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Original Article

The efficacy and safety of sitafloxacin and garenoxacin for the treatment of pneumonia in elderly patients: A randomized, multicenter, open-label trial☆

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ABSTRACT

Oral treatment for elderly outpatients with pneumonia is becoming increasingly important in this super-aged society from the perspective of cost-effectiveness and limited hospital capacities. We evaluated the efficacy and safety of two oral respiratory quinolones, sitafloxacin and garenoxacin, in elderly patients with pneumonia. This randomized, multicenter, open-label trial was conducted among patients aged ≥65 years with clinically and radiographically confirmed pneumonia in Japan. Patients were randomly assigned (1:1) to receive either sitafloxacin (100 mg/day) or garenoxacin (400 mg/day) for 3–10 days. The primary efficacy endpoint was the clinical cure rate at 5–10 days after the end of treatment. From December 2013 to November 2017, we enrolled 120 patients at 11 hospitals and randomly assigned 59 patients to the sitafloxacin group (1 patient withdrew) and 61 patients to the garenoxacin group. These included 30 patients with nursing and healthcare-associated pneumonia (NHCAP) (18 receiving sitafloxacin, 12 receiving garenoxacin) and 37 patients with aspiration pneumonia (16 receiving sitafloxacin, 21 receiving garenoxacin). The clinical cure rates in the sitafloxacin and garenoxacin groups were 88.5% (95% confidence interval: 76.6–95.6) and 88.9% (95% confidence interval: 77.4–95.8), respectively. No significant differences were observed in the incidence rates of drug-related adverse events between the sitafloxacin (20.7%; 12/58 patients) and garenoxacin (27.9%; 17/61 patients) groups. The most common adverse event was hepatic dysfunction, which occurred in seven patients in each group. We conclude

Abbreviations: A-DROP, age, dehydration, respiration, disorientation, and blood pressure; CAP, community-acquired pneumonia; EOT, end of treatment; ITT, intention-to-treat; MITT, modified ITT; NHCAP, nursing and healthcare-associated pneumonia; PORT, Pneumonia Outcomes Research Team; PP, per-protocol; TOC, test of cure.

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that sitafloxacin and garenoxacin are comparably effective and safe for the treatment of pneumonia, including NHCAP and aspiration pneumonia, in elderly patients.

1. Introduction

Pneumonia is a leading cause of death for which morbidity increases with age. In Japan, pneumonia-associated mortality has increased with the aging population and has been the third leading cause of death since 2011 [1]. Although the etiology of these cases varies, they often include community-acquired pneumonia (CAP), nursing and healthcare-associated pneumonia (NHCAP), and aspiration pneumonia [2]. Keeping in mind that pneumonia in elderly patients is mainly aspiration pneumonia, regardless of the classification of pneumonia, physicians should have appropriate treatment strategies.

The importance of oral treatment for non-severe CAP and NHCAP in outpatients is increasing in this super-aged society because it is cost-effective and does not require hospital admission. Oral quinolones are recommended for the treatment of CAP and NHCAP in outpatients with chronic heart and/or lung disease [3]. Sitafloxacin and garenoxacin are quinolones with a broad spectrum of antibacterial activity *in vitro* but are potent against gram-negative bacteria and gram-positive bacteria, respectively [4,5]. Sitafloxacin is the most potent respiratory quinolone against anaerobic bacteria [4]. Since sitafloxacin has been actually demonstrated to be effective for oral infections with which anaerobic bacteria are primarily associated [6], it can be expected to be useful in elderly patients with pneumonia, including aspiration pneumonia. Sitafloxacin and garenoxacin have been shown, so far, to be effective for CAP [7–11]. Although garenoxacin has been sufficiently studied [11], no comparative study has been reported to address the question of the respiratory quinolone that is more effective in elderly pneumonia patients.

We hypothesized that sitafloxacin has high effectiveness and safety similar to garenoxacin in elderly patients with pneumonia aged ≥65 years and performed a prospective clinical trial to test this hypothesis preliminary in a small sample size.

2. Patients and methods

2.1. Study design

This was a randomized, multicenter, open-label clinical trial. We used a parallel-group design to study sitafloxacin therapy against garenoxacin therapy for the treatment of pneumonia in elderly patients from December 2013 to November 2017. This study was registered with the UMIN Clinical Trials Registry (UMIN000012627) on December 19, 2013, before patient enrollment.

2.2. Ethics

The study was approved by the institutional review boards of all participating sites and was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Written informed consent was obtained from each patient before enrollment in this study.

