adverse events. Further research with a larger study population is needed.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the main diseases classified as chronic respiratory disease (CRD) [1, 2]. Both disorders possess similar clinical features, including chronic airway inflammation and obstructive flow reduction, and they are exacerbated by airway infection [3, 4]. Acute exacerbation of bronchial asthma is caused by viral or bacterial infection [3]. Globally, 300 million people are affected by asthma, and its prevalence is growing in developing countries in Asia and Africa [5]. Even with adequate maintenance therapy using inhaled corticosteroids, approximately 12 million people experience acute exacerbation of asthma in the United States, and 15,000 asthmatic patients die in Europe because of exacerbation of the condition [6]. COPD is a common disease affecting more than 10% of the global population over the age of 40. The World Health Organization (WHO) predicts it will be the third leading cause of death by the year 2030 [2, 4].

The causes of acute exacerbation of asthma include tobacco smoking, inhalation of aeroallergens, alcohol consumption, exercise, and, above all, bacterial and viral infections [2, 4, 7]. In most of cases, symptoms of asthma exacerbation include respiratory symptoms and chest wheezing. About 5–28% of patients with acute exacerbation of asthma are diagnosed with pneumonia, a complication that could be lethal in some cases [8, 9]. The most common treatment for asthma patients undergoing acute exacerbation is the administration of systemic corticosteroids; severe cases require hospitalization [3, 10]. Use of systemic corticosteroids has not been established as a treatment protocol for the exacerbation of asthma associated with bacterial respiratory infection, and there is no gold standard in those cases [11, 12].

Fluoroquinolones are synthetic, broad-spectrum, antimicrobial agents commonly used to treat a series of infections. They act on DNA gyrase and DNA topoisomerase IV to inhibit the transcription and replication of DNA within bacterial organisms [13]. In vitro and in vivo models have shown several quinolones, including garenoxacin mesilate hydrate (GRNX), to have significant immunomodulatory effects in addition to their antimicrobial properties [14]. GRNX (FUJIFILM Toyama Chemical Co., Ltd.) is a newly synthesized quinolone that demonstrates high potential against *Staphylococcus aureus*, *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Klebsiella pneumoniae*, all of which cause upper and lower respiratory infections [15, 16]. When compared to levofloxacin, gatifloxacin, and moxifloxa-

cin, GRNX had the lowest minimum inhibitory concentration for 90% (MIC90) of *S. pneumoniae* when measured using methods recommended by the Clinical Laboratory Standards Institute (CLSI) [17, 18].

GRNX's effects on bacterial organism eradication have been well demonstrated in both clinical and in vitro settings. The clinical efficacy of GRNX against bacterial pneumonia, otorhinolaryngological infection, and otitis media has also been shown in several studies. In a phase III study conducted on 136 patients with CRDs, including 18 asthmatic patients and 28 COPD patients, the overall clinical efficacy was 85.1% after a 10-day course of 400 mg GRNX [19]. Another phase III study targeting respiratory tract infection caused by penicillin-resistant *S. pneumoniae* and penicillin intermediate-resistant *S. pneumoniae* showed GRNX had efficacies of 88.9 and 93.8%, respectively [20]. In the current study, *M. catarrhalis* was the most frequent isolated bacteria causing upper and lower respiratory infection. Previous study showed β -lactamase-producing *M. catarrhalis* isolates were 92.4%, and the maximum MIC was 1.0 $\mu\text{g/mL}$ [21]. Accordingly, 5 out of 6 isolates in the current study showed resistance to penicillin, but GRNX treatment resulted in bacterial eradication and management of acute exacerbation of CRDs in all patients. *K. pneumoniae* was the second-most frequent isolated bacteria, and the 7-day GRNX treatment successfully eliminated the bacterium and treated acute exacerbation of asthma or COPD without further exacerbation.

Since bacterial infection is one of the major causes of acute exacerbation of bronchial asthma and COPD, we hypothesized that the highly potent quinolone GRNX would inhibit exacerbation among bacteria-infected asthmatic and COPD patients. To test this hypothesis, we conducted a study on bacteria-infected asthmatic and COPD patients treated daily with 400 mg GRNX for 7 days. Our aim was to determine the clinical benefits of GRNX for bacteria-infected CRD patients and to explore new methods to treat and, ultimately, prevent acute exacerbation of CRDs.

Materials and Methods

Study Design

This single-center, single-arm study was conducted at Showa University Hospital in Tokyo, Japan, from January 2015 to March 2016. The targeted study population included asthma or COPD patients with acute respiratory bacterial infection and fever over 37°C. Participants showed worsening of either respiratory symptoms such as cough or dyspnea, or the amount and/or viscosity of

Table 1. The diary questionnaire

1. Daily body temperature
2. Degree of cough (0 [none] to 3 [worst])
3. Degree of sputum (0 [none] to 3 [worst])
4. Sputum color (0 [clear] to 3 [green])
5. Degree of breathlessness (0 [none] to 2 [worst])
6. Chest pain or tightness (0 [no] to 1 [yes])
7. Self-assessment of general health status (100 [best] to 0 [worst])

sputum. Acute respiratory bacterial infections included bacterial pneumonia, bronchiolitis, pharyngitis, and tonsillitis. All participants were over 20 years of age and gave written informed consent to participate in the current study. The exclusion criteria were patients with severe conditions requiring inpatient care, patients suspected of having a GRNX-untreatable infection, patients administered other antibacterial agents or systemic steroids prior to the current study, patients with allergies or major adverse events due to administration of quinolone or GRNX, pregnant subjects, patients with a body weight less than 40 kg, patients with severe kidney (creatinine clearance rate less than 30 mL/min) or liver dysfunction, or patients deemed unsuitable for the current study. Patients took daily oral doses of 400 mg of open-labeled GRNX for 7 consecutive days. Other antibiotics or systemic steroids were prohibited during the study period.

Primary and Secondary Outcomes

The primary outcome was the effectiveness of GRNX among the targeted patients, based on clinical symptoms and laboratory data on the 7th day (visit 2; V2) after the initial visit (visit 1; V1). Clinical status and blood test results were evaluated and rated as effective, not effective, or not able to rate. Secondary outcomes were: (1) comparison of blood tests, chest radiograph findings, and bacterial culture surveillance before and after treatment; (2) effectiveness of GRNX 3 days after initial administration (day 3; D3); (3) analysis of symptoms based on patients' diaries; and (4) continued effectiveness of GRNX on the 14th day after initial treatment (visit 3; V3). Other clinical evaluations included patient information such as age, sex, height, body weight, and pregnancy status, if needed. The severity of asthma and COPD was determined using criteria based on Japanese guidelines for asthma and COPD, respectively. All patients were asked to take notes in a diary every day to record body temperature, degree of cough, dyspnea, chest pain, amount and color of sputum, any use of a fever reducer, adherence to taking GRNX, and, lastly, a self-assessment of general health status (Table 1).

Acute respiratory infection was diagnosed using a combination of SpO₂ measurement, blood test results, chest X-ray, and sputum culture. The severity of bacterial pneumonia was determined using the Japanese guideline for pneumonia, and a validated scoring system was applied to bronchiolitis, pharyngitis, and tonsillitis.

GRNX was determined to be clinically effective if: (1) the maximum body temperature of the day was less than 37°C; (2) the patient displayed recovery of infection-related symptoms, such as a lower frequency of cough, lower viscosity or amount of sputum, and disappearance of chest pain or dyspnea; (3) results showed a decline in

Table 2. Patient characteristics

	Asthma patients <i>n</i> = 34	COPD patients <i>n</i> = 10	All patients <i>n</i> = 44
Median age, years	52.5	74.5	57
Females, <i>n</i> (%)	23 (67.7)	8 (80)	31 (70.5)
Asthma severity (mild, moderate, severe), <i>n</i>	7, 18, 9	NA	NA
COPD severity (I, II, III, IV), <i>n</i>	NA	3, 5, 1, 1	NA
Smoking status (never, former, current), <i>n</i>	26, 7, 1	2, 6, 2	28, 13, 3
Clinical diagnosis of infection			
Acute bronchiolitis	20	8	28
Bacterial pneumonia	6	2	8
Acute pharyngitis	5	0	5
Acute tonsillitis	3	0	3
Severity of infection (mild, moderate, severe), <i>n</i>	18, 16, 0	4, 6, 0	22, 22, 0

white blood cell count (WBC) to less than 9,000/mm³; (4) results showed decline of C-reactive protein (CRP) to less than 30% of visit-1 data; and (5) a chest radiograph showed improvement.