2.3. Patients

Participants were included if they had new pulmonary infiltrates suggestive of infection on chest x-ray or computed tomography within 48 h before the study and if they had at least one sign or symptom of infection. The following were considered indicative clinical findings: cough, purulent sputum or increased purulence of sputum, abnormal findings on auscultation and percussion (including moist rales, percussion dullness, and decreased breath sounds), dyspnea or tachypnea, fever (axillary temperature ≥37 °C), increased white blood cell count (>10,000/mm^3), stab leucocytes >15%, decreased white blood cell count (<4500/mm^3), increased C-reactive protein, or hypoxemia. Only those patients considered suitable for treatment with oral antibiotics were enrolled in the study.

The main exclusion criteria were anaphylaxis to sitafloxacin or garenoxacin, prior quinolone use for the current episode, severe hepatic dysfunction, QTc prolongation, hypokalemia, under treatment with a class IA or class III antiarrhythmic agent, low body weight (<30 kg), severe renal dysfunction (creatinine clearance <30 mL/min or estimated glomerular filtration rate <30 mL/min), or a Pneumonia Outcomes Research Team (PORT) score of 5. Further detailed exclusion criteria are available in Table S1.

Patients were enrolled at 11 medical centers or hospitals in the Nagasaki and Saga Prefectures of Japan. Patients were allocated (1:1) by the random permuted block method (block size = 4) with stratification by clinical sites. The allocation table was generated by a Specified Nonprofit Corporation (NEOCI, Tokyo, Japan) using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Patients were registered by central registration system, and each study drug was administered according to the allocation table.

2.4. Interventions

Patients received either oral sitafloxacin 100 mg (50 mg if they had renal dysfunction [creatinine clearance <50 mL/min]) or oral garenoxacin 400 mg once a day, using commercial products. The study drugs were administered for 3 days, and if the patients showed any clinical response on Day 4, administration was continued to Day 8. The clinicians were free to continue the study drug to a maximum of 10 days based on clinical judgment. If patients or their proxies requested to withdraw from the study, the study drug was immediately discontinued, and an alternative treatment was started. Administration was also discontinued for any of the following reasons: unanticipated side effects, severe adverse events, symptom deterioration, aggravation of complications, or for unforeseen reasons at the discretion of the investigator. Details regarding the permitted concomitant medications and prohibited medications are available in Table S2.

2.5. Efficacy assessments

Efficacy was evaluated according to the “Clinical Evaluation Methods for New Antimicrobial Agents to Treat Respiratory Infections (Second Version)” published by the Japanese Society of Chemotherapy [12]. Patients were assessed at screening (baseline), Day 4 (early evaluation), the day of discontinuation or at the end of treatment (EOT), and at test of cure (TOC; 5–10 days after the EOT). At these points, we performed clinical, hematological (e.g., white blood cell count and C-reactive protein), imaging (e.g., chest x-ray), and microbiological examinations (Table S3).

CAP and NHCAP were diagnosed according to the Japanese guidelines (CAP [13] & NHCAP [14]). The diagnostic criteria of aspiration pneumonia are in Table S4, and the patients diagnosed as "confirmed," "probable," and "suspected" were regarded as having aspiration pneumonia. The severity of pneumonia was evaluated using the PORT score [15] and A-DROP (age, dehydration, respiration, disorientation, and blood pressure) score [16].

2.6. Microbiological assessments

Culture of sputum and identification of bacterial species were conducted at each institution. Strains obtained prior to administration of the study drug were sent to LSI Medience Corporation (Tokyo, Japan) and the minimum inhibitory concentrations of various antibiotics, including sitafloxacin and garenoxacin, were measured.

Bacteriological efficacy was categorized and documented as eradicated (baseline pathogen absent in follow-up cultures); presumed eradicated (no follow-up material available for culture with improvement of clinical symptoms); persisted (baseline pathogen present in follow-up cultures); presumed persisted (no follow-up material available for culture with no improvement of clinical symptoms); microbial substitution (baseline pathogen absent but resistant pathogen emerged in follow-up cultures); or indeterminate.

2.7. Sitafloxacin concentrations in sputum and serum

Sputum and blood samples were collected from 5 patients in the sitafloxacin group at the same time on Day 4, and the sitafloxacin concentration was measured at LSI Medience by high-performance liquid chromatography [17].