The effect of GRNX on bacteria was assessed by comparing sputum cultures taken on visits 1 and 2. The sputum culture was assumed to be negative for bacteria if sputum was not obtained on visit 2 due to improvement of the patient's condition. The antibiotic sensitivity test was based on the CLSI method.

Blood was drawn on visits 1 and 2 to evaluate the efficacy of GRNX and any adverse events; results of the blood tests were used to determine the severity of infectious disease. WBC, CRP, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase, alanine aminotransferase, and amylase were evaluated. Any adverse events related to this study were monitored and carefully addressed until recovery.

Statistical Analysis

All data are presented as the mean ± standard error of the mean (SEM) unless otherwise noted. Differences between the groups were analyzed using the Kruskal-Wallis ANOVA with Dunnett's post hoc testing and the Mann-Whitney U test. Correlations were assessed using Spearman's rank correlation coefficient. The data from culture experiments were analyzed using both parametric (Student's *t* test) and nonparametric (Kruskal-Wallis ANOVA with Dunnett's post hoc testing) statistical analyses; both provided similar results. Data from nonparametric testing are shown. In all cases, *p* < 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism 5.0 software (GraphPad Software, La Jolla, CA, USA).

Ethical Approval

This clinical study was approved by the ethics committee at Showa University and was registered in the UMIN Clinical Trials Registry (<http://www.umin.ac.jp/ctr/index-i.htm>).

Table 3. Primary and secondary outcomes

	Asthma patients <i>n</i> = 34			COPD patients <i>n</i> = 10			All patients <i>n</i> = 44		
Primary outcome									
Clinical efficacy on V2 (effective, not effective, not able to rate)	32, 0, 2			8, 0, 2			40, 0, 4		
Secondary outcome									
Clinical efficacy on day 3 (effective, not effective, not able to rate)	29, 3, 2			8, 0, 2			36, 3, 5		
Chest radiograph findings (better, worse or no change, not able to rate)	6, 2, 26			2, 2, 6			8, 4, 32		
Bacterial culture findings after treatment (negative, positive, not able to rate)	31, 0, 3			7, 2, 1			38, 2, 4		
Sustained clinical efficacy on V3 (remission, not effective, not able to rate)	33, 0, 1			10, 0, 0			43, 0, 1		
	V1	V2	<i>p</i> value	V1	V2	<i>p</i> value	V1	V2	<i>p</i> value
Secondary outcome									
Changes of symptoms based on patient's diary from V1 to V2									
Amount of sputum (scale 1–10)	1.7	0.9	<0.05	1.1	0.9	0.35	1.6	0.9	<0.05
Dyspnea (scale 1–10)	0.7	0.3	<0.05	0.5	0.3	0.35	0.7	0.3	<0.05
Cough (scale 1–10)	1.4	0.8	<0.05	0.6	0.6	0.73	1.2	0.7	<0.05
Average body temperature, °C	37.4	36.4	<0.05	37.5	36.5	0.08	37.4	36.4	<0.05
General condition (scale 1–10)	3.4	6.3	<0.05	5.0	6.3	0.14	3.8	6.3	<0.05
Changes of clinical parameters from V1 to V2									
Blood test findings									
WBC, average, μ L	6,715.15	6,394.12	00.35	8,100	8,100	0.86	7,011.9	6,782	00.39
CRP, average, mg/dL	1.86063	0.31667	<0.05	5.17889	1.192	0.09	2.58902	0.536	<0.05
BUN, average, mg/dL	12.7515	13.4676	00.62	18.6667	16.13	0.05	14.019	14.07	00.60

Results

Clinical Backgrounds of Enrolled Patients

Forty-nine patients were screened for eligibility, and 44 met the criteria for study participation with consent. Participants included 34 asthma and 10 COPD patients (Table 2). The mean age was 58.5 years, and 25 (56.8%) were females. Twenty-seven and 7 were moderate-to-severe asthma and COPD patients, respectively. Clinical diagnoses made for respiratory infections included 28 acute bronchiolitis, 8 bacterial pneumonia, 5 acute pharyngitis, and 3 acute tonsillitis. In addition, 50% of the infections were classified as moderate; none of the cases were considered severe. All participants attended the assigned visits, and adherence to GRNX intake was over 98% during the 7-day treatment.

Pathogen Detection Results

M. catarrhalis (*n* = 6) and *K. pneumoniae* (*n* = 4) were the most frequently detected bacteria. In 25 patients, we

were not able to detect any bacterial pathogen. None of the isolated bacteria showed resistance to fluoroquinolone.

Primary Outcome Analysis

Forty patients were analyzed for the primary outcome, and all patients were categorized as “effective,” regardless of their initial clinical status. Due to missing data, we were not able to analyze 4 patients (Table 3).

Secondary Outcome Analysis

Early effectiveness of GRNX on day 3 was evaluated based on the patients' diaries. We were able to evaluate 39 patients, and 36 of them reported the GRNX effect was evident by the 3rd day of treatment (Table 3). On visit 2, 6.8% of the patients reported feeling dyspnea, compared to 52.3% on the initial visit (*n* = 44). Accordingly, the respiratory rate dropped from 15.8 to 14.0 breaths/min, and SpO₂ improved from 96.8 to 97.5% (*n* = 43). Body temperature decreased from 37.4 to 36.4 °C after treatment

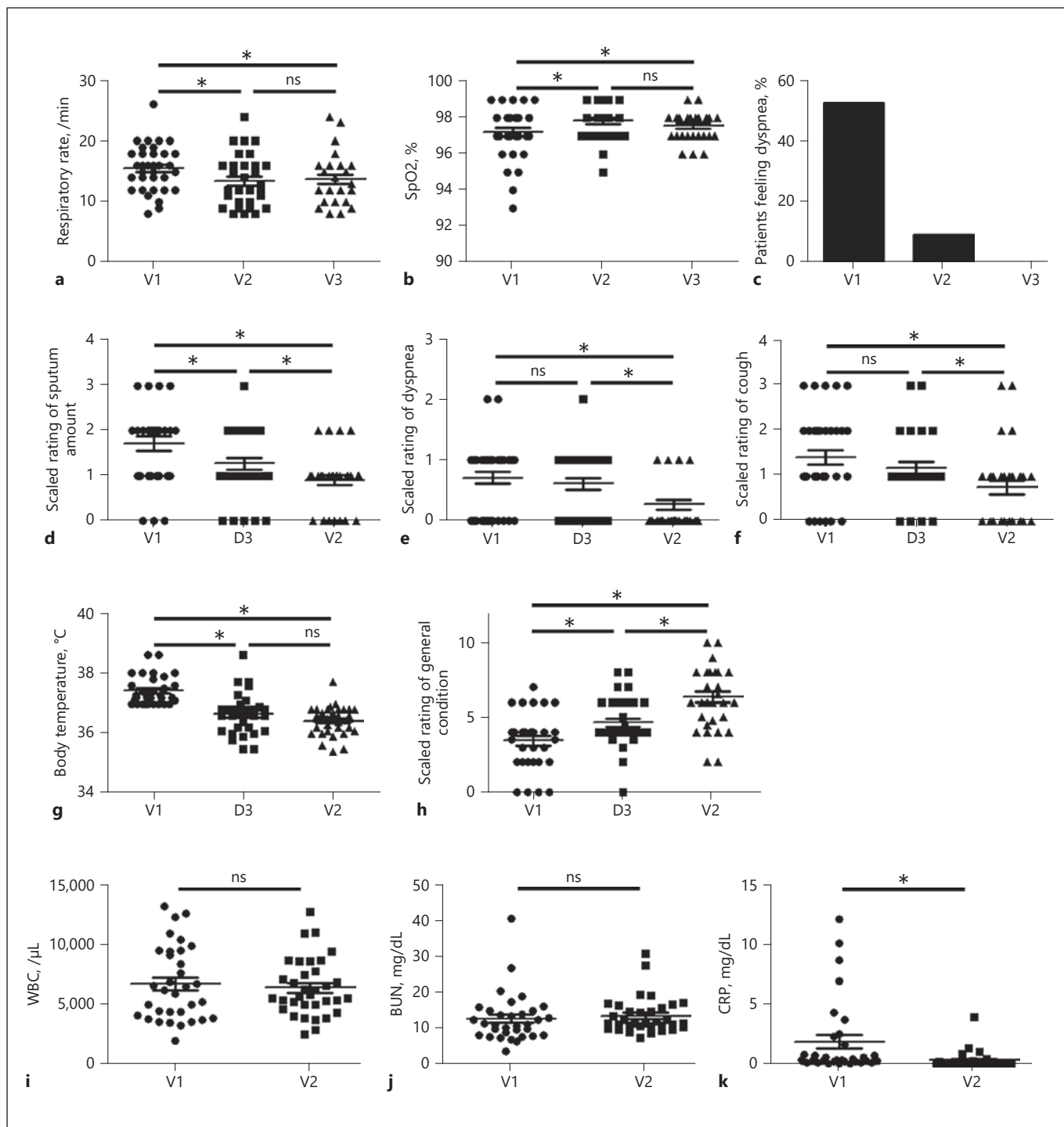


Fig. 1. Changes of asthma- and respiratory infection-related clinical parameters among asthma patients during the study period. Changes of respiratory rate (/min) (a), SpO2 (%) (b), percentage of patients feeling dyspnea (%) (c) on visit 1 (V1), visit 2 (V2), and visit 3 (V3). Each patient recorded a self-assessment in their diary, with symptoms scaled from a minimum of 0 to a maximum of 10 and evaluated for the changes of amount of sputum (d), degree of dyspnea (e), frequency of cough (f), maximum daily body tem-

perature (°C) (g), and general condition (h) on V1, 3rd day after V1 (D3), and V2. Blood was drawn on V1 and V2 to evaluate the differences of white blood cell count (WBC; / μ L) (i), blood urea nitrogen (BUN; mg/dL) (j), and C-reactive protein (CRP; mg/dL) (k). All values were analyzed using Student's *t* test, and *p* values below 0.05 were considered statistically significant (*). ns, not significant.

($n = 35$), and the general condition reported by the patients improved from 37.1 to 63.3 ($n = 42$). Although clinical symptoms improved during the course, most of the blood test results, except for CRP, did not change from the initial visit. None of the patients showed worsening in the chest radiograph.

Subgroup Analysis