2.8. Safety assessments

Adverse events were reported according to the guidelines of Japanese Society of Chemotherapy [18]. We only received spontaneous reports until the patient attended the TOC visit, but at each point we interviewed patients to collect safety data, without requiring confirmation by symptom-specific questions because of the open-label design. In addition, we included data from clinical laboratory examinations in the safety assessment.

2.9. Endpoints

The primary efficacy endpoint was the clinical cure rate at the TOC. Secondary endpoints were the treatment effective rates on Day 4 and at the EOT, the bacteriological eradiation rates, and the safety outcomes. After these endpoints were judged by the attending physician at each clinical site, the case report forms submitted were again assessed and confirmed by a judging committee consisting of the principal investigator and co-investigators, based on the definitions (Table S3). The efficacy rate was calculated as the percentage of patients who were evaluated as "cured" or "effective" divided by the number of all "per-protocol population" patients except those who were evaluated as "indeterminate."

2.10. Statistical assessments

The primary endpoint of clinical cure rates was assumed to be 85% for both drugs based on the previous studies in adult patients [8–10]. When there was a 20% loss of data due to early discontinuation, a sample size of 60 patients per group was necessary for estimating the clinical cure rate at 95% confidence interval (CI) with a width of $\leq$20% based on the normal approximation of the binomial distribution.

We performed analyses based on intention-to-treat (ITT) and per-protocol (PP) populations. The ITT population comprised all randomized subjects who received the assigned study drug at least once and were analyzed at baseline and for safety outcomes. The modified ITT (MITT) population comprised all patients who met the inclusion criteria. The PP population was the subset of patients in the MITT population who adhered to the key aspects of the protocol and provided data for analysis of clinical efficacy. Bacteriological MITT and PP population were also created. The bacteriological MITT population was the subset of the MITT population that included cases in which the study drugs exerted antibiotic activity at the start of administration and that had either typical (known to cause respiratory infections) or atypical causative bacteria. The bacteriological PP was the subset of patients in the PP population who were adherent to the key study protocols and who underwent microbiological assessments.

Descriptive statistics were calculated and reported with their 95% CIs using the Clopper–Pearson exact method for the proportions or the Santner–Snell exact method for the difference between two proportions [19]. Age and body weight, treatment periods, and severity of pneumonia were compared using *t*-tests, the Wilcoxon test, the Mann–Whitney *U* test, respectively, whereas the other measurements were compared by Fisher's exact tests with a one-sided significance level of 5%. The clinical efficacy rates, including the primary endpoint, were also assessed using Fisher's exact test, but with a two-sided significance level of 5%. Furthermore, clinical cure rates were analyzed according to subgroups in the PP population without indeterminate patients, based on sex, age, hospitalization, severity of pneumonia, and diagnosis of aspiration pneumonia, using Fisher's exact test with a two-sided significance level of 5%. All efficacy and safety analyses were conducted using SAS version 9.3 or higher.

2.11. Role of the funding source

Financial support to conduct the study was provided by Daiichi Sankyo Co., Ltd. The funding source was not involved in the study design; in the collection, analysis, or interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

3. Results

3.1. Patients disposition and analysis sets

Between March 26, 2014, and November 9, 2017, we enrolled 120 patients aged $\geq$65 years with pneumonia, and the final sitafloxacin and garenoxacin groups included 59 and 61 patients, respectively (1 patient in the sitafloxacin group withdrew before receiving the first treatment). There was no violation of the inclusion/exclusion criteria, but there were 7 violations of the protocol (six exceeding the protocol-defined treatment period and one overdose of the study drug). The bacteriological PP population in which the causative bacteria were known comprised 60 patients (Fig. 1).

3.2. Patient demographic and clinical characteristics

The baseline characteristics were similar between the treatment groups among the 119 patients in the ITT population (Table 1). Their ages ranged from 65 to 98 years, with median ages of 77.0 years in the sitafloxacin group and 77.5 years in the garenoxacin group. Of note, 89 patients (71.4%) required hospitalization, of whom 45