Asthmatic patients were analyzed for secondary outcomes from visit 1 to visit 3 regarding respiration rate, SpO₂, and dyspnea (Fig. 1a–c). Respiration rate and SpO₂ were significantly improved after 7 days of GRNX. Dyspnea was originally seen in 52.9% of asthma patients, and all recovered by 14 days after the initial visit. Other asthma exacerbation-related symptoms were scored from 1 to 10 every day by the patients and recorded in their diaries. The amount of sputum, degree of dyspnea, frequency of cough, body temperature, and general condition were evaluated, and data from visits 1, 2 and 3 were compared (Fig. 1d–h). All items improved by visit 3, and a surprising number of cases showed improvement in sputum, body temperature, and general condition by day 3 based on patients' diary. Blood tests were done on visits 1 and 2 to evaluate WBC, BUN, and CRP (Fig. 1i–k). Parallel to clinical symptoms, CRP significantly decreased from visit 1 to visit 2, while meaningful changes were not observed in WBC or BUN.

Safety

None of the 44 patients receiving GRNX showed severe adverse events leading to discontinuation of the study. Serological tests did not show any event such as elevation of aspartate aminotransferase, alanine aminotransferase, or amylase.

Discussion and Conclusion

Recent studies utilizing specific bacterial 16S-rRNA screening showed bacterial colonization, including colonization of quinolone- or GRNX-sensitive bacteria, in both upper and lower airways of patients with asthma and COPD [22–25]. Exacerbation of CRDs were also related to microbial dysbiosis in lower airways, suggesting antibiotics may play a role in these settings [24, 26]. Wang et al. [24] reported that *Firmicutes veillonella*, a bacterium usually found in the gut microbiome, was involved in acute exacerbation of COPD. In addition, Dicker et al. [27] showed a relation between *Haemophilus* spp. colonization – also the pathogen of some patients in the current

study – and COPD exacerbation. Exacerbation of asthma was also related to microbial dysbiosis in the lower airway [28]. These findings indicate that, since airway epithelial cells express Toll-like receptors (TLRs), bacteria-induced activation of TLRs may account for exacerbation of CRDs. Furthermore, GRNX therapy may have a beneficial effect in clinical settings [29]. Further research is warranted to clarify the beneficial effect of antibiotics in microbiome-associated exacerbation of CRDs, especially asthma and COPD.

In addition to bacterial eradication, recent in vitro studies suggest GRNX may have anti-inflammatory or immunomodulatory effects. Shiratori et al. [30] studied quinolone-induced osteopontin, which plays an important role in the immune and inflammatory response in asthma and COPD, from human lung epithelial cells. Among ciprofloxacin, gatifloxacin, moxifloxacin, sparfloxacin, and sitafloxacin, GRNX was the most potent inducer of osteopontin from lung epithelial cells. Lipopolysaccharides induced neutrophil chemoattractant CXCL8 from human airway epithelial cells and monocytes using A549 cells and THP-1 cells, respectively, and the resulting inflammation was inhibited by coincubation with GRNX for 24 h [31]. This suppression mechanism of GRNX, shown in the inhibition of phospho-ERK1/2, again suggests that GRNX affects not only infected bacterium, but airway and local inflammatory cells. We have recently shown, together with previous findings, that GRNX may inhibit *S. aureus*-related inflammation as well [32]. Further study is warranted to elucidate the anti-inflammatory effect of GRNX on bacterial- and respiratory disease-related responses.

GRNX was well tolerated among the patients in this study. Previously, the safety of a daily dose of 400 mg GRNX was evaluated in 702 patients. Three deaths were observed in the 30-day posttreatment observation, but none of the deaths were drug-related. There were 89 drug-related adverse events, and 2 were considered serious: one case of rash and one case of *Clostridium* infection causing colitis. The most frequent mild to moderate adverse events were diarrhea (2.4%), loose stool (1.3%), nausea (1.0%), and headache (1.0%), usually seen with the use of other antibiotics. No specific adverse events related to GRNX were observed. QTc prolongation, blood glucose abnormality, liver dysfunction, photosensitive reaction, arthropathy, and central nervous system disorders were previously reported as a class effect of fluoroquinolones. Prior GRNX clinical studies showed that all of the class effects were mild to moderate, and some of the events, such as occurrence rate of asymptomatic

blood glucose alteration, were similar to those of levofloxacin.

There were several limitations to this study. First, the CRD participants were limited in both asthma and COPD components. As asthma and COPD share several characteristics, such as obstructive findings in spirometry, infection as a trigger of acute exacerbation, and similar treatment drug profiles, GRNX may play a role in both patient groups. Moreover, since our targets were specific to febrile CRD patients suspected of having a bacterial infection, asthma and COPD patients showed a similar trend toward improvement of their symptoms. A second limitation was that bacterial culture findings were only seen in a minority of the patients ($n = 14$). Some of the recruited patients' symptoms may have been caused by viral infection, since our study did not include viral testing as an exclusion criterion. It was encouraging that no severe adverse events were observed due to underlying airway disease.

Up-to-date clinical studies describing treatment of bacterial infection and acute exacerbation of CRDs with GRNX are limited. Kobayashi et al. [19] showed that the efficacy rates of daily administration of 400 mg GRNX for 7 days in patients with asthma and pulmonary emphysema were 93.8 and 92.9%, respectively. On the other hand, Horiguchi et al. [33] demonstrated that *Chlamydia pneumoniae*-infected patients with asthma administered sparfloxacin had decreased peripheral eosinophil counts compared to the non-fluoroquinolone-treated group, suggesting fluoroquinolones have an anti-allergic effect. Together with our current and previous findings, this suggests that fluoroquinolones, including GRNX, possess not only antibacterial properties, but also an anti-asthma exacerbation effect through modulation of the immune system.

In the current study, GRNX effectively treated both asthma and COPD patients with acute bacterial infection without any severe adverse events. Although participants were limited, these findings suggest that GRNX could be

an option for bacterial infection-induced acute exacerbation of asthma and COPD. Further investigations involving a larger study population are needed.

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Statement of Ethics

This clinical study was approved by the ethics committee at Showa University and was registered in the UMIN Clinical Trials Registry (<http://www.umin.ac.jp/ctr/index-i.htm>). All study participants provided written informed consent.

Disclosure Statement

All authors have no conflicts of interest to declare.

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Author Contributions

Conception or design of the work: T.H., M.Y., Y.K., Y.M., S.O., M.Y., Y.W., H.Y., S.K., H.S. Acquisition, analysis, or interpretation of data: T.H., T.K., H.M., T.U., H.S., A.F., Y.U., Y.F., R.M., H.I., N.K., T.K., K.H., Y.M., M.J., H.S. Manuscript drafting and revising: T.H., S.S., A.T., T.Y., T.O., H.S. Final approval of the version to be published: T.H., H.S.

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