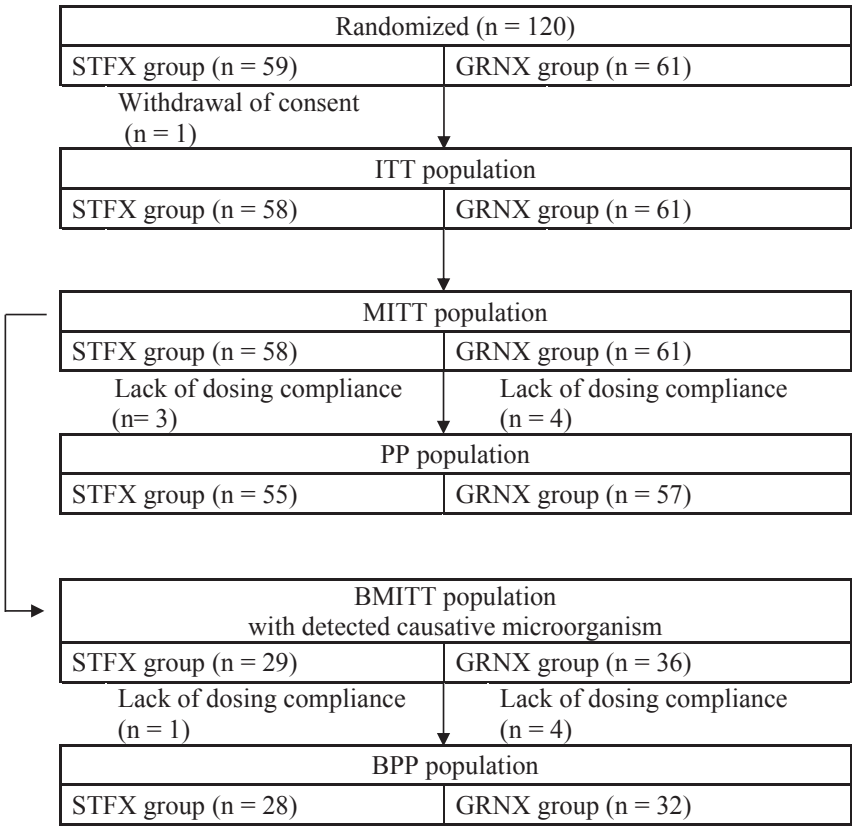

Fig. 1. Diagram of patient disposition. STFX, sitafloxacin; GRNX, garenoxacin; ITT, intention-to-treat; MITT, modified intention-to-treat; PP, per-protocol; BMITT, bacteriological modified intention-to-treat; BPP, bacteriological per-protocol.

(77.6%) were in the sitafloxacin group and 40 (65.6%) were in the garenoxacin group. Also, 98 patients (82.4%) had underlying diseases, of whom 51 (87.9%) were in the sitafloxacin group and 47 (77.0%) were in the garenoxacin group. No patients with renal failure or chronic heart failure were included in both groups. Regarding the severity of pneumonia, as evaluated using the A-DROP scale, "mild," "moderate," and "severe" disease was present in 25.2%, 68.1%, and 6.7% of patients, respectively. There was no significant difference in severity (PORT and A-DROP scores) between the treatment groups. Of note, there were 8 patients in the sitafloxacin group and 5 patients in the garenoxacin group who had been administered antibiotics other than quinolones just before the enrollment: cefcapene pivoxil (n = 1), cefditoren pivoxil (n = 1), cefdinir (n = 1), ceftriaxone (n = 1), piperacillin (n = 1), and clarithromycin (n = 3) in the sitafloxacin group and cefditoren pivoxil (n = 1) and clarithromycin (n = 4) in the garenoxacin group. Because these prior treatments were ineffective in all the patients, these patients met the entry criteria (Table S2). In total, NHCAP and aspiration pneumonia were diagnosed in 30 patients (18 receiving sitafloxacin, 12 receiving garenoxacin) and 37 patients (16 receiving sitafloxacin, 21 receiving garenoxacin), respectively. The treatment periods in PP population (mean ± SD) were 7.3 ± 1.4 days (n = 55) for the sitafloxacin group and 7.6 ± 1.7 days for the garenoxacin group (n = 57) and showed no significant difference (p = 0.17).

3.3. Clinical efficacy

The primary endpoint of cure rate at TOC in the PP population was 88.5% (95% CI: 79.8%–97.1%) in the sitafloxacin group and 88.9% (95% CI: 77.4%–95.8%) in the garenoxacin group, both 95% CIs overlapped and there was no statistically significant difference. Likewise, the secondary endpoints of effectiveness on Day 4 and at the EOT were not different between the two groups (Table 2).

There were no significant differences between the two treatment groups in sex, age, hospitalization, severity, or diagnosis of aspiration pneumonia (Table 3). Indeed, sitafloxacin and garenoxacin were comparably effective, regardless of age, with respective cure rates of 76.2% and 95.7% among those aged 65–74 years, 95.5% and 86.7% among those aged 75–84 years, and 100% and 81.3% among those aged ≥85 years. Cure rates among inpatients were also comparable between the sitafloxacin (87.5%) and garenoxacin (84.8%) groups. Equally, cure rates were similar between the treatment groups among patients with moderate-to-severe disease and among patients with mild disease according to the A-DROP scale. Of note, patients with confirmed aspiration pneumonia (14/15 patients) were cured by sitafloxacin (93.3%), whereas 89.5% (17/19 patients) were cured by garenoxacin.

Antibiotics used as salvage therapy were doripenem (n = 2), biapenem plus azithromycin (n = 1), and unknown (n = 1) in the sitafloxacin group and sulbactam/ampicillin (n = 1), biapenem plus azithromycin (n = 1), faropenem (n = 1), and unknown (n = 3) in the garenoxacin group.

3.4. Microbiological efficacy

At baseline there was no significant difference in the distribution of causative bacterial species between the two groups. The most common bacteria were *Haemophilus influenzae* and *Klebsiella pneumoniae* in the sitafloxacin group and pneumococcus and *H. influenzae* in the garenoxacin group (Table S5). Susceptibilities of the isolates to sitafloxacin and garenoxacin are shown in Table S6. MICs of sitafloxacin were lower than those of garenoxacin for most

Table 1
Baseline characteristics (ITT population).

Characteristic		STFX (n = 58)		GRNX (n = 61)		P value[a]
		n	%	n	%	
Sex	Male	34	58.6	36	59.0	1.00
Age (years)	Median (Min, Max)	77.0 (65, 98)	(65, 98)	77	(65, 93)	0.91
Body weight (kg)	Mean ± SD	51.8 ± 8.5	±8.5	51.1	±9.5	0.67
Hospitalization	Inpatient	45	77.6	40	65.6	0.16
	Outpatient	13	22.4	21	34.4	
Medical history	Yes	51	87.9	53	86.9	1.00
	No	7	12.1	7	11.5	
	Unknown	0	0	1	1.6	
Underlying disease/complication	Yes	52	89.7	50	82.0	0.30
	No	6	10.3	11	18.0	
	Bronchitis chronic	5	8.6	4	6.6	0.74
	Bronchiectasis	4	6.9	4	6.6	1.00
	Asthma bronchial	1	1.7	5	8.2	0.21
	Old pulmonary tuberculosis	0	0	2	3.3	0.50
	Pulmonary fibrosis	1	1.7	2	3.3	1.00
	COPD	7	12.1	9	14.8	0.79
	Gastroesophageal reflux disease	1	1.7	2	3.3	1.00
	Diabetes mellitus	4	6.9	3	4.9	0.71
	Hepatic disease	0	0.0	2	3.3	0.50
	Malignant tumor	0	0.0	1	1.6	1.00
	Cerebrovascular disorder	2	3.4	6	9.8	0.27
	Dementia	2	3.4	2	3.3	1.00
	Central nervous system disease	2	3.4	0	0.0	0.24
Type of pneumonia	Bacterial (suspected)	52	89.7	56	91.8	0.76
	Atypical (suspected)	6	10.3	5	8.2	
Severity of pneumonia (PORT score)	1	3	5.2	2	3.3	0.94
	2	11	19	16	26.2	
	3	28	48.3	23	37.7	
	4	16	27.6	20	32.8	
Severity of pneumonia (A-DROP score)	Mild	13	22.4	17	27.9	0.80
	Moderate	44	75.9	37	60.7	
	Severe	1	1.7	7	11.5	
Antibiotics pretreatment		8	13.8	5	16.4	0.39
Risk factor for resistant bacterial infection	≥2 days hospitalization within 90 days	8	13.8	6	9.8	0.58
	Immunocompromised state	4	6.9	4	6.6	1.00
	Use of antimicrobials within 90 days	10	17.2	9	14.8	0.80
	Use of acid suppressant	14	24.1	20	32.8	0.32
	Enteral feeding	1	1.7	0	0	0.49
	Ambulation difficulty	3	5.2	3	4.9	1.00
NHCAP	Resident in long-term recuperation[1)]	4	6.9	1	1.6	0.20
	History of Hospitalization[2)]	6	10.3	6	9.8	1.00
	Elderly receiving nursing care[3)]	8	13.8	4	6.6	0.23
	Endovascular treatment[4)]	0	0	1	1.6	1.00
Aspiration pneumonia	Yes	16	27.6	21	34.4	0.67
	No	37	63.8	34	55.7	
	Unknown	5	8.6	6	9.8	

[a] *t*-test for weight and age, and Fisher's exact test (one-sided) for the others.[1)] Pneumonia diagnosed in a resident of an extended care facility or nursing home.[2)] Pneumonia diagnosed in a person who has been discharged from a hospital within the preceding 90 days.[3)] Pneumonia diagnosed in an elderly or disabled person who is receiving nursing care.[4)] Pneumonia diagnosed in a person who is receiving regular endovascular treatment as an outpatient (dialysis, antibiotic therapy, chemotherapy, immunosuppressant therapy). ITT, intent-to-treat; STFX, sitafloxacin; GRNX, garenoxacin; SD, standard deviation; Min, minimum; Max, maximum; PORT, Pneumonia Patient Outcomes Research Team; A-DROP, pneumonia severity score proposed by Japanese Respiratory Society, consisting of age, dehydration, respiration, disorientation and blood pressure; NHCAP, nursing and healthcare-associated pneumonia.

gram-negative bacteria isolated in this study. The bacteriological efficacy was then assessed using the bacteriological PP population at the EOT. After treatment, causative bacteria were eradicated in 22 of 28 patients in the sitafloxacin group and in 24 of 32 patients in the garenoxacin group. The bacterial eradication rates were 88.0% (95% CI: 68.8%–97.5%) in the sitafloxacin group and 88.9% (95% CI: 70.8%–97.6%) in the garenoxacin group (Table 4).

3.5. Sputum sitafloxacin concentration

Sputum and serum samples were collected between 1 h 45 min and 4 h 10 min after taking sitafloxacin on Day 4. The median sputum sitafloxacin concentration of all patients collected was 0.313 μg/g (range: 0.0795–0.479 μg), while the median serum sitafloxacin concentration was 1.39 μg/mL (range: 0.119–2.20 μg/mL). The median transfer rate of sitafloxacin from serum to sputum was 23.2% (range: 14.7%–26.3%).

3.6. Safety

Adverse events were reported in 15 of 58 patients in the sitafloxacin group (25.9%) and in 18 of 61 patients in the garenoxacin group (29.5%). Of these, 12 adverse events (20.7%) in the sitafloxacin group and 17 adverse events (27.9%) in the garenoxacin group were considered drug-related, with hepatic dysfunction being common to both groups (Table 5). There was no significant difference between the treatment groups in the incidence of adverse events or drug-related adverse events. In the sitafloxacin group, a male

Table 2
Clinical response and treatment efficacy (PP population).

Time point	Treatment	Clinical response			Cure rate (95% CI)	P value[a]
		Cured	Not cured	Indeterminate		
TOC	STFX (n = 55)	46	6	3	88.5% (76.6–95.6)	p = 1.00
	GRNX (n = 57)	48	6	3	88.9% (77.4–95.8)	
Time point	Treatment	Treatment efficacy			Effective rate (95% CI)	P value[a]
		Effective	Not effective	Indeterminate		
Day 4	STFX (n = 55)	46	6	3	88.5% (76.6–95.6)	p = 1.00
	GRNX (n = 57)	50	6	1	89.3% (78.1–96.0)	
EOT	STFX (n = 55)	47	5	3	90.4% (79.0–96.8)	p = 0.47
	GRNX (n = 57)	54	3	0	94.7% (85.4–98.9)	

PP, per-protocol; TOC, test of cure performed 5–10 days after end of treatment; CI, confidence interval; STFX, sitafloxacin; GRNX, garenoxacin; Day 4, the day after the first 3 days treatment; EOT, end of treatment.
[a] Fisher's exact test.

Table 3
Clinical cure rates in subgroup analyses.

Subgroup		Cure rate (%)		Difference in cure rate (95% CI)	P value[a]
		STFX group	GRNX group		
Total		46/52 (88.5)	48/54 (88.9)	−0.4 (−19.8–18.2)	p = 1.00
Sex	Male	26/29 (89.7)	26/30 (86.7)	3.0 (−21.8–28.3)	p = 1.00
	Female	20/23 (87.0)	22/24 (91.7)	−4.7 (−31.9–23.9)	p = 0.67
Age (years)	65 to 74	16/21 (76.2)	22/23 (95.7)	−19.5 (−47.3–9.4)	p = 0.88
	75 to 84	21/22 (95.5)	13/15 (86.7)	8.8 (−23.6–40.2)	p = 0.55
	85 or over	9/9 (100.0)	13/16 (81.3)	18.8 (−21.2–55.5)	p = 0.28
Hospitalization	Inpatient	35/40 (87.5)	28/33 (84.8)	2.7 (−20.1–25.4)	p = 0.74
	Outpatient	11/12 (91.7)	20/21 (95.2)	−3.6 (−38.5–31.6)	p = 1.00
Severity of pneumonia (PORT score)	1	2/2 (100.0)	2/2 (100.0)	–	–
	2	8/10 (80.0)	14/15 (93.3)	−13.3 (−51.3–27.8)	p = 0.54
	3	24/28 (85.7)	18/20 (90.0)	−4.3 (−32.5–24.3)	p = 1.00
	4	12/12 (100.0)	14/17 (82.4)	17.6 (−18.6–51.4)	p = 0.25
Severity of pneumonia (A-DROP)	Mild	10/12 (83.3)	14/15 (93.3)	−10.0 (−46.4–28.5)	p = 0.57
	Moderate or severe	36/40 (90.0)	34/39 (87.2)	2.8 (−19.3–24.2)	p = 0.74
Aspiration pneumonia	Yes	14/15 (93.3)	17/19 (89.5)	3.9 (−29.3–36.3)	p = 1.00
	No	28/32 (87.5)	26/30 (86.7)	0.8 (−23.4–26.0)	p = 1.00
	Unknown	4/5 (80.0)	5/5 (100.0)	−20.0 (−75.7–47.5)	p = 1.00

STFX, sitafloxacin; GRNX, garenoxacin; PORT, Pneumonia Patient Outcomes Research Team; A-DROP, pneumonia severity score proposed by Japanese Respiratory Society, consisting of age, dehydration, respiration, disorientation and blood pressure.
[a] Fischer's exact test.

Table 4
Bacteriological efficacy (BPP population).

Treatment	Documented eradicated	Presumed eradicated	Documented persisted	Presumed persisted	Microbial substitution	Indeterminate	Eradication rate (95% CI)	P value[a]
STFX (n = 28)	13	9	0	2	1	3	88.0% (68.8–97.5)	p = 1.00
GRNX (n = 32)	16	8	0	3	0	5	88.9% (70.8–97.6)	

BPP, bacteriological per-protocol; CI, confidence interval; STFX, sitafloxacin; GRNX, garenoxacin.
Eradication rate (%) = ("documented eradicated" + "presumed eradicated")/(all − "indeterminate") × 100.
[a] Fisher's exact test.

patient aged 85 years had a serious episode of pseudomembranous colitis after completing treatment. He required a longer hospital stay to be treated with vancomycin for 14 days and made a full recovery. In the garenoxacin group, a 76-year-old male patient developed non-serious but severe agitation on Day 3 and was transferred to another hospital the following day. The outcome of this patient is not known.

4. Discussion

This randomized prospective trial demonstrated that oral administration of sitafloxacin and garenoxacin were comparably effective for the treatment of patients aged ≥65 with pneumonia, producing high clinical cure rates of 88.5% and 88.9%, respectively. There was also no statistically significant difference in the secondary efficacy points (including the bacteriological efficacy) on either Day 4 or at the EOT. These findings were consistent with the results of clinical trials for CAP, in which sitafloxacin and garenoxacin showed a high efficacy [8–10].

In the present study, most participants required hospitalization (71.4%) and had underlying disease (82.4%) and A-DROP scores of at least moderate severities (74.8%). A clinical diagnosis of aspiration pneumonia (including suspected cases) was made in 34.3%. These backgrounds are seen in routine clinical practice where elderly patients often suffer from aspiration pneumonia as a consequence of deteriorated swallowing function with age [20].

Oral streptococci and anaerobic bacteria should be assumed to be causative in most cases [21], although the involvement of anaerobic bacteria requires careful judgment. MICs of sitafloxacin for the causative bacteria of respiratory infections, in particular

Table 5
Adverse events (ITT population).

	STFX group (n = 58)				GRNX group (n = 61)			
	Adverse event		Drug-related event		Adverse event		Drug-related event	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of events	17		13		20		19	
Number of patients	15	(25.9)	12	(20.7)	18	(29.5)	17	(27.9)
Adverse event								
Hepatic dysfunction	8	(13.8)	7	(12.1)	7	(11.5)	7	(11.5)
Hyperkalemia					2	(3.3)	2	(3.3)
Diarrhea					2	(3.3)	2	(3.3)
Renal dysfunction					2	(3.3)	2	(3.3)
Gout attack	1	(1.7)						
Pseudogout					1	(1.6)	1	(1.6)
Nausea					1	(1.6)	1	(1.6)
Right pneumothorax	1	(1.7)						
Pseudomembranous enteritis	1	(1.7)	1	(1.7)				
Disseminated papules					1	(1.6)	1	(1.6)
Rashes	1	(1.7)	1	(1.7)				
Agitation					1	(1.6)	1	(1.6)
Fever	1	(1.7)						
Increase of AST, ALT level	1	(1.7)	1	(1.7)				
Increase of amylase level					2	(3.3)	2	(3.3)
increase of γ-GTP level	1	(1.7)	1	(1.7)	1	(1.6)		
Increased eosinophil ratio	1	(1.7)	1	(1.7)				
Eosinophilia	1	(1.7)	1	(1.7)				

STFX, sitafloxacin; GRNX, garenoxacin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transpeptidase.

gram-negative bacteria and anaerobic bacteria, are lower than those of other respiratory quinolones (garenoxacin, moxifloxacin, and levofloxacin) [4,22]. The median serum and sputum concentrations of sitafloxacin were 1.39 μg/mL and 0.313 μg/g, respectively, which are within the previously reported range [23] and higher than the MICs for major causative organisms of respiratory infections [22]. These results are consistent with evidence of its high efficacy against infections in dentistry, oral cavity surgery, and otorhinolaryngology [6]. By contrast, garenoxacin was able to maintain a high plasma concentration due to a long half-life [24], which probably contributed to its effectiveness in elderly patients with pneumonia. However, overall efficacy rates and efficacy rates in aspiration pneumonia of both drugs were comparable. Thus, in this study with a small cohort, we could not find a clinically significant difference between both drugs with different characteristics with respect to antimicrobial and pharmacological activities.

No significant differences were observed in the incidence of drug-related adverse events between the sitafloxacin and garenoxacin groups. The most common adverse event was hepatic dysfunction with both drugs, and no new adverse events were observed. Pseudomembranous colitis is one of the common adverse events caused by antibiotics [25]. One patient in the sitafloxacin group developed pseudomembranous colitis after the completion of the study drug but this was treatable with the standard therapy. Collectively, we identified no major difference of safety concerns between sitafloxacin and garenoxacin.

Fluoroquinolones have been frequently used in Japan, especially among the working age and elderly groups [26]. In accordance with the Global Action Plan on Antimicrobial Resistance (AMR) from the World Health Organization [27], the Government of Japan also developed a National Action Plan on AMR in 2016 [28]. Because antimicrobial use is closely associated with the development of AMR, the outcome indices for this action plan include the reduction of the use of oral cephalosporins, quinolones, and macrolides per day per 1000 inhabitants in 2020 by 50% from the level in 2013 [28]. Because both sitafloxacin and garenoxacin have broad antimicrobial spectra, including anti-*Pseudomonas* activity, it is essential to avoid misuse and overuse of these drugs by promoting antimicrobial stewardship to prevent the development of AMR.

There was no tuberculosis case in the patients included in this study, whereas pneumonia patients, especially among elderly people, may have tuberculosis infections in daily clinical practice. Because fluoroquinolones are temporarily effective for tuberculosis, there is an increased risk that the diagnosis of tuberculosis will be delayed. In addition, the fluoroquinolone resistance of *Mycobacterium tuberculosis* has become a worldwide problem because of the frequent and careless use of fluoroquinolones. Therefore, these risks should always be kept in mind when using fluoroquinolones.

This study has some limitations. Notably, it was performed with a limited sample size in which therapy was allocated on site rather than by patient. Therefore, we could not confirm noninferiority or superiority between sitafloxacin and garenoxacin. This was also an open-label study, with both the investigators and the participants being aware of the assigned treatment, which possibly affected the evaluation of safety and efficacy of the drugs being studied. Nevertheless, the present results indicate that further large-scale studies are certainly justified to characterize the preferable use of each drug in the various types of pneumonia in elderly patients.

Based on several factors, such as underlying diseases, risk of deterioration, and social factors, elderly patients with pneumonia are, in principle, hospitalized and treated with antibiotics by injection [3,29]. However, as patients with NHCAP, including aspiration pneumonia, are increasing, strategies are required to reduce overall cost and prevent the emergence of drug-resistant bacteria. Oral respiratory quinolones, including sitafloxacin and garenoxacin, with high efficacy and safety, can be considered a useful option for the treatment of pneumonia in elderly patients. Further research is now warranted.

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Conflicts of interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Appendix A. Supplementary data

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